

Analysis of Radicals by EPR

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1 INTRODUCTION

1.1 Background and Scope

All radicals contain one or more unpaired electrons (UPEs), each with its own magnetic dipole moment arising from its spin. Radicals are therefore paramagnetic and possess net spin moments that can interact with the magnetic component ($\mathbf{B}_1$) of incident electromagnetic radiation. This interaction gives rise to electron paramagnetic resonance (EPR) spectra, one of the most versatile and useful techniques for studying radicals. There is a close analogy between EPR (also called *ESR*, *EMR*) and the more familiar nuclear magnetic resonance (NMR) spectra. This article focuses on the isotropic spectra obtained from organic mono radicals and radical ions in solution. Numerous textbooks and monographs are available covering anisotropic spectra, electron nuclear double resonance (ENDOR) spectra, pulsed EPR techniques, and related topics.^{1–4}

Paramagnetic resonance absorption was first observed on a $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ sample by Zavoiskii using radio frequency irradiation and a low field.⁵ Continuous wave (CW) EPR instruments operating in the microwave region at about 9 GHz with magnetic fields of about 300 mT (X-band) were the workhorses of the technique until around the start of the twenty-first century. Since then high field/high frequency spectrometers, pulsed spin-excitation spectrometers, double resonance instruments, and so on have become commercially available and are enabling EPR to expand into new

areas of biology and materials science. Extensive and valuable tables of EPR data, particularly for organic radicals at X-band, have been published in the Landolt–Börnstein series.⁶

1.2 Basis of the EPR Technique

In a CW EPR experiment, the paramagnetic sample is placed in a static magnetic field $\mathbf{B}_0$ where it is irradiated with electromagnetic radiation of frequency ν having oscillating magnetic component $\mathbf{B}_1$. The static magnetic field is scanned and the electron undergoes transitions between available energy levels. These transitions occur when the energy of the incident photons ($h\nu$) matches the separation of the energy levels (ΔE).

$$\Delta E = h\nu \quad (1)$$

At each transition, power is absorbed from the incident microwave radiation and this is detected and amplified. The EPR spectrum is usually a display of the first derivative of this absorption as a function of the applied magnetic field.

The energies of the electron and nuclear dipoles in the radical are proportional to the strength of the static field and also depend on their orientations with respect to it. Radicals of small to moderate size undergo random Brownian motion in fluid solvents and this usually averages the anisotropies of the Zeeman and hyperfine couplings to zero. Under these conditions, and taking the static magnetic field to be in the z -direction, the energies can be obtained

from the spin Hamiltonian $\hat{H}$ given to first order by (2)^{7–9}:

$$\hat{H} = g\beta_e \mathbf{B}S_z + \sum a_i I_{z,i} S \quad (2)$$

The first term in (2) represents the electron Zeeman interaction and contains the dimensionless spectroscopic splitting g -factor, β_e , the *Bohr magneton* (a constant equal to $eh/4\pi m_e c$), $\mathbf{B}$ the vector of the magnetic field, and S_z , the spin angular momentum operator of the UPE in the z -direction. The constants a_i are the isotropic hfs constants that quantify the isotropic interaction of the electron with each magnetic nucleus. They can be positive or negative but only the magnitudes are directly accessible from EPR measurements (the signs can be determined by NMR). The spin operators, S_z and I_z , act on the spin wave functions to yield eigenvalues $m_s = \pm 1/2$ and $m_I = -I, -I+1, \dots, I$ for the electron and nuclear components, respectively. The available energy levels are given by (3):

$$E_{\text{iso}} = g\beta_e B m_s + m_s \sum a_i m_{I,i} \quad (3)$$

where B is the field at resonance. The resonance lines appear in the EPR spectrum at the following fields:

$$B = \mathbf{B}_0 - \sum a_i m_{I,i} \quad (4)$$

In the case of a radical containing no magnetic nuclei, (3) yields $E_{\text{iso}} = g\beta_e B m_s$. Radiation induces transitions, that is, changes in the orientation of the electron spin relative to B_z , between the lower and the upper energy levels. Since $m_s = -1/2$ and $+1/2$ for the lower and the upper levels, respectively, ΔE becomes $g\beta_e B$ and hence the condition for an EPR transition is as follows:

$$\Delta E = h\nu = g\beta_e B \quad (5)$$

Consider a radical containing two $I = 1/2$ nuclei coupled to the UPE with hfs a_1 and a_2 ($a_1 > a_2$). Equation (4) indicates there will be four resonance fields at $B_1 = \mathbf{B}_0 - 1/2 a_1$, $B_2 = \mathbf{B}_0 - 1/2 a_2$, $B_3 = \mathbf{B}_0 + 1/2 a_2$, and $B_4 = \mathbf{B}_0 + 1/2 a_1$. The allowed EPR transitions are those in which m_s alters by ± 1 , while the nuclear spins stay unchanged ($\Delta m_I = 0$). The spectrum will consist of four lines separated by a_1 and a_2 as shown in Figure 1. Since each nuclear

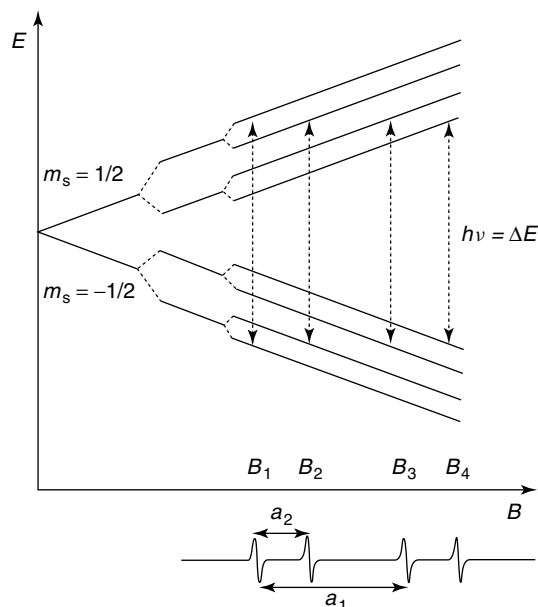


Figure 1 Energy levels and transitions for a mono-radical containing two spin $1/2$ nuclei. The corresponding EPR spectrum is below the field axis.

spin state is equally probable, the four lines are of equal intensity.

For radicals with groups of two, three, four, and so on of equivalent nuclei, the corresponding spectra are triplets, quartets, quintets, and so on with intensities according to the coefficients of the binomial series. For radicals with several nonequivalent sets of nuclei and with nuclei having $I > 1/2$, the EPR spectra can be extremely complex; such spectra are often incompletely resolved and analyzing them is a nontrivial task. Second-order spectra, sometimes containing additional lines, are obtained for radicals with relatively large values of a_i .¹⁰

1.3 Relaxation Phenomena and Line Shapes

When electromagnetic radiation interacts with an assemblage of free radicals in a magnetic field, there is an equal probability of spin flip from the upper or the lower level. For net absorption of radiation, giving an observable EPR spectrum, it is necessary for there to be more electrons in the lower state. The ratio of the number of spins in the lower level

(N_L) to the number of spins in the upper level (N_U) is determined by the Boltzmann distribution:

$$\frac{N_U}{N_L} = \exp\left(\frac{-\Delta E}{kT}\right) = \exp\left(\frac{-g\beta_e B}{kT}\right) \quad (6)$$

As long as the assemblage of radicals remains in thermal equilibrium, N_L will exceed N_U and net absorption will ensue. Although the energy gap at X-band $g\beta_e B$ is small in comparison with the average thermal energy kT , sophisticated instrumentation ensures that EPR is a very sensitive technique. In solution, radical concentrations of 10^{-8} M can routinely be detected and, under favorable circumstances (simple spectra, low temperatures) nanomolar concentrations can be studied.

When a sample of radicals absorbs radiation, the number in the upper level will increase until $N_U = N_L$, or even $N_U > N_L$, for large energy pulses. When $N_U = N_L$, there will be zero net absorption of microwave radiation and the EPR spectrum will shrink to zero. In this situation, the spectrum is said to be “saturated” and this occurs for most radicals at high enough power of the incident microwave radiation. There exist mechanisms whereby the electrons in the upper level lose energy to the surrounding medium, or internally, such that they return or “relax” to the lower level. The loss of excess energy to the surroundings takes place by an exponential decay, which is characterized by the spin–lattice relaxation time τ_1 . The spin–lattice relaxation time is related to the mean lifetime of a given spin state and so has an effect on the linewidth.

According to the Heisenberg uncertainty principle, the “width” or energy range δE of a short-lived excited state is not well defined but is related to its lifetime τ by $\tau\delta E = h/2\pi$. A certain broadening will be observed in the resonance transition and, on substitution from Plank’s equation, the following relationships are obtained:

$$\Delta\nu \approx \frac{1}{\tau} \quad \text{or} \quad \Delta B \approx \frac{h}{g\beta_e \tau} \quad (7)$$

This kind of line broadening is called *lifetime broadening* and defines the *minimum* linewidth for a given system. Spin–lattice interactions are particularly important for radicals in condensed phases where the spin system can be directly

coupled to the vibrations of the lattice (phonons). In this case, τ in (7) will be dominated by τ_1 .

In fluid solution, the motions of the solvent molecules provide a less efficient thermal sink and a second process known as *spin–spin relaxation* usually plays a more important role. Magnetic interactions between nuclei and electrons, and between like spins, are an extremely efficient means of relaxing both nuclear and electron spins. This dipolar interaction causes *mutual* spin flips so that the lifetime of spins in the upper state is limited, but the total number of spins in the state remains the same. It follows that this spin–spin relaxation, with relaxation time τ_2 , contributes to the lifetime broadening of the resonance line but does not affect the level of saturation. For free radicals in solution, it is often τ_2 that limits the linewidth; that is, $\Delta B = h/g\beta_e \tau_2$.

Deeper insight into spin relaxation is obtained from solutions to the Bloch equations for the time dependence of the magnetic moment of an ensemble of spins under the conditions of EPR experiments.^{11,12} The Bloch equations furnish expressions for the real (χ') and imaginary (χ'') parts of the magnetic susceptibility of the ensemble of radicals in terms of just the two relaxation times τ_1 and τ_2 . The real part χ' relates to the EPR *dispersion spectrum*, which is less useful than the *absorption spectrum* and is rarely recorded. The expression obtained for χ'' relating to the conventional *absorption spectrum* far from saturation is

$$\chi'' = \chi_0 \frac{\tau_2 \omega_0}{1 + \tau_2^2 \gamma_e^2 (B_0 - B)^2} \quad (8)$$

χ_0 is the bulk static magnetic susceptibility, ω_0 is the angular frequency of the microwave radiation at resonance ($\omega = 2\pi\nu$), and $\gamma_e (= -2\pi g\beta_e/h)$ is the magnetogyric ratio of the electron. The power P absorbed per unit sample volume (V) by the ensemble of radicals from the microwave radiation is

$$P = 1 \frac{\omega \chi'' B_1^2}{\mu_0 V} \quad (9)$$

where μ_0 is the magnetic permeability of the vacuum. The expression (8) takes the form of a Lorentzian function and this is the EPR lineshape observed under conditions of slow field sweep and with power levels below saturation. With these conditions, the linewidth at half height ($\Delta B_{1/2}$) is

given by (10):

$$\Delta B_{1/2} = \frac{2}{\gamma_e \tau_2} = 3^{1/2} \Delta B_{pp} \quad (10)$$

Equation (9) shows that the power absorbed by the sample is proportional to χ'' , and therefore to the number of paramagnetic species present. The power absorbed by the whole sample (P_w), during a scan through the whole EPR spectrum, is given by $\int P dB$ which is a measure of the area under the absorption curve. Hence, the number of spins in a sample is proportional to the integral of the absorption curve, or the double integral of the more usually recorded first derivative spectrum.

In a real CW EPR spectrum of a radical in solution, the lines are often Lorentzian or nearly Lorentzian in shape (Figure 2). However, when additional factors come into play such as slight anisotropies due to inefficient tumbling, unresolved hyperfine interactions from substituents or the surrounding liquid, or static dipolar interactions, the lineshapes tend to Gaussian, in which case the linewidths are given by (11):

$$\Delta B_{1/2} = \frac{2(\pi \ln 2)^{1/2}}{\gamma_e \tau_2} = (2 \ln 2)^{1/2} \Delta B_{pp} \quad (11)$$

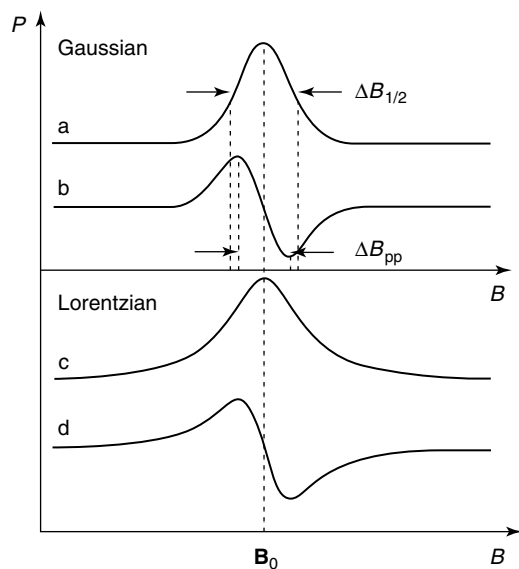


Figure 2 Gaussian EPR lineshape; (a) absorption curve, (b) first derivative. Analogous Lorentzian lineshapes (c) and (d). Note the difference between $\Delta B_{1/2}$ and the peak to peak linewidth ΔB_{pp} .

2 ISOTROPIC g -FACTORS

The field experienced by an UPE will differ from the static magnetic field $\mathbf{B}$ because of local fields, which may be permanent or may be induced by the external magnetic field. To allow for this, the dimensionless g -factor of (3) is understood to be variable. The effective field can be written as

$$\mathbf{B}_{\text{eff}} = (1 - \sigma)\mathbf{B} = \left(\frac{g}{g_e}\right)\mathbf{B} \quad (12)$$

Here, σ is the analog of the “chemical shift” parameter of NMR spectroscopy and it is replaced by g in EPR spectroscopy. Orbital angular motion of the UPE is an important contributor to the local field. In many transition metal ions, spin–orbit coupling is large so that g deviates greatly from $g_e(2.00232)$. For most organic radicals in solution, on the other hand, the ground state has zero orbital angular momentum and so the isotropic g is close to g_e . However, in the majority of radicals, a small amount of orbital angular momentum from excited states is mixed in causing g -factors to diverge from g_e . The observed g -factors are sensitive to the local environment surrounding the UPE and can be used for radical characterization in much the same way as chemical shifts from NMR spectroscopy.

Experimentally, the g -factor of a radical can be determined from the EPR spectrum by the use of (5). This requires the measurement of the frequency ν and the field B with an accuracy beyond that of most commercial spectrometers. It is normal, therefore, to add a standard of known g -factor (in a capillary tube, or otherwise) to the sample of the unknown radical such that spectra of both the standard and unknown are simultaneously scanned. Symmetrical spectra free from distortions are required for the uncorrected fields at the center of the standard (B_S) and the center of the unknown (B_X) to be read off the spectrum. The unknown g -factor g_X can then be obtained from (13):

$$g_X = g_S - \frac{g_S(B_X - B_S)}{B_S} \quad (13)$$

Standard radicals frequently used include DPPH ($g = 2.00354$ in PhH soln.), perylene ($g = 2.00257$ in conc. H_2SO_4), weak pitch ($g = 2.0028$ in KCl powder), and TEMPONE ($g = 2.0062$ in PhH

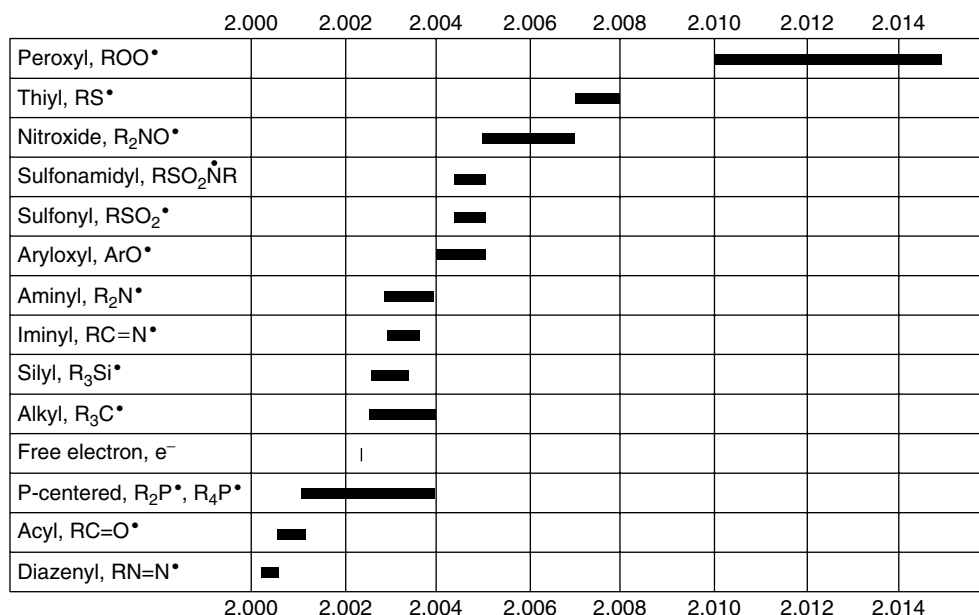


Figure 3 Central ranges of isotropic g -factors of organic radicals in solution (data from Ref. 6).

soln.). The central ranges for g -factors of common radical types are presented in Figure 3.

For an unknown radical, the g -factor is a valuable indicator of the principal site of the UPE. The ranges of values (Figure 3) occur because additional functional groups in the vicinity of the UPE affect the spin–orbit coupling. A few radicals such as acyl, diazenyl, and some phosphorus-centered radicals have g -factors $<g_e$. Most C- and Si-centered radicals, and radical ions, have g -factors of about 2.0026, but multiple substituents substantially increase this. Nitrogen-centered radicals including iminyls and aminyls have g -factors in the range 2.003–2.004. Nitroxides (aminoxyls) are the most common type of persistent radical and they have very characteristic g -factors around 2.006. Most aryloxy radicals and semiquinone radical anions have g -factors around 2.0045. Many alkylperoxyls have large g -factors close to 2.015. Extensive tables of isotropic g -factors for many radical types can be found in Ref. 6.

3 INTERPRETATION OF COMPLEX SPECTRA

At X-band, the applied field $\mathbf{B}$ is large compared to almost all hfs, so isotropic spectra show a

symmetrical cluster of resonance lines around the central field B_0 . A set of hfs (a_i ; analogous to j in NMR spectroscopy) quantifies the electron–nuclear interactions. For radicals in which the UPE interacts with only a few sets of nuclei, the spectra can be interpreted and the a_i values determined by simple inspection of the multiplets that appear. The line heights should also be symmetrical, but non-ideality can result from slow tumbling of the radicals. Serious asymmetry usually indicates that spectra from two or more radicals, with different g -factors, are superimposed. Hyperfine splittings are usually expressed in millitesla or Gauss [$a(\text{G}) = 10a(\text{mT})$] but can also be reported in MHz [$a(\text{MHz}) = 1.3996ga(\text{mT})$].

The following rules are helpful in analyzing spectra:

1. The separation between the two outermost lines at high field (or low field) is almost always the smallest hfs. Note, however, that the outermost low intensity lines may be hidden in noise.
2. The spectral extent ΔB_w is the separation between the low and high field outermost lines and for $I = 1/2$ nuclei, it is given by $\Delta B_w = \sum n_i a_i$, where $i = 1, \dots, N$. Here, N is the number of sets of equivalent nuclei and n_i is the number of equivalent nuclei with hfs a_i .

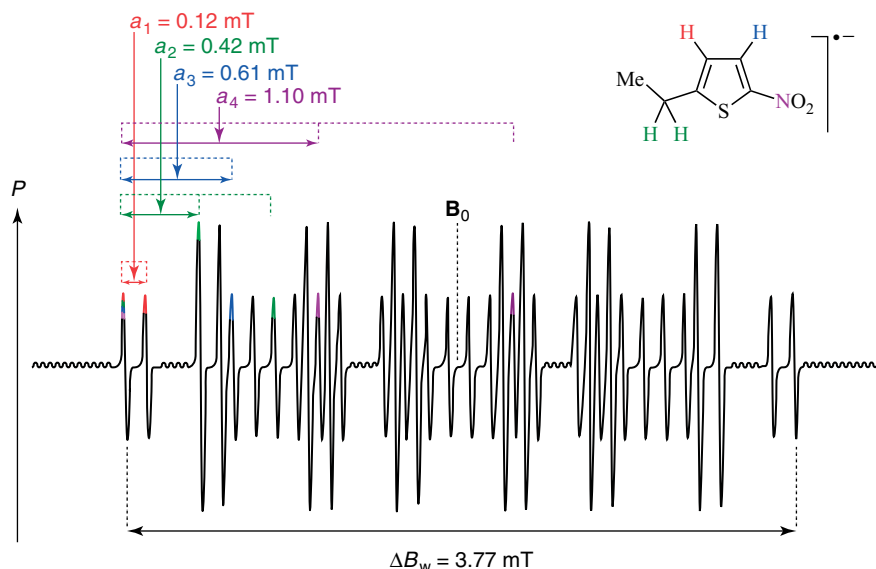


Figure 4 Deduction of hyperfine splittings a_i from an EPR spectrum.

3. A spectrum with a central line indicates the presence of an even number of $I = 1/2$ nuclei. However, the presence of central line does not exclude an odd number of nuclei.

For the model spectrum shown in Figure 4, the two outermost lines form a doublet with separation 0.12 mT and so this is the smallest hfs a_1 . The doublet pattern indicates that this results from interaction with one $I = 1/2$ nucleus. A triplet splitting from two $I = 1/2$ nuclei starts 0.42 mT upfield from the first (a_2). A doublet from one $I = 1/2$ nucleus starts 0.61 mT upfield again (a_3). The measured spectral extent ΔB_w is 3.77 mT. Thus, the final hfs can be found from the difference: $\Delta B_w - [1 \times 0.12 + 2 \times 0.42 + 1 \times 0.61] = 2.20$ mT. Inspection shows that this corresponds to a 1:1:1 triplet with hfs 1.10 mT from an $I = 1$ nucleus (N, a_4). In this species, therefore, the UPE interacts with two nonequivalent H-atoms, a CH_2 group, and an N-atom as expected for the radical anion of 5-ethyl-2-nitrothiophene. Analyses such as this should be confirmed by computer simulation of the spectrum using one of the freely available packages for isotropic spectra. (The WINEPR SimFonia package is freeware available from Bruker Corporation and runs in the MS Windows environment).¹³

Definitive analyses of complex and imperfectly resolved spectra present formidable problems. It

may be possible to deduce one or two of the a_i values using the above rules. The Winsim2002 software, and the MATLAB-based package EasySpin,¹⁴ are particularly useful because they directly read experimental EPR spectra from several different file formats. The simulated spectrum is compared with the experimental spectrum and a correlation coefficient is outputted as a measure of the goodness of fit. Application of the Winsim2002 autocorrelation function to the experimental spectrum provides a list of hyperfine parameters. The list contains all the required a_i values for the unknown radical mixed up with sums and differences of the a_i values. On the basis of this list, a likely set of a_i can often be guessed and the resulting simulation compared with experiment. Help in estimating appropriate a_i values can also be obtained from literature data for model radicals or from *ab initio* computed hfs. By working through several iterations of inputted a_i and comparison of the simulated and experimental spectra, it is often possible to obtain good simulations of even very complex spectra of unknown provenance.

In difficult cases, it is necessary to obtain and compare spectra from a series of radical isotopomers. Deuterium (D , ^2H) has $I = 1$ and since $a(\text{H})/a(\text{D}) = [\mu_{\text{D}}/I_{\text{D}}]/[I_{\text{H}}/\mu_{\text{H}}] = 6.5$ substitution of H by D usually means the hfs from the substituted H-atom is removed (to within the linewidth) or becomes a smaller set of 1:1:1 triplets.¹⁵

A simplified spectrum, which is easier to interpret, often results. Similar simplification can be achieved by substitution of ^{14}N ($I = 1$) by ^{15}N ($I = 1/2$). Occasionally, ^{17}O ($I = 5/2$) has been introduced in place of ^{16}O ($I = 0$) to confirm the site of an O-atom, notably in peroxy radicals.^{16,17}

4 INTERPRETATION OF ISOTROPIC HYPERFINE SPLITTINGS

4.1 The Origin of Hyperfine Splitting

The magnitude of the isotropic interaction depends on the probability of finding the electron at the nucleus. Clearly, this hinges on the character of the orbital containing the UPE. In general, the spins of electrons and nuclei are coupled by the *Fermi contact interaction*, which represents the energy of the nuclear moment in the magnetic field produced at the nucleus by the spinning electron. The Hamiltonian operator corresponding to this is given by (14)

$$\hat{H}_c = \left(\frac{8\pi}{3} \right) g\beta g_n \beta_n \delta(\mathbf{r}) \mathbf{S} \cdot \mathbf{I} \quad (14)$$

The Dirac delta function $\delta(\mathbf{r})$ ensures that this is only effective when the electron has a finite probability of being at the nucleus. Thus, $\hat{H}_c$ only has finite values for s-orbitals because p-, d-, f-, and so on orbitals have zero density at nuclei, and hence only electrons with some s-character can interact with the corresponding nucleus. The hfs derived from (14) takes the form

$$a_n = \left(\frac{8\pi}{3} \right) g\beta g_n \beta_n \rho(r_n) \quad (15)$$

where $\rho(r_n)$ is the *spin density* evaluated over the volume of the nucleus.

In π -type neutral radicals (methyl, allyl, cyclohexadienyl, etc.), aromatic radical ions, and similar species, the UPEs are contained in π -molecular orbitals (MOs) that extend over much of the molecular framework. The π -MOs have a node in the plane of the radical, where many of the H-atoms, ^{13}C , and other magnetic nuclei reside. At first sight, it appears that electron–nuclear coupling should be zero, but in practice exchange forces bring about coupling of the π -electron with σ -electrons in the

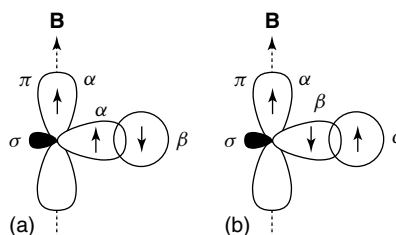


Figure 5 Spin polarization in a C–H fragment of a π -radical.

molecular framework. This phenomenon, known as *spin polarization*, can be understood by reference to a C–H fragment forming part of a π -radical. Two arrangements of the spins (a) and (b) are possible (Figure 5). However, because of exchange coupling between the π - and σ -orbitals, arrangement (a) is slightly lower in energy.

In (a), the two spins on the C-atom (α) are parallel, leading to a favorable exchange interaction. Hence, there is a slight excess of α -spin in the σ -orbital and a corresponding excess of β -spin in the H-atom's s-orbital. The α -spin on the π -orbital induces β -spin at the H-atom and hence the spin density at the H-atom is negative, and so is the H-atom hfs to the π -electron. In (a), the α -spin of the π -electron induces α -spin in the σ -orbital centered on the C-atom and hence the hyperfine coupling to the ^{13}C -nucleus ($I = 1/2$) will be positive.

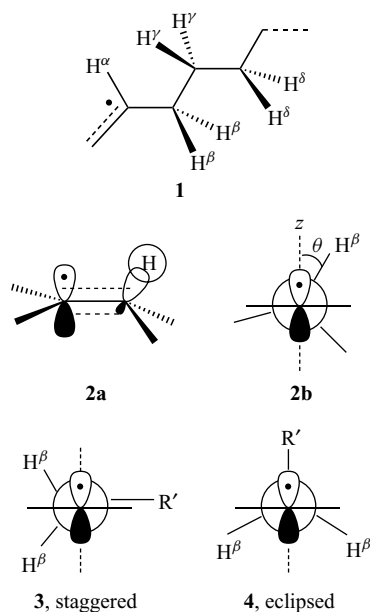
McConnell showed that the hfs $a(\text{H})$ of H-atoms in π -type radicals are directly proportional to the π -electron spin densities ρ_π in the p-orbitals of the C-atoms to which they are attached^{18,19}:

$$a(\text{H}) = Q\rho_\pi \quad (16)$$

The relationship has been tested for many diverse series of π -type radicals and radical ions and reasonable linearity resulted with Q usually in the range -2.2 to -2.9 mT.²⁰ This simple relationship enables a rough picture of the distribution of unpaired spin in a free radical to be built up from the experimental hfs of “reporter” H-atoms.

4.2 Hyperfine Splitting from Nuclei Two or More Bonds from the UPE

The distances of H-atoms from a radical center, which may or may not be part of a π -delocalized



Scheme 1 Conformations of $R_2C^\bullet-CH_2^\beta R'$ radicals.

system, are usually indexed as shown in **1** (Scheme 1).

Thus, H^α are one bond away from the π -orbital containing the UPE, while H^β , H^γ , H^δ , and so on are two, three, four, and so on bonds, respectively, removed from the radical center. For H^β -atoms, interaction with the UPE occurs mainly by a hyperconjugative mechanism. The π -orbital containing the UPE has correct symmetry for direct overlap with the σ -orbital of the $C^\beta-H^\beta$ bond (**2a**, Scheme 1). This mechanism implies that H^β hyperfine splittings should be positive and this has been confirmed by NMR experiments. The direct nature of the overlap in **2a**, **b** leads to sizeable β -hfs, which are often larger than α -hfs. For example, in the ethyl radical, where there is free rotation about the $C^\alpha-C^\beta$ bond, the measured $a(H^\alpha)$ is 2.24 mT, whereas the $a(H^\beta)$ is larger at 2.69 mT.

In nonrigid radicals, a degree of torsion about the $C^\alpha-C^\beta$ bond takes place in solution. The extent of overlap, and hence the magnitude of $a(H^\beta)$, will depend on the dihedral angle θ between the π -orbital and the $C^\beta-H^\beta$ bond (**2b**). This angle varies with the rate of internal rotation about the $C^\alpha-C^\beta$ bond, which depends on temperature. It follows that $a(H^\beta)$ are also significantly temperature dependent. Extensive studies of alkyl radicals^{21,22}

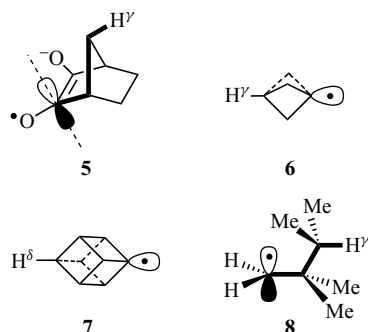
have shown that β -hfs follow a Karplus type relationship (17):

$$a(H^\beta) = A + B \cos^2 \theta \quad (17)$$

Constant A is small (<0.4 mT) and can often be neglected; B is ≈ 5.0 mT for C-centered radicals. There are two particular cases: (i) $R_2C^\bullet-CH_2^\beta R'$ where there are two β -H-atoms and (ii) $R_2C^\bullet-CH^\beta R_2'$ with one β -H-atom. For (i) the value of θ is 60° when R' eclipses the π -orbital (**4**) and 30° when the conformation is staggered (**3**). For free rotation, the average value of θ is 45° . If the preferred conformation is eclipsed (**4**), $a(H^\beta)$ will be in the range $A + 1/4B$ to $A + 1/2B$, and will *increase* toward the latter with increasing temperature. If the preferred conformation is staggered, $a(H^\beta)$ will be in the range $A + 3/4B$ to $A + 1/2B$ and will *decrease* toward the latter with increasing temperature. In case (ii), the limits are wider, that is, from A to $A + B$. These expectation values can be useful for determining the preferred conformation about the $C^\alpha-C^\beta$ bonds of nonrigid radicals. For example, the EPR spectrum of the *n*-propyl radical displayed $a(H^\alpha) = 2.21$ and $a(H^\beta) = 3.32$ mT at 100 K. On increasing the temperature to 200 K, $a(H^\beta)$ dropped to 2.92 mT. It follows that the preferred conformation of the *n*-propyl radical is staggered **3**. On the other hand, for the $CH_3SCH_2CH_2^\bullet$ radical $a(H^\beta)$ increased from 1.35 mT at 150 K to 1.49 mT at 205 K showing that its preferred conformation is eclipsed **4**. In general, radicals $RXCH_2CH_2^\bullet$ tend to adopt conformation **3** if X is a first row element but **4** if X is from the second or subsequent rows of the periodic table.

Longer range hfs generally decrease with the number of σ -bonds between the H-atom and UPE. Hfs from γ -H-atoms are normally much smaller [$< 1/10 \times a(H^\alpha)$]. In general, the prerequisite for observation of a substantial long-range hfs is a “frozen” conformation (on the EPR timescale). Most EPR studies of long-range hfs have involved bicyclic or polycyclic radicals in which the rigid structures place particular H-atoms at sites that are favorable for hyperfine interactions.^{23–26} For example, in the bicyclo[2.2.1]heptylsemidione radical anion **5** a large γ -hfs of 0.65 mT was observed for the indicated H^γ (Scheme 2).

Generally, γ -H-atoms for which the σ -bonds and the orbital containing the UPE adopt a “W-plan”



Scheme 2 Large long-range hyperfine interactions.

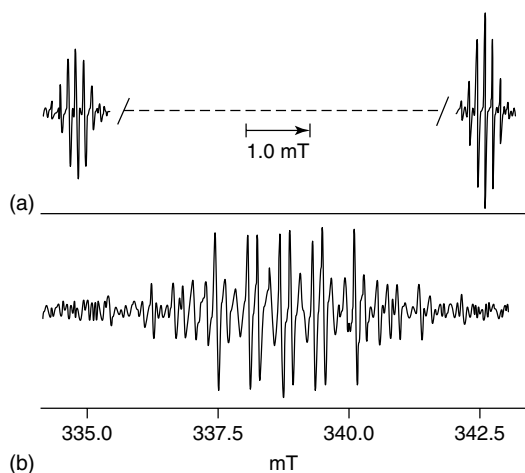


Figure 6 (a) EPR spectrum of bicyclo[1.1.1]pentyl radical **6** in liquid DTBP at 240 K. (The intensity difference of the two multiplets is due to a CIDEP effect.) (b) Spectrum of cubyl radical **7** in liquid DTBP at 245 K.

conformation (see **5** and **8**) show substantial hfs. The EPR spectra of the bicyclo[1.1.1]pentyl radical **6** and the cubyl radical **7** (Figure 6) were quite remarkable in that huge hfs of 6.96 mT were observed for the single H^γ of **6** (the intensity difference of the two multiplets is due to a CIDEP effect).^{27,28} and 0.63 mT for the single H^δ of **7**,^{29,30} because of multiple W-plan through bond and through space interactions.

Small long-range hfs are often resolvable in acyclic radicals,^{21,31,32} and in radicals containing oxygen, usually in an ether linkage.^{33–35} Many alkane radical cations in “rigid” conformations in low temperature matrices exhibit large long-range hfs.³⁶

In *n*-propane solvent, in the temperature range $90 < T < 125$ K tumbling remains fast for small to medium-sized radicals, but internal rotations may cease, so that long-range hfs can be resolved.³⁷ In the “rigid” conformations adopted at these temperatures γ -H-atoms situated trans (W-plan) with respect to the singly occupied molecular orbital (SOMO) show large hfs. For example, three of the γ -H-atoms of the neopentyl radical exhibit $a(H^\gamma) = 0.40$ mT and, even more remarkably, the unique H^γ of the 2,2,3-trimethylbutyl radical **8** had $a(H^\gamma) = 0.80$ mT.^{38,39}

4.3 Quantum Chemical Computation of EPR Parameters

The straightforward picture of just one UPE in a particular orbital interacting with nearby magnetic nuclei is a gross oversimplification.⁴⁰ In fact, radicals contain many electrons all of whose spins interact to some extent. For a more complete and accurate picture, all the populated molecular orbitals have to be taken into account in evaluating the spin density $\rho(r_n)$, which is actually the net difference between the α -spin and β -spin at the nucleus. In-depth treatments of the calculation of EPR parameters can be found in the compilation edited by Kaupp *et al.*⁴¹ Modern quantum mechanical MO packages based on DFT, or other *ab initio* methods, can compute optimum geometries of free radicals, together with the energies and eigenvectors associated with their occupied (and virtual) orbitals.^{42,43} Considerable effort has gone into finding the most effective quantum mechanical models and basis sets^{44,45} for the computation of isotropic EPR parameters.^{46–48} Methods based on the unrestricted Kohn–Sham (UKS) approach to DFT are among the most efficient. Quadratic configuration interaction (QCI) and coupled cluster (CC) methods give accurate results but are not practical for medium- or larger-sized radicals (> 10 non-hydrogen atoms). Hybrid functionals such as the popular B3LYP and the parameter-free PBE0 model provide good descriptions of the EPR spectra of many types of radicals. A combined PBE0/QCISD approach is recommended for more accurate work with species containing several heteroatoms such as nitroxides. Particular basis sets such as EPR-II,⁴⁹ and the much larger triple-zeta

quality EPR-III,⁵⁰ usually enable good agreement of computed and experimental hfs to be achieved for H-atoms. However, for heteroatoms (even the first row N, F) considerably more computational effort is often required. A number of well-tried electronic packages are now available to implement the quantum mechanics (QM) computations including GAMESS-UK,⁵¹ Jaguar,⁵² and Spartan.⁵³ The Gaussian 03 and 09 series of packages⁵⁴ are convenient because isotropic and anisotropic spin densities and hfs are directly computed and spin density maps can be plotted.

For example, the 1,3-dimethylimidazolyldihydro-boryl radical **9** was generated by H-atom abstraction from the corresponding HNC-borane and exhibited the isotropic EPR spectrum shown in Figure 7 at 245 K.⁵⁵ The molecular structure was optimized using the DFT method with the B3LYP functional and the 6-31+G(d) basis set and is shown in **9** (Figure 7). The corresponding maps of the SOMO and spin density, computed with the same geometry but the EPR-III basis set, are shown as **10** and **11**. The computed Fermi contact hfs are compared with the experimental parameters below and give a fair idea of the achievable level of agreement:

Hfs/mT	$a(2H^\alpha)$	$a(^{11}B)$	$a(2N)$	$a(2H)$	$a(6H)$
Exptl.	± 1.20	± 0.67	± 0.41	± 0.12	± 0.25
EPR-III	-1.02	+0.52	+0.23	-0.20	+0.28

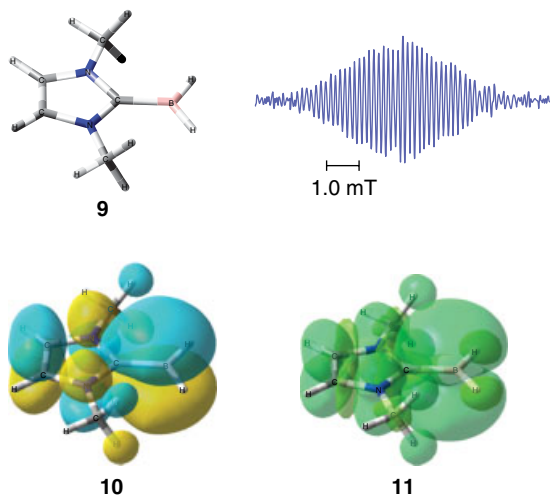
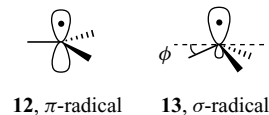


Figure 7 DFT computed structure, SOMO, and orbital spin density map of NHC-boryl radical **9**.

5 GEOMETRIES AT C $^\alpha$ OF C-CENTERED RADICALS

The ground-state structure at C $^\alpha$ of carbon-centered radicals may be planar **12** such that the UPE occupies a p -type orbital, that is, the radical has π -character. Alternatively, the radical may be pyramidal **13** such that the UPE occupies a hybrid orbital of σ -character (Scheme 3). The EPR hfs of adjacent magnetic nuclei can be very helpful in distinguishing between these alternatives. Table 1 shows experimental parameters for archetype C-centered radicals with various substituents.

The $a(^{13}C^\alpha)$ are particularly valuable because they give a direct measure of the amount of s -character in the SOMO. ^{13}C ($I = 1/2$) is present in organic radicals with a natural abundance of 1.1%; thus, signals from the interaction of UPE with this nucleus accompany the main spectrum as small satellites on either side of the main ^{12}C lines. For transient radicals, the ^{13}C satellites are usually undetectable in the noise, so isotope enrichment has to be employed. For the series of radicals $^*CH_nMe_{3-n}$, the $a(^{13}C^\alpha)$ values increase only slightly with increase in the number of Me groups (Table 1). $^{13}C^\alpha$ and H^α hfs usually show small temperature dependencies that result from vibrational motions, particularly from inversions at



Scheme 3 Geometries of π - and σ -radicals.

Table 1 EPR parameters for substituted methyl radicals.^a

Radical	$a(^{13}C^\alpha)$	$a(H^\alpha)$	$a(X)$	g -factor
$^*CH_2-H$	3.85	-2.30	—	2.0026
$^*CH_2-Me$	3.91	-2.24	—	2.0027
$^*CH_2-NH_2$	—	-1.32	0.5 (^{14}N)	2.0029
$^*CH_2-OH$	4.53	-1.80	1.0 (^{17}O)	2.0032
$^*CH_2-F$	5.48	-2.11	6.43 (F)	2.0045
$^*CH(Me)_2$	4.13	-2.21	—	2.0026
$^*CH(OMe)_2$	10.1	-1.36	—	—
*CHF_2	14.9	+2.22	8.42 (F)	2.0041
*CF_3	27.2	—	14.2 (F)	2.0031
*CMe_3	4.52	—	—	2.0026

^ahfs in millitesla; data from Ref. 6. Note that EPR spectra give the magnitude but not the sign of hfs.

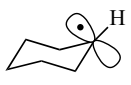
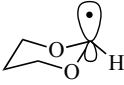
the radical center. These inversion barriers are very low, so the average structures are planar on the EPR timescale; however, pyramidal states make an increasing contribution as the number of Me groups increases.^{56,57}

For the fluoromethyl series of radicals, Table 1 shows that $a(^{13}\text{C}^\alpha)$ increases strongly as the number of F-substituents increases. Thus, the extent of pyramidity of (**13**), measured by the angle ϕ , increases as the number of F-atoms increases. The large $a(^{13}\text{C}^\alpha)$ for $\cdot\text{CF}_3$ (27.2 mT) indicates that this radical is essentially tetrahedral with the sp^3 orbital of the UPE pointing toward one corner of the tetrahedron. Note that the $a(\text{F})$ and $a(\text{H}^\alpha)$ values also increase as the radicals become more pyramidal. Inspection of the $a(^{13}\text{C}^\alpha)$ and $a(\text{H}^\alpha)$ data for radicals with oxygen substitution reveals that this element also induces pyramidity at the radical center and the same is probably true of nitrogen substituents.

The large $a(^{13}\text{C}^\alpha)$ hfs for vinyl⁵⁸ and acyl radicals⁵⁹ (Scheme 4) show that the UPE occupies orbitals with substantial s -character and that these radicals are bent. For acyl radicals $\text{RC}^\bullet = \text{O}$, the $a(^{13}\text{C}^\alpha)$ hfs increase along the series $R = \text{Me} < \text{NH}_2 < \text{O}^\text{t}\text{Bu} < \text{F}$. The degree of bending at the radical center increases with the electronegativity of the substituent, just as with alkyl radicals.

The hfs of C^α - and H^α -atoms (Scheme 4) show that cyclohexyl, cyclopentyl, and cyclobutyl radicals are essentially planar. For these ring sizes, substitution by one O-atom adjacent to the radical center induces significant pyramidity and two O-atoms induce even more s -character. By way of contrast, the $a(^{13}\text{C}^\alpha)$ and $a(\text{H}^\alpha)$ data for cyclopropyl and cyclopropenyl disclose that these radicals are bent, as is the oxiranyl radical.

Bridgehead radicals²⁶ are, of course, necessarily pyramidal and their EPR spectra show large $a(^{13}\text{C}^\alpha)$ values.⁶⁰ Interestingly, $a(^{13}\text{C}^\alpha)$ constants display a linear correlation with the NMR one bond $\text{C}^\alpha\text{--H}$ ($^1J_{\text{C--H}}$) couplings in the parent bridgehead hydrocarbons. Similar linear correlations have been found between the NMR $^1J_{\text{C--H}}$ data of methanes,⁶¹ silanes,⁶² phosphines,⁶³ and aldehydes⁶⁴ and the EPR hfs of the radicals formed by loss of the H-atoms. Morton and Preston provided atomic parameters $\psi^2(0)$, together with the isotropic hfs for unit spin density in the s -orbitals, of nuclei of the elements from He to Bi.⁶⁵ Comparison of

		
$a(^{13}\text{C}^\alpha)$ 10.8	13.4	12.5
$a(\text{H}^\alpha)$ 1.57	13.2	
		
$a(^{13}\text{C}^\alpha)$ 4.13		
$a(\text{H}^\alpha)$ -2.12	-1.58	± 0.19
		
$a(\text{H}^\alpha)$ -2.15	-1.24	+2.15
		
$a(\text{H}^\alpha)$ -2.12	-0.81	
		
$a(^{13}\text{C}^\alpha)$ 9.59		
$a(\text{H}^\alpha)$ -0.66	+3.70	+2.13

Scheme 4 The hfs (millitesla) for vinyl, acyl, and cycloalkyl radicals.⁶

experimental EPR parameters with this data can be very helpful for deducing local geometries.

6 EPR STUDY OF RADICAL CONFORMATIONS AND CONFORMATIONAL INTERCHANGE

NMR spectroscopy is recognized as an extremely valuable tool for studying the conformations of molecules and biomolecules and their dynamic processes. The “timescale” of EPR is much shorter than that for NMR so that faster dynamic processes with free energies of activation much lower than those generally measurable by NMR become accessible (see **Structures and Reactivity of Radicals Followed by Magnetic Resonance**). Much important work has been carried out, mainly with proteins and other biomolecules labeled with nitroxide free radicals (see **Understanding DNA Radicals Employing Theory and Electron Spin Resonance Spectroscopy**). This section focuses on EPR studies

of the conformations of transient species. The use of Karplus type relationships for deducing preferred conformations is outlined in Section 4.2.

Small energy barriers to hindered internal rotations about $C^\alpha-C^\beta$ bonds can be determined from the experimental temperature dependences of $a(H^\beta)$. Torsion in a radical $^{\bullet}CH_2-CHR_2$ is governed by a twofold sinusoidal potential. Each well contains a number of torsional states and above each barrier there exists a set of rotational states. The observed $a(H^\beta)$ is a weighted average taken over all the populated states. Quantum mechanical methods of deriving this average are described by Fessenden^{66,67} and Kochi.⁶⁸ However, for low barriers, a “classical limit” approach generally gives the same results as the more cumbersome quantum mechanical procedures.^{69,70} The barrier to rotation about the $C^\alpha-C^\beta$ bond (V_0) can be estimated by fitting the observed temperature dependence of $a(H^\beta)$ with values calculated from (18):

$$a(H^\beta) = A + \frac{1}{2}B + \frac{1}{2}B \cos 2\theta_0 \left[\frac{I_1(\lambda)}{I_0(\lambda)} \right] \quad (18)$$

where $I_1(\lambda)$ and $I_0(\lambda)$ are modified (hyperbolic) Bessel functions, $\lambda = V_0/kT$, and θ_0 is the value of θ at the potential minimum. (For $V_0 < \text{circa } 2.5 \text{ kJ mol}^{-1}$ (20) may be approximated by: $a(H^\beta) = A + \frac{1}{2}B + \frac{1}{2}B \cos 2\theta_0[\lambda/2 - \lambda^3/16]$.) A and B are known from the Karplus equation and V_0 is varied so as to obtain the best fit between experimental and calculated $a(H^\beta)$ over the accessible temperature range. By these means, barriers, generally in the range $5.0 > V_0 > 1.0 \text{ kJ mol}^{-1}$, have been obtained for many alkyl radicals.

Internal rotation barriers higher than $\sim 10 \text{ kJ mol}^{-1}$ generally lead to selective line broadening in X-band EPR spectra. (EPR observation of selective line broadening also depends on the magnitude of the difference in the hfs of the exchanging magnetic nuclei.) This occurs when the lifetimes of the conformational states become comparable to the reciprocal of the difference in the hfs of two exchanging H-atoms. When the barrier to internal motion is higher still, separate EPR spectra will be observed for each conformational state. Pioneering EPR studies were undertaken on the conformations of persistent cyclic-semidiones⁷¹ and nitroxides.^{72,73} EPR data for transient cyclic radicals including cyclohexyl,^{74,75} other cycloalkyl,^{76–78} and cycloalkenyl⁷⁹ proved useful for charting the

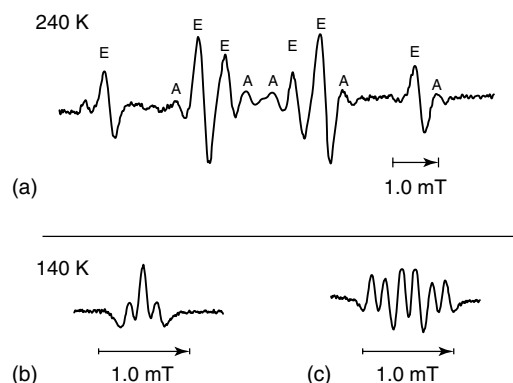
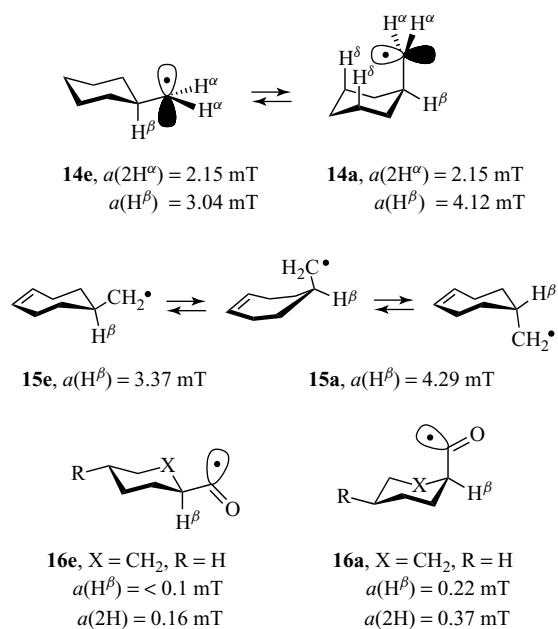


Figure 8 CW EPR spectra from cycloalkylmethyl and cyclohexylacyl radicals. (a) Spectra of cyclohexylmethyls **14e,a** at 240 K in *t*-BuPh solution. (b) and (c) second derivative spectra of 4-*t*-butylcyclohexyl radicals **16e,a** at 140 K in cyclopropane.

conformational changes caused by the introduction of the planar radical center into each type of ring.

A valuable EPR spectroscopic technique for studying the conformations of rings, unperturbed by the presence of a planar radical center, involves using the $CH_2^{\bullet}$ moiety as a spin probe.⁸⁰ The small, neutral, CH_2 group of a cycloalkylmethyl radical, $c-C_nH_{2n-1}CH_2^{\bullet}$, causes minimal perturbation of the adjacent ring. The cyclohexylmethyl radical exists as a pair of conformers **14e** and **14a** in which the $CH_2^{\bullet}$ group is in the equatorial and axial orientations, respectively. The EPR spectrum of the cyclohexylmethyl radical (Figure 8a) showed a large double triplet (E) for the equatorial radical **14e** accompanied by a minor amount of a second double triplet (A) for the axial radical. The main difference was that the axial radical **14a** had a larger doublet hfs from H^β and this enabled the two spectra to be resolved. Steric hindrance from the *syn*-axial hydrogens (H^δ) of **14a** resulted in an increased torsional barrier and consequently the large H^β hfs. From the relative concentrations of the two species **14e** and **14a**, the conformational free energy difference of the $CH_2^{\bullet}$ group ($-\Delta G_{300}^0$) was found to be 3.0 kJ mol^{-1} . The method was also applicable to cycloalkylmethyl radicals with ring sizes up to at least 15,⁸¹ to cycloalkenylmethyl radicals (**15e,a**, Scheme 5),⁸² and to cyclohexylacyl radicals (**16e,a**)⁸³ (Scheme 5, Figure 8b and c).



Scheme 5 Axial and equatorial cycloalkylmethyl and cycloalkylacyl radicals.

7 EXCHANGE BROADENING AND INTERNAL MOTIONS

Section 1.3 established that, for radicals in solution, spin-state lifetimes are governed by spin–spin relaxation phenomena with characteristic time τ_2 . For Lorentzian lines, and with power well below saturation, (10) yields $\Delta B_{1/2} = 2/\gamma_e \tau_2$. Internal rotations, ring inversions, and other intramolecular processes alter the electron spin–nuclear spin interaction and hence can drastically modify τ_2 . Some lines, but not others, may be selectively broadened, depending on the type of motion. Since the rates of internal motions depend on temperature, the EPR linewidths of such radicals are also temperature dependent. The amplitude of a given line in a first derivative spectrum is inversely proportional to the square of the linewidth, so small changes in the latter can lead to striking changes in spectral appearance. For example, the hydroxymethyl radical exists as a 1 : 1 mixture of the 2 equiv planar conformations **17a** and **17b** at low temperatures. In the slow exchange limit at 150 K (Figure 9), the EPR spectrum appears as a double, double doublet from interaction of the UPE with two nonequivalent H^X and H^Y and the

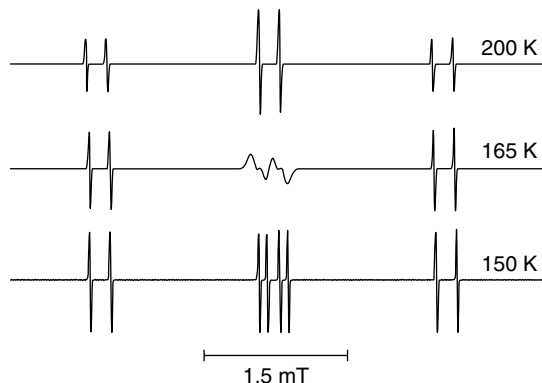
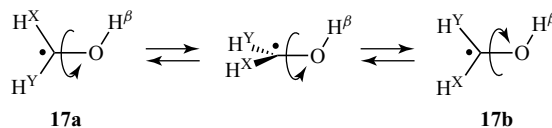


Figure 9 Temperature-dependent linewidths in the EPR spectrum of HO–CH₂•.

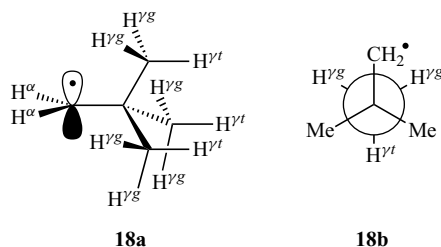


Scheme 6 Interchange of the two planar conformers of the hydroxymethyl radical.

hydroxyl hydrogen H^β (Scheme 6; $a(H^X) = 1.765$, $a(H^Y) = 1.853$, $a(H^{\beta}) = 0.216$ mT).⁸⁴ At a high enough temperature, torsions about the C–O bond are fast leading to rapid exchange of H^X and H^Y. In the fast exchange limit at >200 K, H^X and H^Y are equivalent and the spectrum is a sharp triplet of doublets.

At intermediate temperatures, broadening of the central lines appears. Maximum broadening (coalescence) is reached at about 165 K, where the rate of interchange of H^X and H^Y is equal to the frequency separation of the inner lines ($a(H^Y) - a(H^X) = 0.088$ mT = 0.25×10^6 Hz).

When exchange broadening is due to interchange of two species of equal energy, as with **17a** and **17b**, the forward and backward rate constants (k) are equal. The rate constant for interchange can be simply derived from the difference in the hfs of H^X and H^Y and the linewidth.⁸⁵ Other kinds of selective EPR line broadening with different characteristics are attributable to different types of internal motions.⁸⁶ Software, based on relaxation matrix theory, can be obtained for simulating the line broadening of more complex processes.⁸⁷



Scheme 7 “Frozen” conformer of the neopentyl radical.

The neopentyl radical **18** provided a particularly striking example of exchange broadening.⁸⁸ Above 210 K, the internal rotations about the $C^\alpha-C^\beta$ bond, and about the three $C^\beta-C^\gamma$ bonds, are all in the fast exchange limit, so the solution EPR spectrum of **18** consists of a triplet ($a(2H^\alpha) = 2.14$ mT) having each component split into 10 lines from the 9 equiv H^γ ($a(9H^\gamma) = 0.096$ mT). In the temperature range 210–106 K, exchange broadening is observed as a result of hindered rotation of the three Me groups about their $C^\beta-C^\gamma$ bonds (Figure 10). By 96 K, the “rigid” conformation **18a,b** is reached, in which the Me group rotations are frozen with 3 equiv trans $H^{\gamma t}$ having large hfs because they are in W-plan sites ($a(3H^{\gamma t}) = 0.404$ mT) and 6 equiv gauche $H^{\gamma g}$ ($a(6H^{\gamma g}) = 0.062$ mT). Internal rotation about the $C^\alpha-C^\beta$ bond continues rapidly even at 96 K because of the low sixfold barrier. Figure 10 shows

a selection of exchange broadened experimental EPR spectra in the range 106–210 K alongside computer simulations obtained with a three-jump model having all forward and reverse rate constants equal. An Arrhenius plot of the rate constants yielded an activation barrier of 15.4 kJ mol⁻¹ and a pre-exponential factor of $10^{12.6}$ s⁻¹ for the internal Me rotations. Activation barriers in the range 8–40 kJ mol⁻¹ for group rotations about C–C,^{22,37} C–N,^{89,90} and C–O bonds have been determined by similar means as well as inversion barriers for several types of rings.^{79,80,82,91}

8 EPR SPECTRA OF HETEROATOM-CENTERED RADICALS

Isotropic EPR spectra have been described for many types of radicals containing elements from the first and second rows of the periodic table. This subsection surveys radicals in which the UPE resides mainly on a particular heteroatom and those in which spin is partly delocalized away from the principal heteroatom. Anisotropic spectra have been obtained from many radicals centered on elements from the third and subsequent rows of the periodic table,^{92,93} but solution spectra tend to be broad, and comparatively few have been reported.

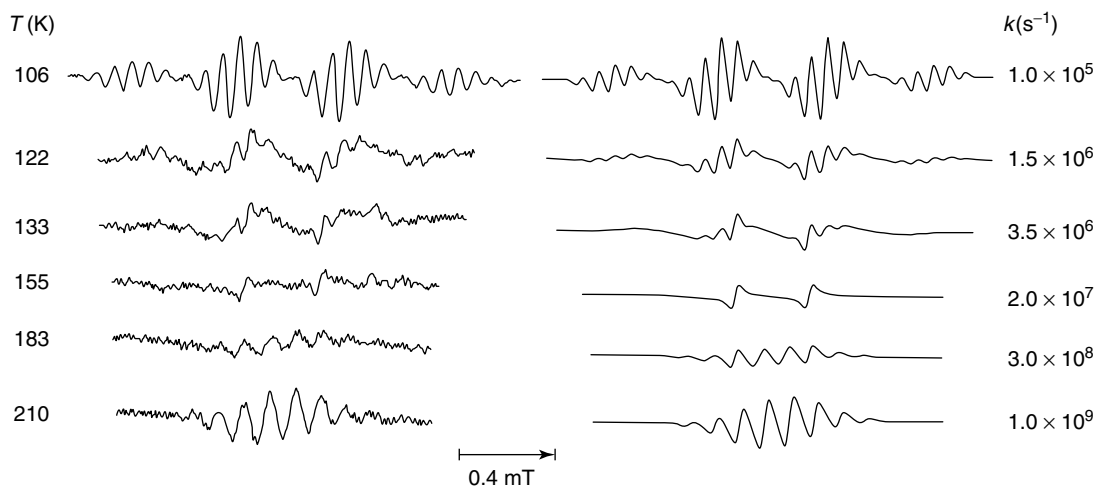


Figure 10 EPR spectra of the central component of the triplet from the neopentyl radical (**18**). Left: Experimental spectra at the indicated temperatures. Right: Simulated spectra with the indicated rate constants. [Adapted with permission from K. U. Ingold, *et al.*, *J. Phys. Chem.*, 1986, **90**, 2859–2869. Copyright 1986 American Chemical Society.]

8.1 Spectra from Transient Boron- and Aluminum-Centered Radicals

Triarylboron radical anions $[\text{Ar}_3\text{B}]^{\cdot-}$ are of interest because they are isoelectronic with neutral C-centered radicals $\text{Ar}_3\text{C}^{\cdot}$. Early EPR studies showed that $[\text{H}_3\text{B}]^{\cdot-}$ (**19**) had $a(^{11}\text{B}) = 1.99 \text{ mT}$ and $a(3\text{H}) = 1.52 \text{ mT}$ ⁹⁴ while for the analog **20** $a(^{11}\text{B}) = 0.78 \text{ mT}$ was obtained.⁹⁵ The UPE is mainly on boron and the low $a(^{11}\text{B})$ values suggest that these are π -type species with planar geometry at boron.^{94,96} Other classes of transient boron-centered radicals that have been extensively studied by EPR spectroscopy in solution include the phosphine-boryl radicals (**21**),^{97,98} dialkyl sulfide-boryl radicals (**22**),⁹⁹ and amine-boryl radicals (**23**).^{100–103} These species were generated by H-atom abstraction from the corresponding ligated boranes and gave rise to well-defined spectra often showing structure from ^{10}B ($I = 3$, 19.9%) as well as ^{11}B ($I = 3/2$, 80.1%); see Figure 11a.^{104,105}

The equilibrium geometries of the boron centers of **21** and **22** (Scheme 8) are planar, or nearly so, as judged by the ^{11}B and H^α hfs (Table 2). In contrast to this, the larger ^{11}B hfs of amine-boryls **23** (Table 2) indicated a pyramidal arrangement of the ligands about boron.

EPR spectroscopy showed the amine boryl radicals **23** to be the most reactive; they underwent β -scission more readily than isoelectronic alkyl radicals and rearranged rapidly to aminyl-borane radicals. Their nucleophilic character was confirmed by a laser flash photolysis (LFP) study of the kinetics of various reactions.¹⁰⁶

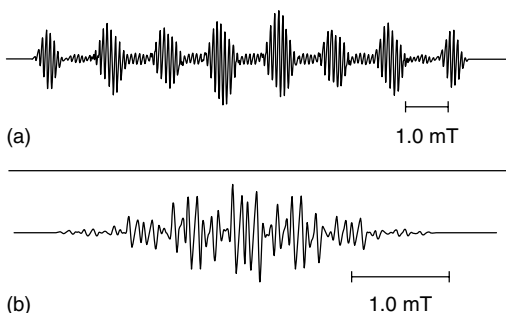
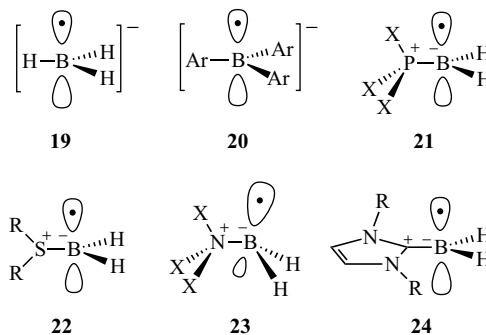


Figure 11 (a) EPR spectrum of the $(\text{MeO})_3\text{P} \rightarrow \text{B}^{\cdot}\text{HBu}-t$ radical at 240 K in cyclopropane showing signals from ^{11}B and ^{10}B containing isotopomers ($a(^{11}\text{B}) = 1.34$, $a(^{10}\text{B}) = 0.45$, $a(\text{H}^\alpha) = 1.55$, $a(^{31}\text{P}) = 3.96$, $a(9\text{H}) = 0.09 \text{ mT}$).¹⁰⁴ (b) EPR spectrum of the α -tocopheroxyl radical **49**.



Scheme 8 Selected boron-centered radicals and ions.

N-Heterocyclic carbene boryl radicals containing imidazole and triazole rings were generated by H-atom abstraction from the corresponding *N*-heterocyclic carbene boranes,^{55,107} and by reduction of analogous cations.¹⁰⁸ The isotropic EPR parameters of model **24** (Table 2) and others, together with DFT computations, showed them to be planar π -delocalized species, in which the UPE is delocalized from boron into the π -system of the adjacent heterocyclic rings. Kinetic EPR studies revealed that their bimolecular self-termination and halogen abstraction reactions were strongly influenced by steric shielding of the boron center.

Apart from anisotropic EPR studies,^{109,110} a few alane radical anions were generated in solution by H-atom abstraction from MX_3AlH salts.¹¹¹ Comparison of the $a(^{27}\text{Al})$ hfs ($I_{\text{Al}} = 5/2$) for $\text{AlH}_3^{\cdot-}$ (Table 2) with that calculated for unit population of the Al 3s orbital (98.5 mT)¹¹² showed that its semi-occupied orbital has about 16% 3s character so that it deviates somewhat from planar.

8.2 Spectra from Transient Silicon-, Germanium-, and Tin-Centered Radicals

Spectroscopic studies of silyl radicals have often been plagued by the buildup, during photolysis, of spectra from secondary persistent radicals that mask transient species. In many spectra, the satellites from ^{29}Si [natural abundance 4.7%, $I(^{29}\text{Si}) = 1/2$] were observed, and the EPR parameters for some model radicals are listed in Table 3.^{113–119} The values of $a(^{29}\text{Si})$ for $\text{H}_3\text{Si}^{\cdot}$ and alkylsilyl radicals ($\sim 18 \text{ mT}$) are $\sim 25\%$ that expected for unit UPE population of the Si 3s orbital ($\sim 80 \text{ mT}$). Therefore, the SOMO of these radicals has about

Table 2 EPR parameters of model boron- and aluminum-centered radicals and anions.^a

Radical	<i>g</i> -factor	<i>a</i> (¹¹ B or ²⁷ Al)	<i>a</i> (2H)	<i>a</i> (³¹ P or ¹⁴ N)	<i>a</i> (other)
H ₃ B [•] (19)	—	1.99	1.52 (3H)	—	—
X ₃ P → BH ₂ [•] (21 , X = Et)	2.0020	1.76	1.68	4.36	—
X ₃ P → BH ₂ [•] (21 , X = Me ₂ N)	2.0020	1.67	1.63	4.25	0.20 (3 N)
X ₃ P → BH ₂ [•] (21 , X = MeO)	2.0019	1.47	1.66	4.39	—
Me ₂ S → BH ₂ [•] (22 , R = Me)	2.0017	2.32	1.66	—	0.09 (6H)
Me ₃ N → BH ₂ [•] (23 , X = Me)	2.0022	5.13	0.96	0.14	0.14 (9H)
Et ₃ N → BH ₂ [•] (23 , X = Et)	2.0023	4.75	1.30	0.22	0.22 (6H)
NHC → BH ₂ [•] (24 , R = Me)	2.0028	0.67	1.20	0.41 (2 N)	0.12 (2H), 0.25 (6H)
H ₃ Al [•]	2.0025	15.42	0.70 (3H)	—	—
(<i>t</i> -BuO) ₃ Al [•]	2.0015	30.07	—	—	—

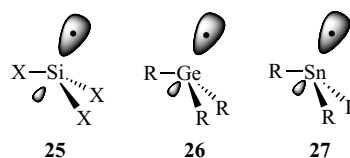
^ahfs in mT; data from Ref. 6 and references in the text.**Table 3** EPR parameters of model silicon-, germanium-, and tin-centered radicals.

Radical	<i>g</i> -factor	<i>a</i> (²⁹ Si or ⁷³ Ge or ^{117,119} Sn)	<i>a</i> (H ^α)	<i>a</i> (other)	Reference
H ₃ Si [•]	2.0032	18.20	0.79	—	113
Me ₂ (H)Si [•]	2.0031	18.30	1.70	0.72 (6H)	114
Me ₃ Si [•]	2.0031	18.30	—	0.63 (9H)	120
F ₂ (H)Si [•]	2.0013	—	8.99	7.78 (2F)	115
F ₃ Si [•]	2.0003	49.8	—	13.66 (3F)	113
Ph ₃ Si [•]	—	15.0	—	—	120
(Me ₃ Si) ₃ CSi [•] (*)HOH	2.0025	21.22	3.78	0.013 (27H)	113
(Me ₃ Si) ₃ CSi [•] (*)HF	2.0026	24.14	4.07	—	113
H ₃ Ge [•]	2.0073	7.5	1.5	—	116 ^a
Me ₃ Ge [•]	2.0107	—	—	0.55 (9H)	117
Ar ₃ Ge [•]	2.0084	6.84	—	0.07 (Me, H ^m)	118 ^b
H ₃ Sn [•]	2.017	38.0	2.6	—	120 ^a
Me ₃ Sn [•]	2.0163	—	—	0.31 (9H)	119

^aData from anisotropic solid-state spectra.^bAr = mesityl.

1/4 s-character and the radicals are pyramidal (**25**, Scheme 9), in contrast to the related C-centered radicals. Introduction of an electronegative ligand X (such as F or OH) confers greater p-character on the Si–X bond and correspondingly greater s-character on the remaining Si–H bonds and the SOMO. The pyramidal character is increased and both *a*(H^α) and *a*(²⁹Si) are increased (Table 3). The introduction of phenyl substituents does not greatly affect the configuration at Si but there is significant delocalization of unpaired spin into the aromatic rings. It was shown that for a good range of species a linear relationship exists between *a*(²⁹Si) and ¹*J*(SiH) of the parent silanes.¹²⁰

EPR spectra have also been obtained for a significant number of germanium- and tin-centered radicals (Table 3). Comparison of the ⁷³Ge (*I* = 9/2, 7.8%) and ^{117,119} Sn (*I* = 1/2, 7.6, 8.6%) hfs with the expected values for unit occupation of the 4s or

**Scheme 9** Pyramidal structures of Si, Ge, and Sn centered radicals.

5s orbital (Ge = 53.0 mT, Sn ~326 mT) indicated pyramidity for both types of radical (**26**, **27**; Scheme 9).

8.3 Spectra from Transient Nitrogen- and Phosphorus-Centered Radicals

Aminyl radicals (R₂N[•]) and the corresponding aminium radical cations (R₃N^{•+}) are isoelectronic

Table 4 EPR parameters for aminyl, oxyaminyl, thioamyl, and acylaminyl (amidyl) radicals and aminium radical cations.

Radical	<i>g</i> -factor	<i>a</i> (¹⁴ N)	<i>a</i> (H ^α)	<i>a</i> (H ^β)	<i>a</i> (H ^{other})	Reference
H ₂ N [•]	2.0046	1.52	2.54 (2H)	—	—	121
Me ₂ N [•]	2.0044	1.48	—	2.74 (6H)	—	122
1-Aziridinyl	2.0043	1.25	—	3.07 (4H)	—	123
1-Pyrrolidinyl	—	1.43	—	5.42 (2H) 2.71 (2H)	—	124
PhNH [•]	2.0034	0.77	1.29 (1H)	—	0.20 (2H), 0.62 (2H), 0.82 (1H)	125
H ₃ N ^{•+}	—	1.96	2.74	—	—	126
Me ₂ NH ^{•+}	2.0036	1.92	2.27	3.42 (6H)	—	122
Me ₃ N ^{•+}	2.0036	1.47	—	2.73 (9H)	—	122
EtON [•] H	2.0050	1.20	2.00	0.31 (2H)	—	127
MeON [•] Me	2.0048	1.43	—	2.19 (3H)	0.26 (3H)	128
EtON [•] Ph	2.044	1.09	—	—	0.16 (2H), 0.48 (3H), 0.16 (2H)	127
<i>t</i> -BuSN [•] Me	2.0073	1.25	—	1.64 (3H)	—	129
PhSN [•] Bu- <i>t</i>	2.0070	1.18	—	—	0.1 (3H)	130
MeC(=O)N [•] Me	2.0055	1.49	—	2.95 (3H)	0.13 (3H)	131
MeC(=O)N [•] Bu- <i>t</i>	2.0044	1.57	—	—	0.27 (3H)	132

with alkyl radicals. Only a few primary alkylaminyls RHN[•] have been detected in solution, but primary arylaminyls ArHN[•] and many secondary alkylaminyls and arylaminyls have been studied; EPR parameters for a selection of model species are displayed in Table 4.^{121–132}

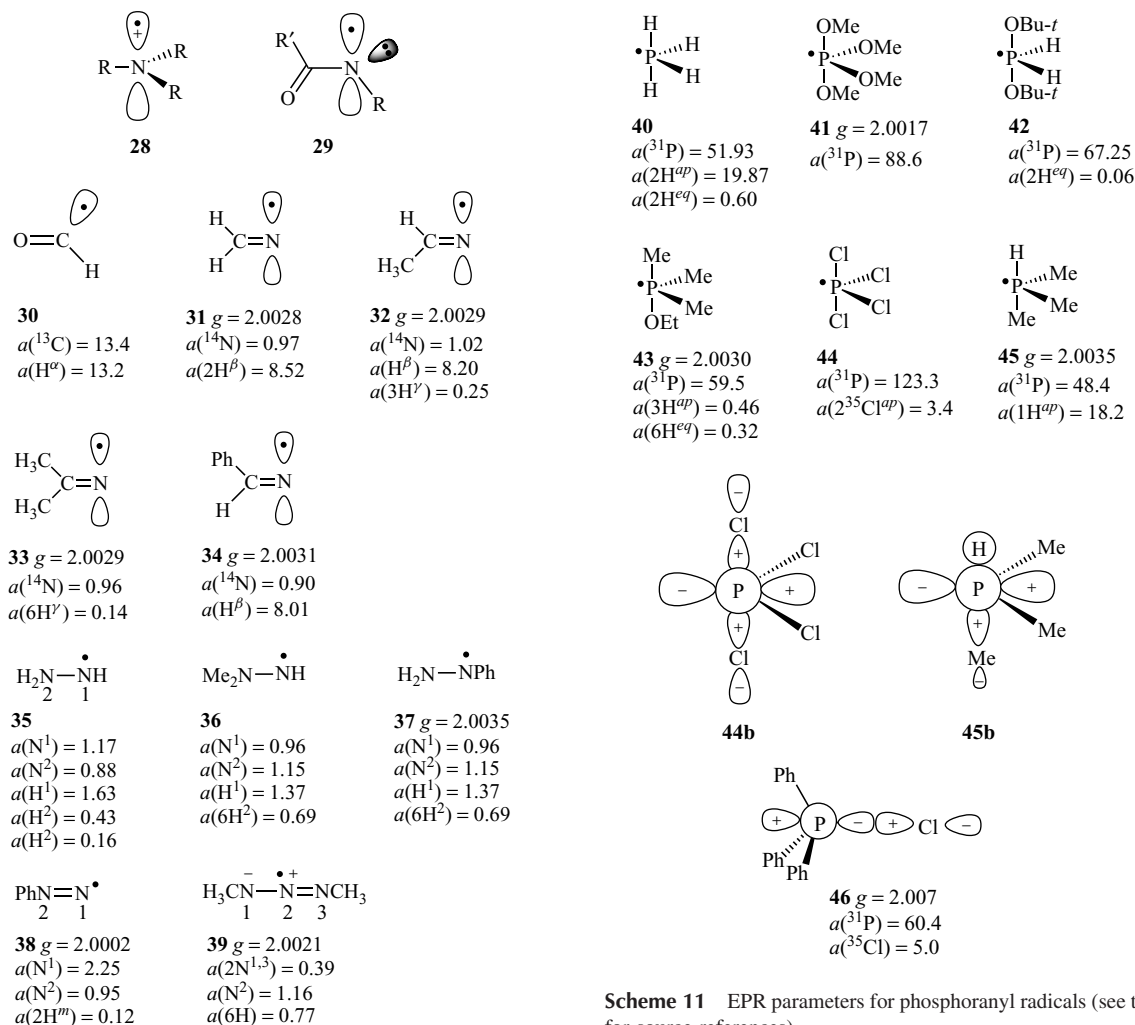
The data indicate that alkylaminyl radicals are bent and that in arylaminyls the UPE is delocalized into the aromatic rings. The ground-state structures of the simple aminium radical cations are planar (**28**), unlike the pyramidal parent amines. Alkoxyaminyl and thioaminyl radicals have smaller *a* (¹⁴N) values than aminyls as might be expected. Amidyl radicals (acylaminyls) have larger *a* (¹⁴N) and the temperature dependence of the *a* (H^β) of model radicals showed that they have π -type structures **29** (Scheme 10).^{131,133,134}

Iminyl radicals (R₂C=N[•]) are isoelectronic with vinyl and formyl radicals **30**¹³⁵ (Scheme 10). These are all σ -type radicals but the UPE in formyl is contained in an orbital with substantial s-character (**30**), whereas the SOMO of iminyls has practically pure p-character (**31**, **32**). EPR data is set out in Scheme 10 for methaniminyl **31**,¹³⁶ and model iminyls **32**,¹³⁷ **33**,¹³⁸ and **34**.¹³⁹ Numerous more complex iminyls have been characterized by EPR spectroscopy and the kinetics of their cyclization reactions has been investigated^{140,141} (see **Radical Kinetics and Clocks**).

Several N-based species in which the UPE is shared between two or more N-atoms are

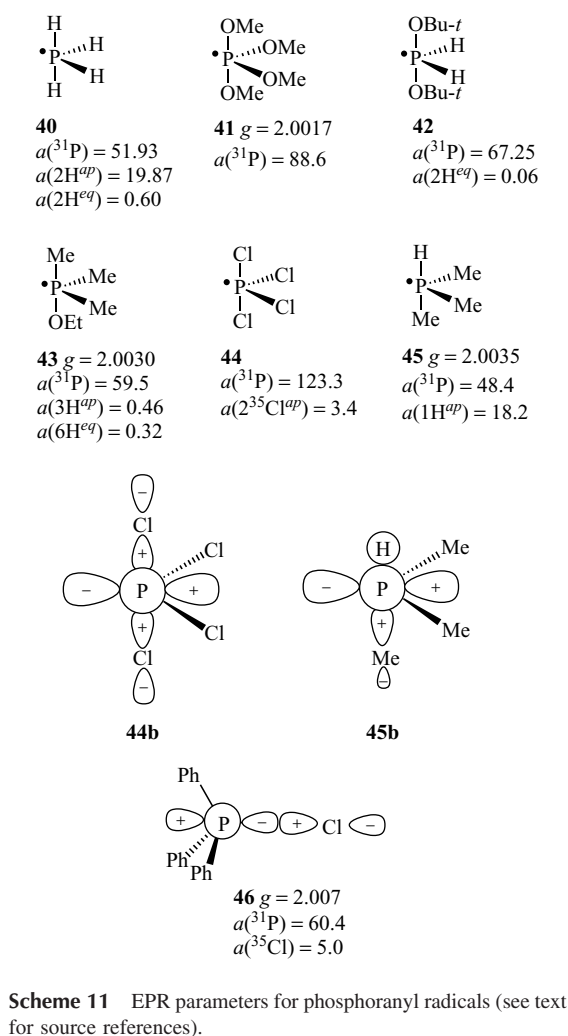
important organic intermediates. Hydrazyl radicals are derivatives of hydrazine, and the EPR data for the parent **35**,¹⁴² and analogs **36**¹⁴³ and **37**¹³⁶ (Scheme 10) show that the UPE is fairly evenly distributed between both N-atoms, probably because of a contribution from structures R₂N–NH[•] $\leftrightarrow$ R₂N^{•+}=NH[–]. Otherwise, hydrazyls resemble aminyls and the geometry is flattened at both N-atoms, as required by their π -structures. Sample EPR data is also displayed in Scheme 10 for diazenyl radical **38**,^{144,145} and triazenyl **39**¹⁴⁶ in which the UPE is also distributed to all the N-atoms. Huge varieties of aminoxyl radicals (nitroxides, R₂N–O[•]) and iminoxyl radicals (R₂C=NO[•]) have been investigated and many are persistent or stable (see **Nitroxide-Mediated Polymerization and its Applications** and **Nitroxides in Synthetic Radical Chemistry**). Their EPR spectra are outside the scope of this article.¹⁴⁷

Scarcely any alkylphosphinyl radical R₂P[•] has been observed in fluid solution but Ph₂P[•] [*a* (³¹P) = 7.87 mT] has been detected in the solid phase at low temperatures.¹⁴⁸ A few phosphonyl radicals, such as (EtO)₂P[•]O [*g* = 2.0018, *a* (³¹P) = 68.86 mT], have also been characterized.¹⁴⁹ In contrast to this, many phosphoranyl radicals (R₄P[•]), mostly generated by addition of neutral radicals to phosphorus(III) compounds, have been studied by EPR spectroscopy.^{150,151} The spectra reveal that the local geometry around phosphorus varies markedly, depending on the nature of the attached ligands.^{152,153} At one extreme, the majority of



Scheme 10 Structures and EPR parameters for N-centered radicals and related species (see text for source references).

phosphoranyls adopt trigonal bipyramidal structures **40–45** (Scheme 11) with two ligands apical, two equatorial, and the final equatorial position occupied by an orbital lobe (TBP). The large hfs for ^{31}P and apical ligands (Scheme 11) show that most of the spin density is associated with these sites. The principal atomic orbitals that contribute to the SOMO of TBP phosphoranyls are illustrated in **44b** and **45b**. At the other extreme, some phosphoranyls such as $\text{Ph}_3\text{P}^+\text{Cl}^-$ adopt structures such as **46** with local C_{3v} symmetry at phosphorus.¹⁵⁴ In this case, the SOMO is a $\text{P}-\text{Cl}\sigma^*$ orbital as shown in **46** (Scheme 11).¹⁵⁵ Quantitative information about

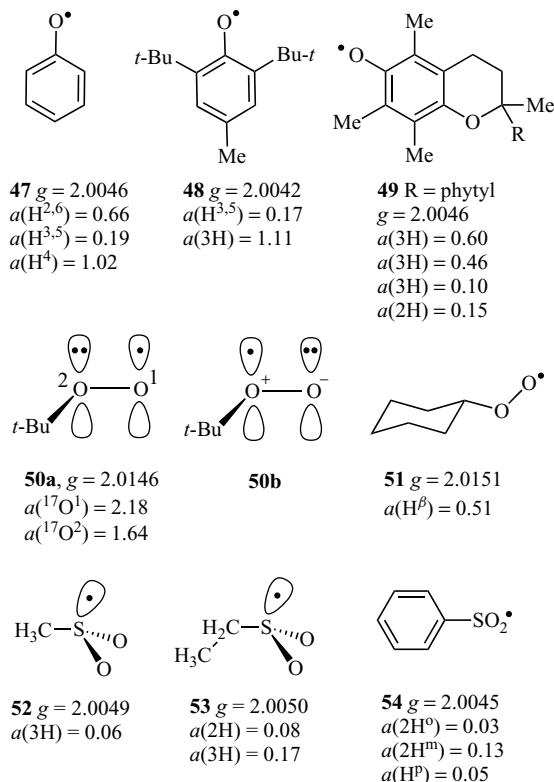


Scheme 11 EPR parameters for phosphoranyl radicals (see text for source references).

ligand apicophilicities, stereochemical permutations, β - and γ -scission processes, and other reactions has been obtained by EPR methods for many phosphoranyls.

8.4 Spectra from Transient Oxygen- and Sulfur-Centered Radicals

Hydroxyl ($\text{HO}^\bullet$) and alkoxyl ($\text{RO}^\bullet$) are not detectable in solution because of unsuitable relaxation times. Aryloxy radicals, semiquinone, and semidione radical anions are very important biochemical species and many derived from phenolic natural products have been examined by EPR



Scheme 12 Structures and EPR parameters of radicals centered on oxygen and sulfur.

spectroscopy. EPR parameters for phenoxyl **47** and the aryloxyl **48**, derived from the artificial antioxidant BHT, are displayed in Scheme 12.¹⁵⁶ The well-resolved spectra that can be obtained are typified by that from the chromanyloxyl radical **49** derived from the natural antioxidant α -tocopherol (Figure 11b). The EPR parameters show that these are π -type species in which spin is extensively delocalized.

Peroxy radicals ($\text{ROO}^\bullet$) are easily formed by the extremely rapid coupling of C-centered radicals with dioxygen. Signals from peroxy radicals often accompany the EPR spectra of alkyl radicals unless all traces of oxygen are excluded. They are easy to identify because of their comparatively large g -factors (~ 2.015). EPR spectra of peroxy radicals have been observed from a wide range of compounds including alkanes, alkenes, substituted alkanes, lipids, aromatics, and others.^{157,158} The spectra are usually broad, and linewidths are highly dependent on temperature, solvent viscosity, and the presence of

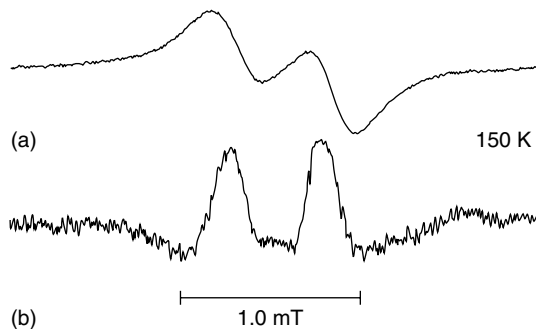


Figure 12 EPR spectrum of the cyclohexylperoxyl radical **51** in cyclopropane at 150 K. (a) First derivative spectrum. (b) Second derivative spectrum.

residual oxygen. Figure 12 shows the spectrum of the cyclohexylperoxyl radical **51** in first and second derivative modes.¹⁵⁹

The isotropic hfs of peroxy ^{17}O isotopomers^{160,161} (Scheme 12) indicate that spin density is partitioned between both oxygens, but more resides on the terminal O^1 . The structures **50a,b** give a reasonable representation of the SOMO showing that peroxy radicals are π -radicals.

EPR spectra for thiyl radicals ($\text{RS}^\bullet$) and sulfinyl radicals ($\text{RSO}^\bullet$) have only been obtained in low temperature matrices. However, well-resolved solution EPR spectra have been recorded for sulfonyl radicals ($\text{RS}^\bullet\text{O}_2$) generated in a variety of ways¹⁶² from sulfinic acids,¹⁶³ sulfonyl chlorides, and sulfonate esters (Scheme 12). The hfs disclose spin distribution that is typical of radicals with a pyramidal center at sulfur (**52**, **53**).^{164,165}

9 KINETIC EPR SPECTROSCOPY

9.1 Radical Decay Curves and Concentration Measurement

The growth and decay of EPR signals can be monitored as a function of time when the EPR setup entails radical generation by UV light (or other radiation). When the irradiation commences, the signal grows in and on shuttering the light the signal decays. Figure 13 shows a typical experiment in which the NHC-boryl radical **55** was generated from irradiation of the NHC-BH_3 precursor and DTBP in the EPR resonant cavity. The CW spectrum shown was recorded and then the field was set to the value

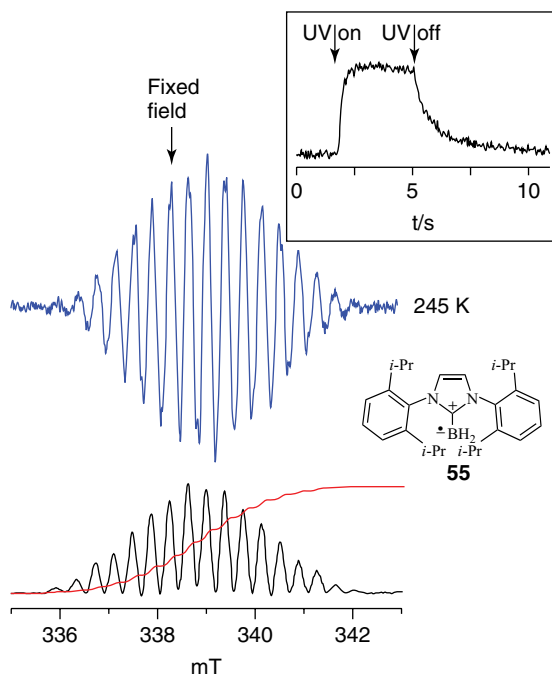


Figure 13 First derivative EPR spectrum of radical **55** in PhBu-*t* at 245 K; the inset shows the growth and decay of the signal as a function of time. The integral and double integral (DI, red) are shown beneath.

near the maximum signal intensity marked by an arrow. The spectrometer time constant was adjusted to a value much less than the half-life of the radical ($t_c = 1.28$ ms). Time scans then enabled growth and decay curves such as that shown in the inset to be obtained.

Absolute radical concentrations are usually needed for kinetic information to be deduced from such decay curves. According to (9) (Section 1.3), the power absorbed by a sample is proportional to the imaginary part of the susceptibility (χ''), and hence to the number of paramagnetic species present. The radical concentration is therefore proportional to the integral of the absorption curve, or the double integral of the first derivative spectrum. For dependable concentration measurements, the spectral data must be obtained on samples of volume less than or equal to the sensitive volume of the cavity and for signals below microwave power saturation. The concentration of a particular radical $[R^*]$ can be obtained by comparing its double integral DI_R to that of a known concentration of a standard persistent radical (S^*) such as

DPPH or galvinoxyl (DI_S). The microwave power, modulation amplitude, receiver gain, scan range ($\Delta H_R/\text{mT cm}^{-1}$), and temperature of the particular radical (T_R/K) are noted. The same sample tube is then filled to the same level with the standard solution which is then scanned under similar conditions at the same power and modulation amplitude. The concentration of R^* can then be obtained from (19):

$$[R^*] = [S^*] \times \frac{DI_R}{DI_S} \times \frac{\text{Gain}_S}{\text{Gain}_R} \times \frac{\Delta H_R^2}{\Delta H_S^2} \times \frac{\text{Ruby}_S}{\text{Ruby}_R} \times \frac{T_R}{T_S} \times F \quad (19)$$

The term $\Delta H_R^2/\Delta H_S^2$ equals 1.0, except when the spectrum of R^* was recorded with a field scale different from the standard. T_R/T_S allows for any temperature difference between the particular radical and the standard. If R^* was in a solvent different from the standard, variations in cavity Q can be corrected for by normalizing the R^* and S^* spectra with respect to the signal (at circa 200 mT) from a single crystal of synthetic ruby, positioned off-center in the microwave cavity. The ruby term can usually be neglected if R^* and S^* were both in hydrocarbon solvents. The whole S^* spectrum is doubly integrated but, if only a fraction of the R^* signal was accessible, then the multiplier F converts to the DI of the entire R^* spectrum.

Most small, unhindered, neutral radicals decay in fluid solutions with half-lives within 1–2 ms. A special technique that enables many identical radical decays to be collected and averaged, so as to improve signal to noise ratio, was devised for this situation.⁶⁷ Applications of the technique to many diverse kinetic problems were reported by Ingold and coworkers in an outstanding series of papers.^{166–168}

In the absence of a suitable reaction partner, most radicals decay by combination and disproportionation processes which are second order in radical concentration. Fischer and coworkers enhanced the kinetic EPR method in several ways and developed a modulation approach.^{169,170} The rate constants they obtained for alkyl radical terminations ($2k_t$) in many different solvents are among the most accurately known. This data established that the termination rates of small radicals are inversely proportional to solvent viscosity and that these processes are diffusion controlled,¹⁷¹ which results in $2k_t \approx 5 \times 10^9$

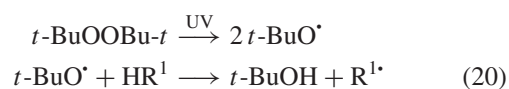
$\text{M}^{-1}\text{s}^{-1}$ in fluid solvents at ambient temperature. The rate constant ($2k_t = 8.7 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ at 298 K) and Arrhenius parameters for *t*-butyl radical termination in *n*-heptane:¹⁷² $\log(2k_t/\text{M}^{-1}\text{s}^{-1}) = 11.63 - 9.61 (\text{kJ mol}^{-1})/2.3 \text{ RT}$ have been widely used as “clock” parameters for calibrating the dynamics of other radical reactions. Kinetic EPR is usually less precise than LFP but has the advantages of good resolution and high specificity. KEPR does not require the potentially awkward reporter chromophores in radicals that are needed with the LFP method (see **Radical Kinetics and Clocks**).

Termination rate constants and equilibrium constants for radical–dimer equilibria have been obtained for many classes of radicals,¹⁷³ including B-centered radicals,^{55,100} a huge range of C-centered radicals with many different structural features,^{58,174–176} as well as other group 14 element-centered radicals.¹⁷⁷ Similarly, the terminations of N- and P-centered radicals including aminyls,^{178,179} amidyls,¹⁸⁰ iminyls,^{141,181} alkoxyaminyls,¹⁸² diazenyls,¹⁴⁵ and phosphoranyl,^{151,183,184} have been investigated by EPR. The terminations and radical–dimer equilibria have also been examined for numerous O-centered species including phenoxyls^{185,186} and peroxy.^{187–189} Most of the latter, particularly secondary and tertiary alkylperoxy, terminate many orders of magnitude more slowly than the diffusion limit.¹⁹⁰

An alternative EPR-based method of studying reaction dynamics relies on the increase of ESR linewidths that results from decreasing lifetime of the observed radicals.^{191,192}

9.2 Steady-State Kinetic EPR Measurements

UV photolysis of DTBP, neat or in solution, produces *t*-BuO $\cdot$ radicals that are EPR “silent” and so do not complicate EPR spectra. In the presence of two substrates HR¹ and HR² (or two sites in the same substrate), unselective abstraction gives rise to two radicals that are destroyed by bimolecular processes. The steady-state system can be represented by (20)–(24):

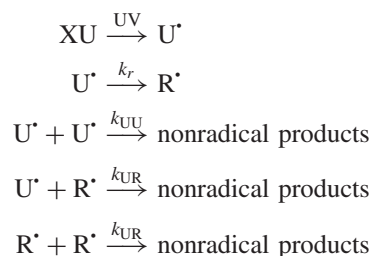


Provided both radicals are transient and terminate at the diffusion-controlled limit ($k_{22} = k_{23} = k_{24}$), the following relation holds:

$$\frac{k_{20}}{k_{21}} = \frac{[\text{R}^1\cdot][\text{HR}^2]}{[\text{R}^2\cdot][\text{HR}^1]} \quad (25)$$

The concentrations of HR¹ and HR², and/or the temperature, are adjusted until, under conditions of steady-state photolysis, spectra of both radicals can be simultaneously recorded. The rate constant ratio k_{20}/k_{21} can then be determined from the known substrate concentrations and the ratio $[\text{R}^1\cdot]/[\text{R}^2\cdot]$ obtained from the EPR spectra. The relative rate data can be put on an absolute scale by using a standard radical “clock,” such as cyclopentane plus *t*-BuO $\cdot$,¹⁹³ as a reference reaction. Many suitable radical clocks¹⁹⁴ have been calibrated and compilations of rate data are available^{173,195–197} (see **Radical Kinetics and Clocks**).

The dynamics of a unimolecular reaction of a radical (U $\cdot$) to some rearranged radical (R $\cdot$) can be probed when the species is generated from some photolabile precursor XU in the absence of substrates.



Under steady-state conditions relationship (26) is easily derived:

$$\frac{1}{[\text{R}\cdot]} = \frac{2k_{\text{UR}}}{k_r} + \frac{2k_{\text{RR}}[\text{R}\cdot]}{k_r[\text{U}\cdot]} \quad (26)$$

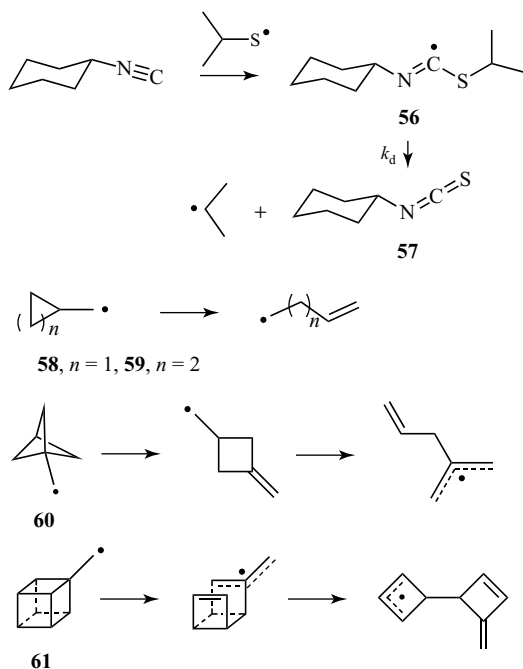
In principle, the radical concentrations can be varied by changing the incident UV intensity.

A plot of $1/[R^*]$ against $[R^*]/[U^*]$ then produces a line of slope $2k_{RR}/k_t$ and intercept $2k_{UR}/k_t$. In practice, the EPR signals are usually too weak to allow a sufficient change of radical concentrations for accurate determinations. If, however, both U^* and R^* terminate at the diffusion-controlled limit, then $2k_{UR} = 2k_{RR} = 2k_t$ and (26) simplifies to

$$\frac{k_r}{2k_t} = [R^*] + \frac{[R^*]^2}{[U^*]} \quad (27)$$

and hence $k_r/2k_t$ can be determined simply from EPR measurements of the U^* and R^* concentrations. If R^* terminates at the diffusion-controlled limit then it is usually accurate enough to use Fischer's $2k_t$ data for *t*-Bu $\cdot$ in *n*-heptane,¹⁷² corrected for the difference in the viscosities of *n*-heptane and the solvent used.¹⁹⁸

Rate constants for many dissociations including decarbonylations^{199,200} and other β -scission processes^{201,202} have been obtained by this method. For example,²⁰³ *i*-propylthiyl radicals, generated by UV photolysis of the corresponding disulfide, added



Scheme 13 β -Scission of thioimidoyl radical **56** and ring-opening reactions of mono- and poly-cycloalkylmethyl radicals.

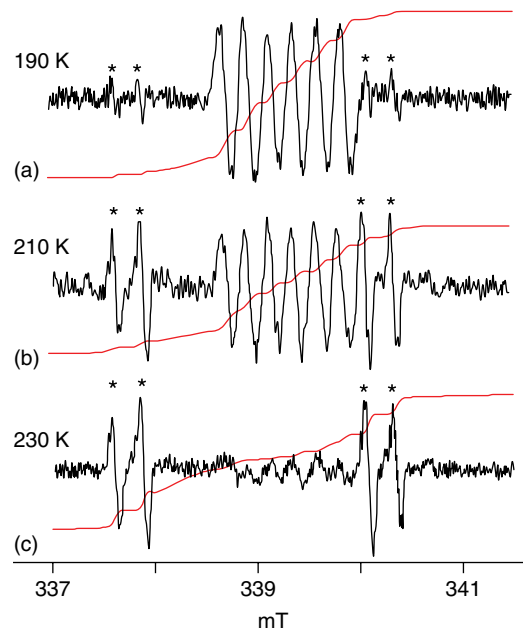


Figure 14 EPR spectra and double integrals of thioimidoyl **56** and *i*-propyl radicals at different temperatures. (a) At 190 K; (b) at 210 K; and (c) at 230 K. The * indicates the central components of the *i*-propyl radical spectrum.

to cyclohexane isonitrile to produce thioimidoyl radicals **56** (Scheme 13). The EPR spectrum of **56** was observed in cyclopropane solution at $T < 180$ K (Figure 14a). Above ~ 190 K, the spectrum of **56** was accompanied by that of the *i*-propyl radical (Figure 14b) and at $T > 240$ K only the *i*-propyl radical could be discerned. This sequence of spectra was reversible on lowering the temperature. The concentrations of **56** and *i*-propyl were obtained at each temperature from the double integrals of the spectra shown in Figure 14 and by use of (19). Then the $k_d/2k_t$ values at each temperature were derived from (27) and, after inclusion of Fischer's $2k_t$ data, gave $\log(A_d/s^{-1}) = 12.1$, $E_d = 38 \text{ kJ mol}^{-1}$ for the dissociation of **56**.

Analogous steady-state EPR methods (SEPR) have been applied to the study of ring opening of cyclopropylmethyl (**58**),^{204,205} cyclobutylmethyl (**59**), cyclobutenylmethyl radicals,^{206–208} and domino ring-opening reactions of bicyclo[1.1.1]pentylmethyl (**60**),²⁰⁹ cubylmethyl (**61**),²⁹ and analogs.^{210,211} SEPR investigations of the kinetics of other types of rearrangements,

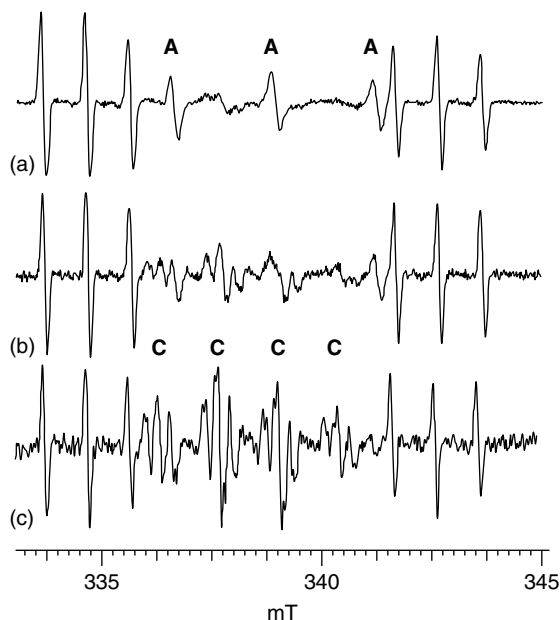
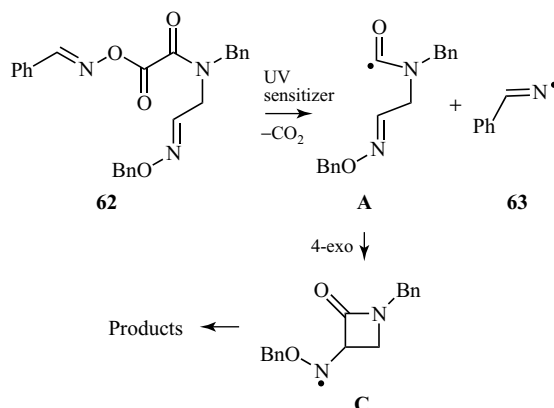


Figure 15 EPR spectra from photosensitized UV irradiation of oxime oxalate amide **62** in *t*-BuPh. High and low field 1 : 1 : 1 triplets are from $\text{PhCH}=\text{N}^\bullet$ (**63**). The carbamoyl radical is marked by **A** and the azetidinylaminy radical is marked by **C**. (a) Spectra at 220 K. (b) Spectra at 240 K. (c) Spectra at 310 K. [Adapted with permission from G. A. DiLabio, *et al.*, *Org. Lett.*, 2005, 7, 155–158. Copyright 2005 American Chemical Society.]

including aryl group migrations,²⁰⁴ and ring-closure reactions,^{136,212,213} have also been published. An example is the SEPR determination of the rate constant of an unusual 4-exo-cyclization as illustrated in Figure 15. Photolysis of oxime oxalate amide **62**, sensitized with 4-methoxyacetophenone, in *t*-butylbenzene at 220 K yielded the phenyliminyl radical **63** and carbamoyl radical **A** (Scheme 14).²¹⁴

Phenyliminyl **63** appeared as a pair of 1 : 1 : 1 triplets one in either wing of the EPR spectrum (Figure 15). Carbamoyl **A** contributed a 1 : 1 : 1 triplet in the central region (Figure 15a). As the temperature was raised, 4-exo-cyclization of **A** into the oxime ether acceptor became important and yielded azetidinylaminy radical **C**. The signals from **C** ($g = 2.0049$, $a(\text{N}) = 1.37$, $a(1\text{H}) = 1.37$, $a(2\text{H}) = 0.25$, $a(2\text{H}) = 0.10$ mT) dominated the EPR spectrum at $T = 310$ K (Figure 15c). The rate constant for cyclization of **A** was found to be $3 \times 10^4 \text{ s}^{-1}$ at 300 K.

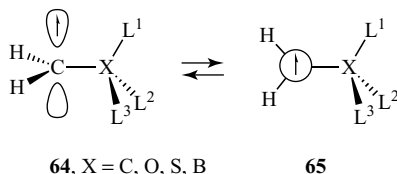


Scheme 14 4-exo-Cyclization of a carbamoyl radical onto an oxime ether acceptor.

10 DETERMINATION OF THERMODYNAMIC PARAMETERS BY EPR SPECTROSCOPY

Radical enthalpies of formation ($\Delta H_{f,300}$), radical stabilization enthalpies (RSEs), and bond dissociation enthalpies [BDE(R–X)] are useful parameters for assessing mechanisms and for planning syntheses. *Relative* thermodynamic parameters can be obtained from EPR measurements of radical concentrations in “radical buffer” systems^{215,216} where an equilibrium is set up between two related radicals and their precursor molecules. The method has been successfully applied for the determination of thermodynamic data for alkanes and alkyl radicals,^{217,218} phenols and aryloxy radicals,^{219,220} pyridinols,^{221,222} and pyrimidinols.²²³

Many moderately stable free radicals exist in solution in equilibrium with their dimers. The equilibrium constants of many such systems have been determined from EPR measurements of the radical concentrations.²²⁴ Rüchardt used BDE(C–C) values derived from equilibrium data to produce a self-consistent set of RSEs that tend to express the difference in stability of a pure hydrocarbon radical $\text{L}_3\text{C}^\bullet$ ($\text{L} = \text{H}$, alkyl) and the corresponding substituted radical $\text{L}_2\text{SC}^\bullet$ ($\text{S} = \text{functional group}$).²²⁵ A good number of empirical relationships between RSEs and spin densities have been suggested.^{226–228} The most comprehensive treatment based on H^α hfs from planar mono- and disubstituted radicals^{229,230}



Scheme 15 Internal rotation in functionalized primary radicals.

gave the following relationships for RSE and BDE (kJ mol^{-1}) where the $a(\text{H}^\alpha)$ are in millitesla:

$$\text{RSE} = 69.0a(\text{H}^\alpha) - 155.0 \quad (28)$$

$$\text{BDE}(\text{C}-\text{H}) = 67.3a(\text{H}^\alpha) + 260.8 \quad (29)$$

Linear relationships were also found for tertiary radicals involving the hfs from β -Me groups.

Another empirical EPR method for BDEs focuses on the torsion barriers (E_0) about the C–X bonds in primary radicals of type $\text{L}_n\text{XCH}_2^\bullet$ (**64**, Scheme 15).^{231–233}

The linear relationship (updated for recent BDE data) found between the two quantities is shown in (30).^{234,235}

$$\text{BDE}(\text{L}_n\text{XCH}_2-\text{H})/\text{kJ mol}^{-1} = 422.6 - 0.86E_0 \quad (30)$$

The correlation has proved useful for estimating and/or checking BDE data in a variety of circumstances.^{230,236}

11 CONCLUSIONS

Isotropic EPR spectra yield invaluable information about a radical's identity, the principal site of its UPE, and how this UPE is distributed around the structure. A very effective partnership with DFT computations enables dependable information about molecular structure and the nature of the frontier orbitals to be deduced. EPR concentration measurements also enable the dynamics of many processes to be quantified. This information is of outstanding service in deducing or supporting reaction mechanisms and as a tool for planning novel syntheses.

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Redox Properties of Radicals

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1 INTRODUCTION

Radicals are chemical species containing at least one unpaired electron in an atomic or molecular orbital. The importance of this class of reactive intermediate has been duly noted in chemical and biological systems.^{1,2} An understanding of the reactivity of radicals has allowed for a better understanding of biochemical pathways in cells and the cause of many diseases.^{3,4} Exploitation of the properties of radicals has provided efficient procedures for synthesizing novel molecular and polymer materials.^{5,6} Of the many pathways available to radicals, the mere loss or gain of a single electron is of tremendous consequence as it yields an even-electron species with different reactivity properties. Hence, knowledge of the redox properties of radicals is imperative for predicting the feasibility for an electron transfer reaction.⁷ Furthermore, accurate knowledge of the standard potentials of free radicals also allows for the estimation of other pertinent thermodynamic information, such as pK_a s and bond dissociation energies, that may not be otherwise readily available.⁸

The ionization potential and the electron affinity of a radical are a measure of its donor and acceptor properties in the gas phase. The oxidation and reduction potential of a radical are a measure of the donor and acceptor properties in the solution phase. In solution, the properties of the solvent contribute to some variation in the oxidation and reduction potentials mainly due to differences in the solvation properties. This article focuses on the redox properties

of radicals measured in solution and on the electrochemical and photoelectrochemical methods used to investigate and characterize them.^{9–15} The article concludes with up-to-date tables of standard reduction and oxidation potentials of radicals. The last extensive compilation of literature data was previously reported by the Aarhus group in 1999.¹³

There are several direct and indirect electrochemical methods that have been developed for the investigation of the redox properties of transient radicals, the majority of which are based on a combination of photochemical and/or electrochemical techniques. The direct evaluation of the oxidation and reduction potentials of radicals by electrochemical techniques includes cyclic voltammetry, which is by far the most widespread, and also other complementary techniques, such as polarography and second harmonic alternating current voltammetry (SHV). Photoelectrochemical techniques rely on light to homolytically cleave a covalent bond, which generates the radicals, and electrochemical means to detect and study them. The two most commonly employed photoelectrochemical methods are photo-modulation voltammetry, in which transient radicals are generated by modulated photolysis, and thermalized laser flash photolysis, in which a laser is used to inject electrons into solution by irradiation of an electrode. Although trivial to many, it is often taken for granted that no matter the analytical technique used to measure a standard potential, it is an intrinsic property of a chemical species and

therefore defined by the same fundamental principles independent of the technique employed. However, each technique has its strengths and weaknesses. Many of them are thoroughly covered in a number of books, including those by Bard and Faulker,¹¹ Wightman and Wipf,¹² and Compton and Banks.¹⁴ A brief overview of these various techniques has been described for the non-specialist.

2 FUNDAMENTALS OF ELECTROCHEMISTRY

2.1 Definition of Standard Potential

A standard potential is defined as the *reduction potential* of a redox system under thermodynamic control according to the Stockholm convention.^{16,17} By definition, the standard reduction potential refers to standard conditions where all reactants are at 1.0 M activity or 1 atm pressure at 298 K. In dilute solutions of 1 mM, it is generally acceptable to use concentrations in place of activities. The standard reduction potential of a radical is given as the addition of an electron to an odd-electron species to yield an even-electron anion as in (1). Likewise, the oxidation potential of a radical species is the addition of an electron to an even-electron cation to generate an odd-electron species as in (2).



The equilibrium for an electron transfer reaction between two species A and B, as defined in (3) at an electrode, is described by the Nernst equation (4), where E is the applied electrode potential, E^0 is the standard potential, $[A]$ and $[B]$ are the concentrations of the redox species at the electrode surface, F is Faraday's constant equal to $96\,485\text{ C mol}^{-1}$, and n is the number of electrons transferred per mole. Thermodynamic control is obtained when both molecular species are stable and in equilibrium at the electrode interface during the course of the experiment. For such a situation, the heterogeneous electron transfer between the substrate and the electrode must be fast ($\sim 1\text{ cm s}^{-1}$) so the interface concentrations can respond to the electrode potential.



$$E = E^0 + \frac{2.303RT}{nF} \log \frac{[A]}{[B]} \quad (4)$$

Due to the transient short-lived nature of radicals, they are generally difficult to isolate. Therefore, measuring the redox potential of a radical generally involves either the oxidation of a stable anion to the radical as in (1) or the reduction of a stable cation to the radical as in (2). A common strategy has involved the deprotonation of a weak acid in the presence of an added strong base and recording the oxidation wave of the anion using cyclic voltammetry. However, this method is limited to those anions stable in the assay solution. Hence, another approach that has been discussed in greater detail involves the generation of radicals by homolytic cleavage of a covalent bond. This can be accomplished by reductive homolytic cleavage of a substrate on accepting an electron via a dissociative electron transfer reaction,^{18–22} either transferred at an electrode or by a radical-anion catalyst in solution, or by homolytic cleavage of a frangible bond on irradiation with a light source.^{23–25}

3 METHODS FOR DETERMINING THE REDOX POTENTIALS OF RADICALS

3.1 Electrochemical Techniques

3.1.1 Cyclic Voltammetry with Microelectrodes

Cyclic voltammetry is a versatile technique for the determination of pertinent thermodynamic and kinetic information of radicals.^{11,14,15} The technique involves changing the potential of the working electrode linearly from an initial potential to a switching potential and back to the starting potential position. Within this potential window between the initial and switching potential, any redox active substrate is oxidized or reduced, according to the direction of the applied potential, and recorded as a change in current. The resulting voltammogram is a plot of the detected current versus the applied potential. The forward scan initiates the heterogeneous electron transfer reaction at the electrode and the reverse scan is diagnostic for detecting redox active intermediates and products. Formation of these stable products can be revealed in the initial scan or

probed by repetitive (multicycling) scans. The time parameter, RT/Fv , is controlled by the scan rate, the rate at which the potential changes as a function of time. The advent of ultramicroelectrodes has extended the upper limit to scan rates of 1 MV s^{-1} such that intermediates with a lifetime on the order of $1 \mu\text{s}$ can be characterized.

The simplest reaction that can be monitored by cyclic voltammetry, as represented by (3), corresponds to a single-electron transfer between the electrode and substrate in which both chemical species are stable and at equilibrium during the timescale of the experiment. A typical cyclic voltammogram for a fully reversible process, as illustrated in Figure 1, is characterized by scan rate and concentration independent peak potentials with a constant peak separation of 59 mV at 25°C and a current cathodic to anodic peak ratio equal to 1. The standard potential is obtained from the midpoint of the cathodic peak potential, E_{RED} , and the anodic peak potential, E_{OX} .

While there are many examples of reversible cyclic voltammograms for the reduction and oxidation of neutral molecules to their corresponding radical anions or radical cations, there are only a limited few examples of persistent free radicals that are stable on the time scale of the voltammetry experiment.²⁶ Examples of these longer lived radicals include trimethylaryl,^{27–29} nitroxyl,^{30–32} perchlorophenalenyl,³³ dithiadiazolyl,³⁴ and verdazyl radicals.³⁵ The use of ultramicroelectrodes in voltammetry has increased the accessible time window available for the direct evaluation of radical

standard potentials. Still, in cases where equilibrium is not obtained, the direct evaluation of the redox properties by cyclic voltammetry is generally not a straightforward task and requires an understanding of the influence of the heterogeneous kinetics as well as the effect of follow-up homogeneous reaction kinetics.

3.1.2 Effect of Heterogeneous Kinetics

Many simple redox systems corresponding to (3) display irreversible voltammograms due to a slow heterogeneous electron transfer from the electrode to the substrate. Strictly speaking, thermodynamically significant standard potentials can only be directly obtained from reversible voltammograms. However, with an understanding of the effects of the heterogeneous kinetics on the observed potential measurement, determination of accurate thermodynamic information is obtainable.

Figure 2 illustrates a series of cyclic voltammograms for a simple redox system as a function of the decreasing apparent rate constants. As the kinetics of the heterogeneous electron transfer get slower, an overpotential is required to transfer the electron to the substrate. The trend one observes as the apparent kinetics get slower is a decrease in the peak current, an increase in the cathodic to anodic peak current ratio, and an increase in the peak-to-peak separation, although the midpoint between the peak currents can still provide an estimate of the standard potential.

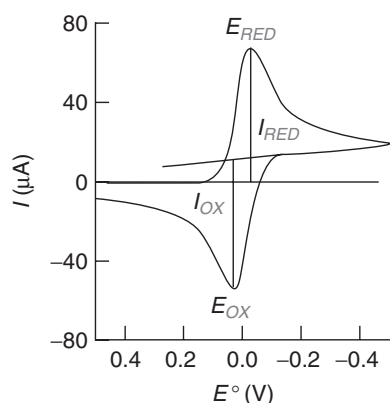


Figure 1 Simulated cyclic voltammogram of a fully reversible one-electron redox system at 25°C with a 3-mm-radius micro-electrode.

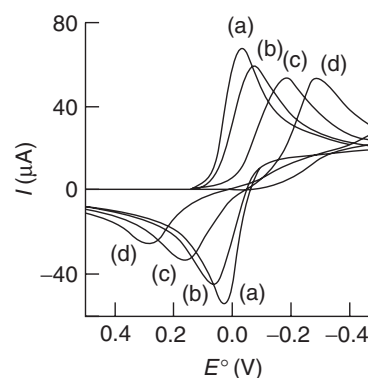


Figure 2 Simulated cyclic voltammograms for a reversible redox system at a standard potential of zero and a heterogeneous forward rate constant k_{HET} of (a) 1, (b) 10^{-1} , (c) 10^{-2} , and $10^{-3} \text{ cm s}^{-1}$.

The peak current is dependent on the square root of the scan rate and the substrate concentration (5). Under these circumstances, the cyclic voltammogram is said to be quasi-reversible:

$$i_p = (2.69 \times 10^5) n^{3/2} A D^{1/2} C v^{1/2} \quad (5)$$

For a reduction process, the apparent heterogeneous rate constant, k_{app} , is related to the standard rate constant, k^0 , at the standard potential and an exponential component that accounts for the overpotential, $E - E^0$, and the symmetry factor, α , as given in (6). When the redox system obeys the Nernst equation and the kinetics are fast, there is no overpotential and the observed rate constant is k^0 . However, any overpotential contribution results in lowering the apparent rate constant and shifting the reduction peak to more negative potentials:

$$k_{app} = k^0 \exp\left(\frac{-\alpha n F}{RT}(E - E^0)\right) \quad (6)$$

Deviation from the Nernst equation for a reduction reaction involving species A converted to B results when the product is reluctant to accept the electron. This could be the consequence of a significant structural change between the neutral and reduced (oxidized) forms, which requires substantially more potential to overcome the intrinsic barrier, resulting in a lower k_{app} . A fast irreversible follow-up reaction after the reversible electron transfer at the electrode results in a reduction current at less extreme potentials compared to the case with no follow-up homogeneous kinetics, which acts as a positive overpotential contribution. Thus, the overpotential is mainly the contribution from the heterogeneous kinetics, but the ensuing homogeneous reactions can, in some cases, counteract the negative overpotential.

Cyclic voltammograms can also appear to have non-Nernstian peak-to-peak distances when there is a considerable ohmic drop (iR), notably in nonaqueous solutions. The potential drop is a measure of the solution resistance between the working and reference electrode. It is proportional to the current at the working electrode and the distance between the two electrodes so at higher scan rates and larger electrodes, its contribution to the applied potential can be quite substantial. If the cyclic voltammograms are not corrected for the iR contribution, the peak-to-peak separation

appears larger and the anodic and cathodic peak currents lower resulting in an error in the k^0 . For example, with a 3-mm glassy carbon (GC) electrode in acetonitrile (ACN) solution containing 0.1 M tetrabutylammonium perchlorate, the ohmic drop is about 200 Ω . Using positive feedback systems incorporated in the electronics of the potentiostat, it is possible to compensate for the majority percentage of the ohmic drop.

3.1.3 Effect of Follow-Up Homogeneous Kinetics

In addition to the rate of the heterogeneous kinetics, the applied potential at the electrode is also dependent on the rate of follow-up homogeneous reactions. Figure 3 illustrates the effect of a homogeneous chemical reaction following the initial electrochemical step.

Curve (a) represents a reversible system with no follow-up chemistry. On introduction of a slow homogeneous reaction, the current peak ratio increases until the reverse wave is no longer observed as in curve (b), and the forward peak potential is found to shift slightly to more positive potentials as compared to case (a) when there is no follow-up homogeneous kinetics. The voltammograms labeled (c) and (d) correspond to follow-up reactions with rate constants three and six orders of magnitude greater than in (b). The curves in Figure 3

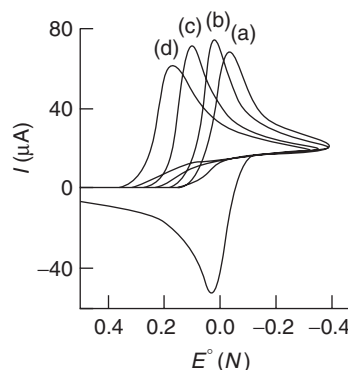


Figure 3 Simulated cyclic voltammograms for a reversible redox system at a standard potential of zero and a heterogeneous forward rate constant k_{HET} of 1 cm s^{-1} (a) and followed by an unimolecular fragmentation with a rate constant of (b) 10^3 , (c) 10^6 , and (d) 10^9 s^{-1} .

exemplify a reduction process where the forward peak potential shifts to more positive potentials; in the case of an oxidation process, the peak potential shifts to more negative potentials. Voltammograms with shapes similar to curves (c) and (d) are also commonly observed when there is a follow-up reaction after dissociative reductive cleavage of a covalent bond. However, in such cases, the peak potential shifts to more negative potentials due to the overpotential required to break the covalent bond.^{18–22} The extent of the peak shifts can be used diagnostically to determine whether the follow-up reaction is first or second order. For a reduction process, the peak potential will shift positively according to (7) and (8). These equations can be used in determining the reduction potential of radicals from the oxidation of chemically generated anions. The peak potential will be of opposite sign for an oxidation process:

$$\text{First order } \frac{\partial E_p}{\partial \log(k/v)} = 29.6 \text{ mV/decade} \quad (7)$$

$$\text{Second order } \frac{\partial E_p}{\partial \log(k[\text{Ox}]/v)} = 19.7 \text{ mV/decade} \quad (8)$$

3.1.4 Cyclic Voltammetry with Ultramicroelectrodes

The ultramicroelectrode is arguably one of the most important contributions to electroanalytical chemistry in the past two decades.^{36–43} The smaller electrode dimensions, on the order of micrometers or less, provide characteristics quite different from that of conventional millimeter diameter electrodes. The several orders of magnitude difference in dimensions between conventional electrodes and ultramicroelectrodes is the source of the advantageous properties of the latter. The current generated at an ultramicroelectrode is dependent on the geometry, so that diffusion toward the electrode is radial rather than linear at microelectrodes, which results in sigmoidal rather than peak voltammograms. Planar diffusion at a large conventional electrode provides a peak voltammogram with a diffusional tail. In contrast, radial diffusion at the ultramicroelectrode gives a sigmoidal steady-state i – E response

with defined plateau currents. For a reversible system where the diffusion coefficients of both species are similar the standard potential is obtained directly from the point of inflexion of the steady-state curve analogous to the determination of the pK_a from a pH titration curve. However, a smaller k^0 causes the sigmoidal curve to be displaced toward more extreme potentials.

Ultramicroelectrodes are useful for measurements in highly resistive media (nonpolar solvents, polymers, gaseous interfaces, and supercritical fluids) and for high-speed voltammetry at scan rates over 1 MV s^{-1} . High-speed cyclic voltammetry has been redefined by ultramicroelectrodes because of the much smaller uncompensated resistance and background capacitance.^{36,37} The distortion observed with microelectrodes is caused by a large uncompensated solution resistance (R), which creates a substantial iR drop between the applied and working electrode potentials. Because of the extremely small currents employed, typically in the nA and pA range, the current density is increased making ultramicroelectrodes much less sensitive to the solution resistance and to the iR between the working and reference electrode. Even at low electrolyte concentrations, voltammetry with ultramicroelectrode is viable. The use of fast CV techniques to measure reversible oxidation and reduction potentials of radicals has extended the scan rate range from the kV s^{-1} to the MV s^{-1} range so that intermediates with lifetimes of $1 \mu\text{s}$ can be detected. The upper limit restriction on the MV s^{-1} range stems from the solution resistance and the double layer capacitance.

3.1.5 Competitive q Method

A valuable alternative to the direct investigation of the reduction characteristics of radicals in aprotic solvents is based on a competition between electron transfer and radical anion-radical coupling.⁴⁴ The technique is based on the concept of homogeneous redox catalysis.^{18,19} An aromatic donor, D, with a known standard potential, as probed by cyclic voltammetry, is electrochemically generated with a bulk electrode to yield a stable solution of the radical anion donor, $D^{\bullet-}$, under inert atmospheric conditions (9). Once an excess of the radical anion is generated, and it is confirmed to be stable, the substrate with a reducible bond, RX, is added to the solution. The radical anion transfers an electron to

the substrate to generate the anion $RX^{\bullet-}$ (10), which normally undergoes a rapid dissociation to yield the radical $R^{\bullet}$ and an anion X^- (11). The radical $R^{\bullet}$ can then react with $D^{\bullet-}$ either by an electron transfer reaction (12) or by coupling together (13). The ratio of products can be measured by linear sweep voltammetry in conjunction with digital simulation,^{45–47} by monitoring the change in current as probed with an ultramicroelectrode or rotating disk electrode^{48–50} or by isolation of the products from preparative electrolysis in conjunction with coulometry.^{51–55} The products DR^- and R^- are often protonated to yield stable products, or in some cases, may react via a nucleophilic substitution reaction with the initial substrate.⁵⁶ Historically, RX has been used to represent alkyl halides, although it is more representative of many chemical classes with a leaving group.^{18,22}



The competition between the homogeneous ET (12), and coupling between the radical anion donor and the radical (13), is defined by the dimensionless parameter q (14):

$$q = \frac{k_{ET}}{k_{ET} + k_c} \quad (14)$$

When the reduction is readily feasible with a rate constant near the diffusion-controlled limit and $k_{ET} \gg k_c$, then q is equal to 1. However, when the reduction is slow compared to the coupling reaction and $k_c \gg k_{ET}$, then q is equal to 0. The resulting q plot exhibits an S-shaped curve with q decreasing with increasing $E_{D/D^{\bullet-}}^0$. The half-wave potential is determined by interpolation among the q points against the standard potential of the various mediators, which corresponds to where $k_{ET} = k_c$ and $q = 0.5$. Obtaining an accurate estimate of the q value generally requires measuring at least five q values per radical. In this manner, the reduction potential of short-lived carbon radicals such as

alkyl,^{45,46} allyl,⁴⁸ acyl,⁴⁸ and benzyl radicals^{44,49,52} have been evaluated. Studies have shown that coupling between aromatic radical anions and alkyl and benzyl radicals is independent of the standard potential of $E_{D/D^{\bullet-}}^0$ with a rate constant of $1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.^{57–59} Equation (14) provides a way of evaluating k_{ET} once q is known. The technique was first applied to alkyl halides, anhydrides, and acid chlorides substrates,^{45–49} and has also been applicable to peroxides with alkoxy radicals that undergo a rapid β -scission fragmentation,⁵² and alternatively based on hydrogen abstraction of aldehydes.⁵⁵

When the electron transfer between the radical anion donor and the radical is an outer-sphere electron transfer, the rate constant is described according to the quadratic-activation relationship given by the Marcus theory accounting for diffusion as in (15)⁶⁰:

$$k_{ET} = \frac{k_d}{1 + \frac{k_d}{K_d Z} \exp \left[\frac{\lambda}{4RT} \left(1 + \frac{\Delta G_{ET}}{\lambda} \right)^2 \right] + \exp \left(\frac{\Delta G_{ET}}{RT} \right)} \quad (15)$$

where k_d is the diffusion-limited rate constant, K_d is the equilibrium constant for formation of the encounter complex, Z is the collision frequency for an adiabatic ET, λ is the reorganization energy and ΔG_{ET} is the free energy of the ET reaction (16). Substitution of (15) into (14) yields an expression relating the q parameter as a function of $E_{D/D^{\bullet-}}^0$ as described by (17)^{61–63}:

$$\Delta G_{ET} = 23.06(E_{D/D^{\bullet-}}^0 - E_{R^{\bullet}/R^-}^0) \quad (16)$$

$$q = \frac{1}{1 + \frac{k_c}{k_d} \left\{ 1 + \frac{k_d}{K_d Z} \exp \left[\frac{\lambda}{4RT} \left(1 + \frac{\Delta G_{ET}}{\lambda} \right)^2 \right] + \exp \left(\frac{\Delta G_{ET}}{RT} \right) \right\}} \quad (17)$$

Nonlinear regression analysis with the assistance of graphing software, such as Kaleidagraph or Sigmaplot, provides a measure of the standard potential and the reorganization energy of the radical. The half-wave potential is reasonably precise

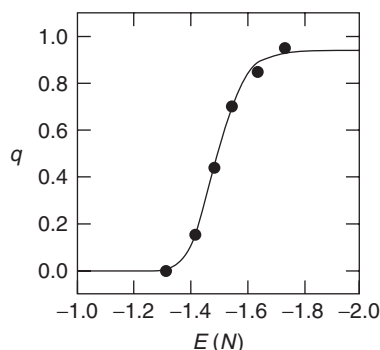


Figure 4 Competition parameter q plot for the benzyl radical as a function of the aromatic donor $E_{D/D^{\bullet-}}^0$ in DMF/0.10 M TEAP solution. [Reproduced from Ref. 52. © Royal Society of Chemistry, 2003.]

within 50 mV, whereas the estimation of the standard reduction potential has a greater uncertainty of 150 mV due to the error in estimating λ . Typical values in aprotic solvents are $k_c = 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $Z = 3 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$, $K_d = 1 \text{ M}^{-1}$, and $k_d = 2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$. Figure 4 illustrates a representative set of data obtained for the benzyl radical and the fitted curve using (16) and (17).

While most q parameter studies applied linear sweep voltammetry, the use of a rotating disk electrode or ultramicroelectrode is advantageously more accurate even with slower reactions with a rate constant as low as $10^{-3} \text{ M}^{-1} \text{ s}^{-1}$.⁵¹ However, this is at the expense of having a thorough understanding of the reaction mechanism and a stable radical anion compared to those employed in linear sweep or chronoamperometry. Measurements in dimethylsulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) tend to be more accurate and reproducible due to the greater solubility of oxygen and faster rate of solvent evaporation in ACN.⁵²

3.1.6 Second Harmonic Alternating Current Voltammetry

SHV is a technique that involves a direct current (DC) sweep applied at a working electrode as in CV and also involves a small 10-mV alternating current (AC) superimposed on the faradaic current.^{64–73} The frequency of the sinusoidal AC is the time parameter. The output is the current at a specific phase relative to the AC potential signal versus the DC potential. The selective detection of the

AC using a lock-in amplifier provides faradaic information, while simultaneously eliminating the double-layer charging current at the electrode. For a reversible system, a compressed symmetrical sine wave is observed and the standard potential is taken as the midpoint of the sine wave. No double-layer nonfaradaic current is observed as in cyclic voltammetry with microelectrodes.

The historic limitation with cyclic voltammetry was the restriction caused by the double-layer charging current at high scan rates. In some cases, CV can be used to outrun the follow-up chemistry, but it comes at the expense of introducing a larger double-layer charging current making it difficult to distinguish the faradaic current of the substrate from the double layer capacitance. Hence, the SHV method once provided a powerful technique for studying electrochemical reactions with fast follow-up chemistry. Nowadays, the combination of cyclic voltammetry with ultramicroelectrodes has tended to replace the utility of this unappreciated technique in the modern laboratory partly due to the complexity of data collection and analysis in SHV experiments.

3.2 Photoelectrochemical Techniques

3.2.1 Laser Flash Electron Photoinjection

This photoelectrochemical approach consists of using a short laser pulse approaching 10^{-9} s^{-1} from an excimer laser with an intensity of $20\text{--}200 \text{ kW cm}^{-2}$ to inject electrons into the electrolyte solution by irradiating a metal electrode.^{74–83} The wavelength is carefully selected in a range where the substrate absorption is weak to prevent direct photochemistry. The result is a source of low-energy electrons, typically on the order of 1–5 eV, about the electrode surface at a mean distance of 60 Å. In the absence of any substrate, the electrons return to the electrode by diffusion with no change in net charge. Pioneering work was done in aqueous solution at a mercury electrode with alkyl,^{74,75} and hydroxyalkyl radicals,^{75,76} but has been extended to methylaryl radicals.^{77–80} Compared to pulse radiolysis, where solvated electrons are generated in addition to hydrogen atoms and hydroxyl atoms (among other species), an advantage of this technique is that it allows for much

better reaction control. The technique has been applied in various organic aprotic solvents with photoelectrode materials other than mercury,^{77,78} which tends to react by absorption with radicals, and as a tool for understanding the dynamics of proton transfer reactions to carbanions.^{81,82}

In the presence of a substrate with a reducible fragile bond, the solvated electron generates a radical and an anion. Alternatively, the radical can be generated indirectly by hydrogen abstract in the presence of hydroxyl radicals generated from a solution of saturated N₂O. The net result, either way, is a thin layer of radicals on the order of 30- to 100-Å thick with a surface concentration of 10⁻¹³ mol cm⁻² at the electrode surface. Any solvated electrons that remain uncaptured by the substrate are taken up by the electrode. The time window ranges approximately from 1 μs to 1 ms. Monitoring of the photogenerated charge as a function of the DC potential applied to the working electrode yields a scattering of points along an S-shaped current-potential trajectory (photopolarograms) characterizing the reduction of the radical intermediate. At an applied electrode potential lower than the reduction potential of the radical, the radical is reduced to the anion and the net current corresponds to a count of two electrons per molecule. However, when the electrode potential is much higher than the radical reduction potential, the net current equates to one electron per molecule. The point of inflexion between the foot and plateau of the curves is the half-wave potential, which is an estimated measure of the reducibility of the radical.

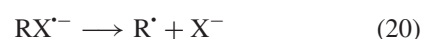
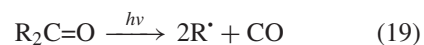
The true meaning of the half-wave potentials requires an understanding of the reduction mechanism, which involves the initial electron transfer step to generate the radical, the following reduction to the anion, as well as the various homogeneous reactions the radical and anions may undergo. The Paris group has tackled these issues, including adsorption at the electrode, and derived a theoretical framework for extracting thermodynamic and kinetic parameters under a number of mechanistic situations.⁸³ In the simplest case, when the radical is stable and obeys a Nernstian electron transfer, the half-wave potential is equivalent to the standard potential, but this is not the norm due to the short-lived nature of radicals. For example, where the radical and anion are stable, but the kinetics are slow and irreversible, the half-wave potential varies linearly with the logarithmic analysis equal to

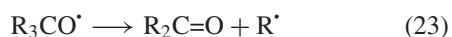
59.2 mV divided by the transfer coefficient at 25 °C, thus allowing the determination of the transfer coefficient from the radical polarogram as a function of time. From (18) and knowledge of the diffusion coefficient, *D*, the standard rate constant, *k_s*, and the time parameter, *t*, the standard potential *E*⁰ can be determined. Other mechanistic scenarios including fast first- and second-order follow-up reactions and adsorption of the radical onto the electrode surface are also theoretically examined in detail⁸³:

$$E_{1/2} = E^0 + 0.2626 \frac{RT}{\alpha F} + \frac{RT}{\alpha F} \ln \left(k_s \sqrt{\frac{t}{D}} \right) \quad (18)$$

3.2.2 Photomodulation Voltammetry

Photomodulated voltammetry was developed by Wayner, Griller, and coworkers at the Steacie Institute in Ottawa.⁸⁴⁻⁹⁴ Recent studies on the redox properties of radicals by this technique have been published by the Danish team in Aarhus⁹⁵⁻⁹⁸ and the Austrian team in Graz.^{99,100} The method involves the photolysis of a labile substrate with modulated light to generate the radical and combines an electrochemical technique to study and characterize the reactive intermediate. Based on the principles of flash photolysis, the radicals are generated continuously in a flow cell by photolysis of the substrate. Two general approaches, one direct and the other indirect, allows for flexibility in the choice of substrate. The first approach is based on photodecomposition of a suitable precursor. Common examples include ketones, which decompose via α-cleavage of a C–C (19) or alkyl halides that decompose via R–X cleavage to yield R[•] directly (20). A second approach involves the photolysis of an organic peroxide, such as di-*tert*-butyl peroxide, which undergoes homolytic cleavage of the O–O bond to yield *tert*-butoxyl radicals (21), which subsequently abstract a hydrogen atom from the parent compound to generate the R[•] species of interest (22). Generation of an alkoxyl radical capable of rapid β-cleavage to yield a ketone and a radical provides an alternative strategy via (23):





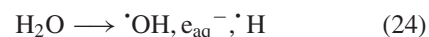
Photolysis is accomplished using a high-power Hg-Xe lamp in an electrochemical cell with a quartz window and a gold mini-grid (or carbon net) working electrode sandwiched between two quartz windows. Modulation of the light is controlled sinusoidally by a mechanical chopper that blocks the light with a specific frequency, which causes the concentration of radicals to oscillate at a fixed frequency. The oscillation produces a small AC up to 500 nA at the same frequency as the lamp. Detection is accomplished with a lock-in amplifier. The technique can be used to detect radicals with lifetimes in the order of 1 ms at concentrations as low as 10^{-7} M, where second-order homogeneous processes are not a mechanistic issue.

The $E_{1/2(\text{R}^\bullet/\text{R}^-)}$ and $E_{1/2(\text{R}^\bullet/\text{R}^+)}$ are determined directly from the points of inflexion of the steady-state voltammograms recorded as plots of the AC versus the electrode potential. Frequently, these half-wave potential provide a reliable estimate of the standard potentials, at times accurate to within 50 mV of the standard reduction potential. However, exceptions are common place as the current is controlled not only by diffusion but also by the heterogeneous kinetics and as well as homogeneous reactions of the species involved as previously discussed.

3.3 Pulse Radiolysis

Pulse radiolysis is a widely used technique for studying the thermodynamic properties of radicals in aqueous media.^{101–110} Radicals are generated using short pulses of high-energy electrons of up to 20 MeV. The source of the irradiation can be particulate matter (electrons and α -particles) or photonic (X-rays, γ -rays, and high-intensity UV laser light). The radiolysis of water is initiated by the excitation and ionization of the solvent resulting in the formation of a number of reactive intermediates, the three most significant species are a hydroxyl radical $\text{OH}^\bullet$, a hydrated

electron e_{aq}^- , and a hydrogen atom $\text{H}^\bullet$ (24) (see **Radiation-Induced Radical Reactions**):

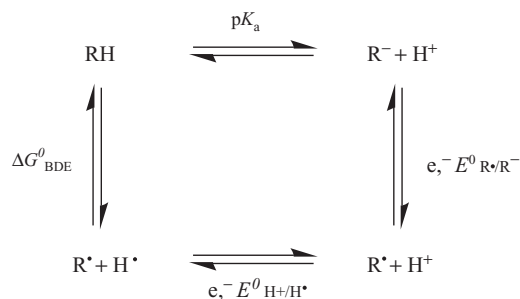


In the presence of a substrate, these three species give rise to various secondary reactive intermediates. The technique is not limited to aqueous solutions; however, most organic solvents are generally not suitable due to poor absorptivity properties of the solvents and/or competing chemical side reactions. Detection methods for the characteristics of the radicals include both optical and electrochemical methods. Commonly used optical techniques include UV–Visible absorption spectroscopy, Rayleigh scattering, and resonance Raman spectroscopy, while common electrochemical methods employed include conductivity, electron paramagnetic resonance, or polarography.

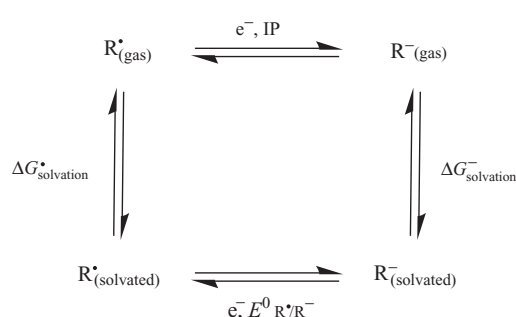
A drawback of the pulse radiolysis technique is poor selectivity. Hydrogen atoms and electrons are strong reductants as well as capable of hydrogen abstraction and alkene addition, while hydroxyl radicals are a powerful oxidant. To circumvent many of these undesirable reactions, various scavengers, such as N_2O , $\text{S}_2\text{O}_8^{2-}$, N_3^- , Br^- , and 2-methyl-2-propanol, are used to manipulate the reactivity conditions in order to obtain conditions supporting the desired radical. Another limitation of the pulse radiolysis technique is the specialized nature of the equipment, which tends to prevent most research groups from easy access to the instrumentation. A compilation of radical standard potentials in water were presented by Wardman in 1989.¹⁰¹

3.4 Thermochemical Cycles

Thermochemical cycles provide a way of obtaining the redox potential of radicals from existing thermodynamic data and group additivity tables.^{111–115} A commonly used scheme includes the $\text{p}K_{\text{a}}$ of the corresponding RH compound, the bond dissociation energy of the RH bond, and the known standard potential of the hydrogen atom. This relationship between the $\text{p}K_{\text{a}}$, the bond dissociation free energy, ΔG_{BDE}^0 , and the standard potential of the radical, $E_{\text{R}^\bullet/\text{R}^-}^0$, is given in Scheme 1 and summarized in (25). The $E_{\text{H}^+/\text{H}^-}^0$ in various solvents is known—for DMF, the value is -2.45 V versus the normal hydrogen electrode (NHE). A detailed review of the



Scheme 1 Thermodynamic cycle for the relationship between the bond dissociation energy, acid dissociation constant, and the standard potentials of a hydrogen atom and a corresponding radical.



Scheme 2 Thermochemical cycle for relating the gas phase ionization potential to solution standard potential.

approach is given by Wayner and Parker^{8,115}:

$$2.303RT\text{p}K_{\text{a}} = \Delta G_{\text{BDE}}^0 + F(E_{\text{H}^+/\text{H}^\bullet}^0 - E_{\text{R}^\bullet/\text{R}^-}^0) \quad (25)$$

3.5 Computational Electrochemistry

With the ever increasing performance in computer processing technology and the continuing increase in experimental free radical data, the time has come to accept computational electrochemistry as mainstream. Many research groups have developed theoretical approaches for predicting the standard redox potentials of radicals in different solutions.^{116–121} The general approach is to employ a theoretical method to correlate gas-phase ionization energies and then calibrated with a solvation model for the solution phase to calculate standard reduction potentials as shown in Scheme 2. Despite the improved reliability in the methods employed, these calculations still come with some assumptions, yet many authors claim to obtain reliable results with high levels of precision. Schmittl *et al.*,¹¹⁶ for example, have recently reported the experimental oxidation potentials of over 40 select enols, enolates, and α -carbonyl radicals and linearly correlated the computed ionization potentials after correcting for solvation. Perhaps the most comprehensive study to date calculated the standard redox potential of over

270 carbon-centered free radicals in ACN to derive a calibrated linear correlation with a precision of 0.2 V.¹¹⁷ The study was limited to compounds with less than 13 nonhydrogen atoms and only for one-electron processes. The one-electron reduction potentials for a range of oxygen- and sulfur-centered radicals in protic and aprotic solvents have also been demonstrated in both protic and aprotic solvents.¹¹⁸

4 TABLES OF REDUCTION, OXIDATION, AND STANDARD POTENTIALS

The reduction $E_{1/2}(\text{R}^\bullet/\text{R}^-)$ and standard potentials $E^0(\text{R}^\bullet/\text{R}^-)$ of the radicals are reported in Table 1 and the oxidation potentials $E_{1/2}(\text{R}^\bullet/\text{R}^+)$ and standard potentials are reported in Table 2. In aqueous solution, the measurement of standard potentials is universally made with respect to the NHE with all components at unit activity in water and defined as the *international accepted zero potential*. As pulse radiolysis experiments are customarily performed in aqueous solution, standard potentials obtained with this technique are reported versus NHE. However, in most cases, electrochemical measurements of many organic substrates are impractical in water, often due to insolubility or instability. Hence, the convention adopted by most laboratories working in nonaqueous solutions is to report experimentally determined potentials versus the saturated calomel electrode (SCE) with respect to a

reference or pseudo reference electrode such as a silver wire. The recommended convention is to report potentials obtained in different solvents using the ferrocenium/ferrocene redox system as an internal standard.^{16,17} This approach allows for the quantitative comparison of standard potentials measured in over 20 various nonaqueous solvents. Because of the popularity of referencing versus SCE, the potentials in Tables 1 and 2 are with respect to this reference. It is worth noting that comparisons of potentials from various literature resources should only be compared against or related to the same reference electrode, otherwise an associated error will be included. The silver–silver chloride electrode is another commonly used reference electrode, which has a potential of 0.197 V versus NHE. Conversion of the tabulated SCE values in Tables 1 and 2 to NHE requires the subtraction of 0.242 V.

Converting from one reference electrode to another, admittedly, introduces an uncertainty error in the measured standard potential. However, the greatest source of error results from the indiscriminate use of irreversible peak potentials as a substitute for the standard potentials when there is a large overpotential either from cleavage of a bond or from some other major structural organization within the substrate. This sort of error can be in excess of 1 V. A number of other parameters also introduce uncertainty and it is always advisable to compare potentials measured with the same solvent, working electrode, electrolyte, and electrolyte concentration. Comparisons of potentials are most accurate when referred to the same reference electrode—such a mix up can easily introduce an error in the order of 0.3 V.^{122,123} In contrast, errors associated with using values from different inert electrodes are generally not severe with typical discrepancies in the order of 0.10 V, but larger inconsistencies in the order of 0.25 V have been observed.⁷⁷ Discrepancies resulting from potentials measured in various organic solvents and electrolytes are also generally limited to errors of 0.10 V. For example, the following documented corrections highlight this point: DMF (0.480 V vs SCE), ACN (0.410 V vs SCE), and DMSO (0.430 V vs SCE).¹³

The redox potentials in Tables 1 and 2 have been mainly limited to those measured in ACN, DMF, DMSO, and aqueous (W) solutions. This restriction

is based on practicality since the largest collection of data is reported in nonaqueous polar solvents, although for biological applications redox potentials in aqueous solution are, of course, the ideal. Measurements are typically made with either GC, mercury (Hg), platinum (Pt), or gold (Au) electrodes. Mercury with its long tradition as an electrode material is often chemically involved in the reaction even in the cases where no stable mercury products are detected. As an electrode, mercury often behaves as a heterogeneous inner-sphere, rather than outer-sphere, electron donor in the reduction reactions. Gold and platinum have demonstrated to be inert for most substrates, although they are known to act as electrocatalysts under certain circumstances. Even GC with a reputation as an inert, outer-sphere electron transfer material is susceptible to reactivity with certain radicals, such as with the phenyl radical, which forms a thin layer and insulates the electrode.¹²⁴ From this perspective, it is advisable to measure the redox properties of radicals by electrochemical means using multiple types of electrode materials and techniques. This concern is reflected in Tables 1 and 2.

Tables 1 and 2 each contain eight columns. In column 1, the name of the radical is given, and in column 2, the molecular formula is provided for the simpler radicals. They are listed in general order of the number of carbon atoms, further subgrouped according to the nature of the radical centre: carbon, oxygen,¹²⁵ nitrogen,¹²⁶ sulfur,¹²⁷ other group IV elements,⁹⁵ and selenium.⁹⁶ Column 3 contains either the half-wave reduction or half-wave oxidation potentials and column 4 the thermodynamic standard potential. Columns 5 and 6 describe the experimental conditions, the electrode material in the case of electrochemical detection, and the solution/electrolyte solution, respectively. The various electrochemical and photoelectrochemical techniques used to measure the redox properties of each radical are listed in column 7 and the primary literature reference is provided in column 8. When the data are available, a number of standard potentials for the same radical species are included in the tables to allow for an appreciation for the differences associated with different experimental techniques and conditions from various laboratories.

Table 1 Reduction and standard potentials of radicals.

Radical	Structure	$E_{1/2}(\text{R}^{\bullet}/\text{R}^{-})$ vs SCE	$E^0(\text{R}^{\bullet}/\text{R}^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
Carbon-centered radicals							
Methyl	$\text{CH}_3^{\bullet}$	-1.78	-1.19	Au	DMF (0.1 M TBAB)	Q	49
			-0.77	Hg	CAN (0.3 M LiP)	LPE	75
Ethyl	$\text{CH}_2\text{CH}_3^{\bullet}$	-2.23	-1.64	Au	DMF (0.1 M TBAB)	Q	49
			-0.95	Hg	ACN (0.3 M LiP)	LPE	75
Propyl	$\text{CH}_2\text{CH}_2\text{CH}_3^{\bullet}$	-2.22	-1.63	Au	DMF (0.1 M TBAB)	Q	49
			-1.18	Hg	ACN (0.3 M LiP)	LPE	75
2-Propyl	$\text{CH}_3^{\bullet}\text{CHCH}_3$	-2.30	-1.72	Au	DMF (0.1 M TBAB)	Q	47
			-1.36	Hg	ACN (0.3 M LiP)	LPE	75
2-Methylpropyl	$\text{CH}_3\text{CH}(\text{CH}_3)_2^{\bullet}$	-2.15	-1.57	Au	DMF (0.1 M TBAB)	Q	47
Butyl	$\text{CH}_2(\text{CH}_2)_2\text{CH}_3^{\bullet}$	-2.20	-1.62	Au	DMF (0.1 M TBAB)	Q	47
		-2.30	-1.44	GC	DMF (0.1 M TBAB)	CV	128
			-1.19	Hg	ACN (0.3 M LiP)	LPE	75
2-Butyl	$\text{CH}_3^{\bullet}\text{CHCH}_2\text{CH}_3$	-2.30	-1.72	Au	DMF (0.1 M TBAB)	Q	47
		-2.38	-1.54	GC	DMF (0.1 M TBAB)	CV	128
<i>tert</i> -Butyl	$\text{C}(\text{CH}_3)_3^{\bullet}$	-2.35	-1.77	Au	DMF (0.1 M TBAB)	Q	47
		-2.47	-1.68	GC	DMF (0.1 M TBAB)	CV	128
		-1.80		Hg	DMF (0.1 M TEAP)	CV	130
Cyclopentyl	H	-2.30	-1.72	Au	DMF (0.1 M TBAB)	Q	47
	2-OCH ₃	-1.96	-1.67	Au	DMF (0.1 M TBAB)	Q	49
Cyclohexyl	H	-2.26	-1.68	Au	DMF (0.1 M TBAB)	Q	47
	2-OCH ₃	-1.98	-1.81	Au	DMF (0.1 M TBAB)	Q	49
Adamantyl		-2.24	-1.92	Au	DMF (0.1 M TBAB)	Q	49
2-Norbornyl		-2.26	-1.67	Au	DMF (0.1 M TBAB)	Q	49
Isobornyl		-2.26	-1.70	Au	DMF (0.1 M TBAB)	Q	49
Bornyl		-2.26	-1.75	Au	DMF (0.1 M TBAB)	Q	49
2-Propenyl	$\text{CH}_2\text{CH}=\text{CH}_2^{\bullet}$	-1.54	-1.39	Au	DMF (0.1 M TBAB)	Q	49
2-Propynyl	$\text{CH}_2\text{CCH}^{\bullet}$	-1.40	-1.25	Au	DMF (0.1 M TBAB)	Q	49
2-Methyl-2-propenyl	$\text{CH}_2\text{C}(\text{CH}_3)_2=\text{CH}_2^{\bullet}$	-1.54	-1.39	Au	DMF (0.1 M TBAB)	Q	49
3-Butenyl	$\text{CH}_3^{\bullet}\text{CHCH}=\text{CH}_2$	-1.70	-1.55	Au	DMF (0.1 M TBAB)	Q	49
3-Pentenyl	$\text{CH}_3^{\bullet}\text{CHCH}=\text{CH}_2\text{CH}_3$	-1.87	-1.72	Au	DMF (0.1 M TBAB)	Q	49
Acetyl	$\text{C}(\text{O})\text{CH}_3^{\bullet}$	-1.98	-1.70	Au	DMF (0.1 M TBAB)	Q	50
Succinyl	$\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CO}_2^{-}$	-2.03	-1.75	Au	DMF (0.1 M TBAB)	Q	50
Phenylacetyl	$\text{C}(\text{O})\text{CH}_2\text{Ph}^{\bullet}$	-1.96	-1.68	Au	DMF (0.1 M TBAB)	Q	50
Benzoyl	$\text{C}(\text{O})\text{PhX}^{\bullet}$						
	H	-1.42	-1.14	Au	DMF (0.1 M TBAB)	Q	50
	4-OCH ₃	-1.44	-1.16	Au	DMF (0.1 M TBAB)	Q	50
	3-OCH ₃	-1.43	-1.15	Au	DMF (0.1 M TBAB)	Q	50
	4-Cl	-1.30	-1.02	Au	DMF (0.1 M TBAB)	Q	50
	4-CN	-1.30	-1.02	Au	DMF (0.1 M TBAB)	Q	50
1-Naphthoyl	$\text{C}(\text{O})\text{C}_{10}\text{H}_7^{\bullet}$	-1.35	-1.07	Au	DMF (0.1 M TBAB)	Q	50
<i>N,N</i> -Dimethyl Aminocarbonyl	$\text{C}(\text{O})\text{N}(\text{CH}_3)_2^{\bullet}$	-1.85	-1.62	Au	DMF (0.1 M TBAB)	Q	55
1-(4-Isobutyl phenyl)ethyl		-1.685	-1.64	GC	ACN (0.1 M TBAP)	Q	61
1-(6-Methoxy-2- naphthyl)ethyl		-1.622	-1.62	GC	ACN (0.1 M TBAP)	Q	61
1-(4- Biphenyl)ethyl		-1.40	-1.15	GC	ACN (0.1 M TBAP)	Q	61
Cyclopropenyl		-1.78		Au	ACN (0.1 M TBAP)	SHV	70
		-1.95		Pt	ACN (0.1 M TBAP)	SHV	70
	Trimethyl	-2.22		Pt	DMSO (0.1 M TBAP)	CV	129
		-2.28		Au	ACN (0.1 M TBAP)	SHV	70
		-2.20		Pt	ACN (0.1 M TBAP)	SHV	70
	Tripropyl	-2.30		Pt	DMSO (0.1 M TBAP)	CV	129
	Dipropylphenyl	-1.90		Au	ACN (0.1 M TBAP)	SHV	70
		-1.91		Pt	ACN (0.1 M TBAP)	SHV	70

Table 1 (continued)

Radical	Structure	$E_{1/2}(\text{R}^{\bullet}/\text{R}^{-})$ vs SCE	$E^0(\text{R}^{\bullet}/\text{R}^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
Cycloheptatrienyl	Triphenyl	−1.73		Pt	DMSO (0.1 M TBAP)	CV	129
		−1.66		Au	ACN (0.1 M TBAP)	SHV	70
		−1.60		Pt	ACN (0.1 M TBAP)	SHV	70
	Tri- <i>tert</i> -butyl	−2.12		Pt	DMSO (0.1 M TBAP)	CV	129
		−2.25		Au	ACN (0.1 M TBAP)	SHV	70
		−2.25		Pt	ACN (0.1 M TBAP)	SHV	70
		−1.51		Pt	DMSO (0.1 M TBAP)	CV	129
		−1.63		Au	ACN (0.1 M TBAP)	SHV	70
		−1.55		Pt	ACN (0.1 M TBAP)	SHV	70
Triphenylmethyl	CPh_3X	−1.05		Pt	DMSO (0.1 M TBAP)	CV	70
		−0.97		Au	ACN (0.1 M TBAP)	SHV	70
		−0.98		Pt	ACN (0.1 M TBAP)	SHV	70
			−1.20	Pt	DME (0.5 TBAP)	CV	27
	4-CH ₃		−1.24	Pt	DME (0.5 TBAP)	CV	27
	4,4'-CH ₃		−1.29	Pt	DME (0.5 TBAP)	CV	27
	4,4',4''-CH ₃		−1.36	Pt	DME (0.5 TBAP)	CV	27
	4,4',4''-Cl	−0.87		Pt	DMSO (0.1 M TBAP)	CV	129
	4-N(CH ₃) ₂	−1.22		Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''-N(CH ₃) ₂	−1.61		Pt	DMSO (0.1 M TBAP)	CV	129
	4-OCH ₃	−1.22		Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''-OCH ₃	−1.42		Pt	DMSO (0.1 M TBAP)	CV	129
	Methylbenzyl	CH ₃ $\cdot$ CHPh	−1.60	Au	ACN (0.1 M TBAP)	PM	88
		CH ₃ $\cdot$ CHPh	−1.59	Au	DMF (0.1 M TBAB)	Q	45
	Dimethylbenzyl	(CH ₃) ₂ $\cdot$ CPh	−1.73	Au	ACN (0.1 M TBAP)	PM	88
Ethylmethylbenzyl		(CH ₃) ₂ $\cdot$ CHPh	−1.59	Au	DMF (0.1 M TBAB)	Q	45
		Et(CH ₃) $\cdot$ CHPh	−1.59	Au	DMF (0.1 M TBAB)	Q	45
	Diphenylethyl	CH ₃ $\cdot$ CPh ₂	−1.34	Au	ACN (0.1 M TBAP)	PM	88
	Hydroxymethyl	$\cdot$ CH ₂ OH		Hg	ACN (0.3 M LiP)	LPE	75
	Hydroxyethyl	CH ₃ $\cdot$ CHOH		Hg	ACN (0.3 M LiP)	LPE	75
	Chloromethyl	$\cdot$ CH ₂ Cl		Hg	ACN (0.3 M LiP)	LPE	75
	Chlorofluoromethyl	$\cdot$ CHFCl		Hg	ACN (0.3 M LiP)	LPE	75
	Diffuoromethyl	$\cdot$ CHF ₂		Hg	ACN (0.3 M LiP)	LPE	75
	Dichloromethyl	$\cdot$ CHCl ₂		Hg	ACN (0.3 M LiP)	LPE	75
	Chlorodifluoromethyl	$\cdot$ CF ₂ Cl		Hg	ACN (0.3 M LiP)	LPE	75
	Dichlorofluoromethyl	$\cdot$ CFCl ₂		Hg	ACN (0.3 M LiP)	LPE	75
	Trifluoromethyl	$\cdot$ CF ₃		Hg	ACN (0.3 M LiP)	LPE	75
	Trichloromethyl	$\cdot$ CCl ₃		Hg	ACN (0.3 M LiP)	LPE	75
	Methoxymethyl	$\cdot$ CH ₂ OCH ₃	−1.3	Au	ACN (0.1 M TBAP)	PM	88
	Ethoxyethyl	$\cdot$ CH ₂ CH ₂ OEt	−1.2	Au	ACN (0.1 M TBAP)	PM	88
2-Hydroxypropyl		Me ₂ $\cdot$ COHMe ₂	−0.79	Au	ACN (0.1 M TBAP)	PM	88
		(Me) ₂ N $\cdot$ CH ₂	−2.0	Au	ACN (0.1 M TBAP)	PM	88
		Et ₂ N $\cdot$ CHCH ₃	−2.0	Au	ACN (0.1 M TBAP)	PM	88
		(PhCH ₂) ₂ N $\cdot$ CHPh	−1.79	Au	ACN (0.1 M TBAP)	PM	88
		$\cdot$ CH ₂ (CH ₃)NPh	−2.03	Au	ACN (0.1 M TBAP)	PM	88
		(CH ₃) ₂ $\cdot$ COH	−0.70	Au	ACN (0.1 M TBAP)	PM	89, 90
					ACN (0.3 M LiP)	LPE	81
	1,3-Dioxolan-2-yl	$\cdot$ C ₄ H ₇ O ₂	−1.2	Au	ACN (0.1 M TBAP)	PM	88
	1,3-Dioxolan-4-yl	$\cdot$ C ₄ H ₇ O ₂	−1.2	Au	ACN (0.1 M TBAP)	PM	88
	1,3,5-Dioxolan-2-yl	$\cdot$ C ₃ H ₅ O ₃	−1.1	Au	ACN (0.1 M TBAP)	PM	88
	1-Naphthylmethyl	$\cdot$ CH ₂ C ₁₀ H ₆ X					
		4-CO ₂ CH ₂ CH ₃	−0.71	Au	ACN (0.1 M TBAP)	PM	84
		3-CN	−0.87	Au	ACN (0.1 M TBAP)	PM	84
		4-CN	−0.55	Au	ACN (0.1 M TBAP)	PM	84
		4-H	−1.27	Au	ACN (0.1 M TBAP)	PM	84
		4-F	−1.33	Au	ACN (0.1 M TBAP)	PM	84
		4-CH ₃	−1.35	Au	ACN (0.1 M TBAP)	PM	84
		2-OCH ₃	−1.36	Au	ACN (0.1 M TBAP)	PM	84

(continued overleaf)

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^{\bullet}/R^{-})$ vs SCE	$E^0(R^{\bullet}/R^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
2-Naphthylmethyl Benzyl	4-OCH ₃	−1.55		Au	ACN (0.1 M TBAP)	PM	84
	4,7-OCH ₃	−1.55		Au	ACN (0.1 M TBAP)	PM	84
	[•] CH ₂ C ₁₀ H ₇ [•] CH ₂ C ₆ H ₄ X	−1.25		Au	ACN (0.1 M TBAP)	PM	84
	4-OCH ₃	−1.75		Au	ACN (0.1 M TBAP)	PM	89
	4-OCH ₃	−1.82		Au	ACN (0.1 M TBAP)	PM	90
	4-OCH ₃	−1.45	−1.43	Au	DMF (0.1 M TBAB)	Q	45
	4-CH ₃	−1.62		Au	ACN (0.1 M TBAP)	PM	89, 90
	4-CH ₃	−1.46		Hg	ACN (0.1 M TEAP)	LPE	77
	4-CH ₃	−1.43		Hg	DMF (0.1 M TEAP)	LPE	77
	4-CH ₃	−1.39		Au	DMSO (0.1 M TEAP)	LPE	77
	3-CH ₃	−1.35		Hg	ACN (0.1 M TBAP)	PM	89, 90
	3-CH ₃	−1.31		Au	DMF (0.1 M TEAP)	LPE	77
	3-CH ₃	−1.36		Hg	DMSO (0.1 M TEAP)	LPE	77
	H	−1.43		Au	ACN (0.1 M TBAP)	PM	89, 90
	H	−1.35		Hg	ACN (0.1 M TEAP)	LPE	77
	H	−1.34		Au	DMF (0.1 M TEAP)	LPE	77
	H	−1.32		Hg	DMSO (0.1 M TEAP)	LPE	77
	H	−1.42	−1.40	Au	DMF (0.1 M TBAB)	Q	45
	H		−1.45	Au	ACN (0.1 M TBAP)	PM	88
	H	−1.45		Au	ACN (0.1 M TBAB)	PM	100
	H	−1.44		Au	DMF (0.1 M TBAB)	PM	100
	H	−1.09		Au	DMSO (0.1 M TBAB)	PM	100
	4-F	−1.50		Au	ACN (0.1 M TBAP)	PM	89, 90
	3-CF ₃	−1.20		Hg	ACN (0.1 M TEAP)	LPE	77
	3-CF ₃	−1.04		Au	DMF (0.1 M TEAP)	LPE	77
	3-CF ₃	−1.16		Hg	DMSO (0.1 M TEAP)	LPE	77
	4-CF ₃	−0.89		Au	DMF (0.1 M TEAP)	LPE	77
	4-Cl	−1.40		Au	ACN (0.1 M TBAP)	PM	89, 90
	4-Cl	−1.28		Hg	DMF (0.1 M TEAP)	LPE	77
	4-Cl	−1.46	−1.44	Au	DMF (0.1 M TBAB)	Q	45
	4-C(O)CH ₃	−0.71		Au	ACN (0.1 M TBAP)	PM	89, 90
	3-CN	−1.11		Au	ACN (0.1 M TBAP)	PM	89, 90
	3-CN	−1.14		Hg	DMF (0.1 M TEAP)	LPE	77
	3-CN	−1.15		Hg	DMSO (0.1 M TEAP)	LPE	77
	4-CN	−0.77		Au	ACN (0.1 M TBAP)	PM	89, 90
	4-CN	−0.91		Hg	ACN (0.1 M TEAP)	LPE	77
	4-CN	−0.69		Au	DMF (0.1 M TEAP)	LPE	77
	4-CN	−0.93		Hg	DMSO (0.1 M TEAP)	LPE	77
Cumyl	(CH ₃) ₂ [•] CC ₆ H ₄ X						
	4-OCH ₃	−1.87		Au	ACN (0.1 M TBAP)	PM	90
	4- <i>i</i> Pr	−1.85		Au	ACN (0.1 M TBAP)	PM	90
	3- <i>i</i> Pr	−1.83		Au	ACN (0.1 M TBAP)	PM	90
	H	−1.73		Au	ACN (0.1 M TBAP)	PM	90
	3-CN	−1.39		Au	ACN (0.1 M TBAP)	PM	90
	3-CF ₃	−1.54		Au	ACN (0.1 M TBAP)	PM	90
	4-CN	−1.01		Au	ACN (0.1 M TBAP)	PM	90
Diphenylmethyl	CH ₃ [•] CPh ₂ X						
	4-OCH ₃	−1.33		Au	ACN (0.1 M TBAP)	PM	90
	4,4'-(CH ₃) ₂	−1.25		Au	ACN (0.1 M TBAP)	PM	90
	2-OCH ₃	−1.27		Au	ACN (0.1 M TBAP)	PM	90
	4-CH ₃	−1.18		Au	ACN (0.1 M TBAP)	PM	90
	H	−1.14		Au	ACN (0.1 M TBAP)	PM	90
	H	−1.11		Au	DMF (0.1 M TEAP)	LPE	78
	H	−1.09	−1.07	Au	DMF (0.1 M TBAB)	Q	45
	H	−1.14		Au	ACN (0.1 M TBAP)	PM	88
	3-CN	−0.91		Au	ACN (0.1 M TBAP)	PM	90
	4-CN	−0.72		Au	ACN (0.1 M TBAP)	PM	90

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^+/R^-)$ vs SCE	$E^0(R^+/R^-)$ vs SCE	Electrode material	Solvent	Techniques	Reference
9-Fluorenyl	$\cdot C_{13}H_9$	−0.76		Au	ACN (0.1 M TBAP)	PM	88
9-Anthrylmethyl	$\cdot C_{15}H_{12}$		−1.02	Au	DMF (0.1 M TEAP)	LPE	78
9-Phenoxy-10-phenylanthracene	$\cdot C_{26}H_{19}O_2$	−0.85		GC	ACN (0.1 M TEAP)	Q	53
	$\cdot CH_2CO_2CH_2CH_3$		−0.63	GC	ACN (0.1 M TEAB)	Q	63
	$\cdot CH(CH_3)CO_2CH_3$		−0.66	GC	ACN (0.1 M TEAB)	Q	63
Phenyl	$\cdot C_6H_4X$						
	4-H		0.05	GC	ACN(0.1 M TBAB)	CV	124
	4- H	−1.35		Hg	W (0.5 M KCl)	LPE	76
	4-CH ₃		−0.02	GC	ACN(0.1 M TBAB)	CV	124
	3-N(CH ₃) ₃	−1.06		Hg	W (0.5 M KCl)	LPE	76
	4-N(CH ₃) ₃	−1.06		Hg	W (0.5 M KCl)	LPE	76
	3-CH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	4-CH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	3-OCH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	4-OCH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	3-OCH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	4-OCH ₃	−1.35		Hg	W (0.5 M KCl)	LPE	76
	CH ₃ COC•HCOCH ₃	0.92		Pt	DMSO (0.1 M LiP)	CV	131
	CH ₃ COC•HCO ₂ Et	0.81		Pt	DMSO (0.1 M LiP)	CV	131
	EtO ₂ CC•HCO ₂ Et	0.82		Pt	DMSO (0.1 M LiP)	CV	131
	EtO ₂ CC•CH ₃ CO ₂ Et	0.46		Pt	DMSO (0.1 M LiP)	CV	131
Cyanomethyl	$\cdot CH_2CN$		−0.69	GC	DMF (0.1 M TBAI)	Q	62
	$\cdot CH_2CN$		−0.72	GC	ACN (0.1 M TEAB)	Q	63
Dicyanomethyl	NC•CHCN	0.465		Pt	DMSO (0.1 M LiP)	CV	131
Dicyanoethyl	NC•CHCH ₂ CN	0.165		Pt	DMSO (0.1 M LiP)	CV	131
Diamidomethyl	(NH ₂ CO) ₂ C•H	0.23		Pt	DMSO (0.1 M LiP)	CV	131
Diamidoethyl	(NH ₂ CO) ₂ C•HCH ₃	−0.095		Pt	DMSO (0.1 M LiP)	CV	131
Dicyanomethyl	(NC) ₂ CH•COCH ₃	1.19		Pt	DMSO (0.1 M LiP)	CV	131
	MeC•HCNCHO	0.37		Pt	DMSO (0.1 M LiP)	CV	131
	EtC•HCNCHO	0.355		Pt	DMSO (0.1 M LiP)	CV	131
	PrC•HCNCHO	0.345		Pt	DMSO (0.1 M LiP)	CV	131
	BuC•HCNCHO	0.515		Pt	DMSO (0.1 M LiP)	CV	131
	PhCOC•HCHO	0.69		Pt	DMSO (0.1 M LiP)	CV	131
	MeO PhCOC•HCHO	0.51		Pt	DMSO (0.1 M LiP)	CV	131
	PhCOC•HCH ₃ CHO	0.455		Pt	DMSO (0.1 M LiP)	CV	131
	PhCOC•HCOOEt	0.89		Pt	DMSO (0.1 M LiP)	CV	131
XPhC•HCNCHO	H	0.41		Pt	DMSO (0.1 M LiP)	CV	131
	4-CH ₃	0.32		Pt	DMSO (0.1 M LiP)	CV	131
	4-OCH ₃	0.23		Pt	DMSO (0.1 M LiP)	CV	131
	α -Naphthyl	0.40		Pt	DMSO (0.1 M LiP)	CV	131
	Beta naphthyl	0.38		Pt	DMSO (0.1 M LiP)	CV	131
	4-CN	0.42		Pt	DMSO (0.1 M LiP)	CV	131
XPhC•HCNCOMe	H	0.315		Pt	DMSO (0.1 M LiP)	CV	131
	4-Cl	0.37		Pt	DMSO (0.1 M LiP)	CV	131
	4-CH ₃	0.28		Pt	DMSO (0.1 M LiP)	CV	131
	4-OCH ₃	0.17		Pt	DMSO (0.1 M LiP)	CV	131
	H	0.23		Pt	DMSO (0.1 M LiP)	CV	131
XPhC•HCNCO ₂ Et	4-Cl	0.325		Pt	DMSO (0.1 M LiP)	CV	131
	4-CH ₃	0.165		Pt	DMSO (0.1 M LiP)	CV	131
	4-OCH ₃	0.08		Pt	DMSO (0.1 M LiP)	CV	131
XPhCHCNCOPh	H	0.385		Pt	DMSO (0.1 M LiP)	CV	131
	4-Cl	0.455		Pt	DMSO (0.1 M LiP)	CV	131
	4-CH ₃	0.295		Pt	DMSO (0.1 M LiP)	CV	131
	4-OCH ₃	0.20		Pt	DMSO (0.1 M LiP)	CV	131
Oxygen-centered radicals							
Butoxyl	$\cdot OC(CH_2)_3CH_3$		−0.20	GC	ACN (0.1 M TEAP)	T	132
			−0.15	GC	DMF (0.1 M TEAP)	T	132

(continued overleaf)

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^{\bullet}/R^{-})$ vs SCE	$E^0(R^{\bullet}/R^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
<i>tert</i> -Butoxyl	$\bullet\text{OC}(\text{CH}_3)_3$		−0.30	GC	ACN (0.1 M TEAP)	T	132
			−0.23	GC	DMF (0.1 M TEAP)	T	132
Cumyloxyl	$\bullet\text{OC}(\text{CH}_3)_2\text{Ph}$		−0.19	C, Hg	ACN (0.1 M TEAP)	CV	132
			−0.12	C, Hg	DMF (0.1 M TEAP)	CV	132
2-Methyl-1-phenyl- 2-propoxyl	$\bullet\text{OC}(\text{CH}_3)_2\text{CH}_2\text{Ph}$		−0.20	GC	ACN (0.1 M TEAP)	CV	52
			−0.13	GC	DMF (0.1 M TEAP)	CV	52
Triphenylmethoxyl	$\bullet\text{OCPh}_3$		−0.03	C, Hg	DMF (0.1 M TBAP)	CV	133
<i>tert</i> -Butylcarboxyl	$\bullet\text{OOC}(\text{CH}_3)_3$		0.82	GC	DMF (0.1 M TBAP)	CV	134
2-Naphthoxyl	$\bullet\text{OC}_{10}\text{H}_7$		0.65	Pt	ACN (0.1 M TBAP)	CV	135
Phenoxyl	$\bullet\text{OPhX}$		0.68	Pt	ACN (0.1 M TBAP)	CV	135
	4-Cl		0.81	Pt	ACN (0.1 M TBAP)	CV	135
	4-CN		1.00	Pt	ACN (0.1 M TBAP)	CV	135
	2-NO ₂		1.08	Pt	ACN (0.1 M TBAP)	CV	135
	4-NO ₂		1.18	Pt	ACN (0.1 M TBAP)	CV	135
	3,5-Di- <i>tert</i> -butyl		0.61	Pt	ACN (0.1 M TBAP)	CV	135
	2,3,5,6-Tetramethyl		0.30	Pt	ACN (0.1 M TBAP)	CV	135
	$\bullet\text{OC}_6\text{H}_4\text{CH}_2\text{Ph}$		0.67	Pt	ACN (0.1 M TBAP)	CV	135
Phenoxyl (R ₂ , R ₄ , R ₆)	$\bullet\text{OPh}$						
	Me, Me, Me		0.25		W, pH 9.2 > pK _a	PR	105
	Me, Me, Me	−0.205		Au	ACN (0.08 M TBAB)	PM	99
	H, <i>t</i> Bu, H		0.52		W, pH 9.2 > pK _a	PR	105
	Cl, Cl, Cl		0.64		W, pH 9.2 > pK _a	PR	105
	Br, Br, Br		0.64		W, pH 9.2 > pK _a	PR	105
	I, I, I		0.61		W, pH 9.2 > pK _a	PR	105
	MeO, H, MeO		0.23		W, pH 9.2 > pK _a	PR	105
	MeO, <i>t</i> Bu, MeO		0.23		W, pH 9.2 > pK _a	PR	105
	MeO, COO [−] , MeO		0.30		W, pH 9.2 > pK _a	PR	105
Phenoxyl (R ₄)	H		0.55		W, pH 9.2 > pK _a	PR	104
	H	0.159		Au	ACN (0.08 M TBAB)	PM	99
	Me		0.44		W, pH 9.2 > pK _a	PR	104
	Me	0.052		Au	ACN (0.08 M TBAB)	PM	99
	F		0.52		W, pH 9.2 > pK _a	PR	104
	Cl		0.56		W, pH 9.2 > pK _a	PR	104
	Br		0.58		W, pH 9.2 > pK _a	PR	104
	I		0.58		W, pH 9.2 > pK _a	PR	104
	MeO		0.30		W, pH 9.2 > pK _a	PR	104
	CO ₂ [−]		0.66		W, pH 9.2 > pK _a	PR	104
	MeCO		0.76		W, pH 9.2 > pK _a	PR	104
	CN		0.88		W, pH 9.2 > pK _a	PR	104
	NO ₂		0.98		W, pH 9.2 > pK _a	PR	104
		0.668		Au	ACN (0.08 M TBAB)	PM	99
	3-Me, 4-Me	0.032		Au	ACN (0.08 M TBAB)	PM	99
	2- <i>t</i> Bu, 6- <i>t</i> Bu	−0.151		Au	ACN (0.08 M TBAB)	PM	99
	2- <i>t</i> Bu, 4- <i>t</i> Bu, 6- <i>t</i> Bu	−0.295		Au	ACN (0.08 M TBAB)	PM	99
	2- <i>t</i> Bu, 4-OH, 5- <i>t</i> Bu	−0.374		Au	ACN (0.08 M TBAB)	PM	99
	2-OH, 3- <i>t</i> Bu, 5- <i>t</i> Bu	−0.061		Au	ACN (0.08 M TBAB)	PM	99
Phenylcarboxyl	$\bullet\text{OCOPhX}$						
	H		1.50	GC	DMF (0.1 M TBAP)	CV	135
	4-OCOCH ₃		1.56	GC	DMF (0.1 M TBAP)	CV	135
	4-COCH ₃		1.57	GC	DMF (0.1 M TBAP)	CV	135
	4-CN		1.58	GC	DMF (0.1 M TBAP)	CV	135
	3-NO ₂		1.43	GC	DMF (0.1 M TBAP)	CV	135
	4-NO ₂		1.48	GC	DMF (0.1 M TBAP)	CV	135
<i>t</i> BuNO•Ph <i>t</i> Bu			−1.16	GC	ACN (0.1 M TBAB)	CV	137

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^+/R^-)$ vs SCE	$E^0(R^+/R^-)$ vs SCE	Electrode material	Solvent	Techniques	Reference
<i>t</i> BuNO•PhCR(CH ₃) ₂	R = CO ₂ CH ₃		−1.03	GC	ACN (0.1 M TBAB)	CV	137
<i>t</i> BuNOPhR <i>t</i> Bu	R = 2-CO ₂ CH ₃	−1.18		GC	ACN (0.1 M TBAB)	CV	137
	R = 2-CO ₂ [−] K ⁺	−1.4		GC	ACN (0.1 M TBAB)	CV	137
9-Fluorenyl	H	−0.077		Pt	DMSO (0.1 M TEAB)	CV	140
	H	−0.028	0.047	Au	DMSO (0.3 M TBAB)	CVU	141
	2-OCH ₃	−0.072		Pt	DMSO (0.1 M TEAB)	CV	140
	2,7-OCH ₃	−0.078		Pt	DMSO (0.1 M TEAB)	CV	140
	3-OCH ₃	−0.199		Pt	DMSO (0.1 M TEAB)	CV	140
	2-CH ₃	−0.104		Pt	DMSO (0.1 M TEAB)	CV	140
	3-CH ₃	−0.142		Pt	DMSO (0.1 M TEAB)	CV	140
	2-F	0.029		Pt	DMSO (0.1 M TEAB)	CV	140
	3-F	−0.052		Pt	DMSO (0.1 M TEAB)	CV	140
	2-Br	0.079		Pt	DMSO (0.1 M TEAB)	CV	140
	2,7-Br	0.229		Pt	DMSO (0.1 M TEAB)	CV	140
	2-CN	0.179		Pt	DMSO (0.1 M TEAB)	CV	140
	2,7-CN	0.398		Pt	DMSO (0.1 M TEAB)	CV	140
	3-SCH ₃	−0.055		Pt	DMSO (0.1 M TEAB)	CV	140
	3-SPh	0.056		Pt	DMSO (0.1 M TEAB)	CV	140
	2-PhCO	0.100		Pt	DMSO (0.1 M TEAB)	CV	140
	2-S(O)CH ₃	0.158		Pt	DMSO (0.1 M TEAB)	CV	140
	2-SO ₂ CH ₃	0.117		Pt	DMSO (0.1 M TEAB)	CV	140
	2-SO ₂ Ph	0.200		Pt	DMSO (0.1 M TEAB)	CV	140
	3-SO ₂ Ph	0.296		Pt	DMSO (0.1 M TEAB)	CV	140
	9-Ph	−0.036		Pt	DMSO (0.1 M TEAB)	CV	140
		0.017	0.039	Au	DMSO (0.3 M TBAB)	CVU	141
	9-OCH ₃	−0.332		Pt	DMSO (0.1 M TEAB)	CV	140
		−0.283	−0.208	Au	DMSO (0.3 M TBAB)	CVU	141
	9-CH ₃	−0.238		Pt	DMSO (0.1 M TEAB)	CV	140
		−0.190	−0.115	Au	DMSO (0.3 M TBAB)	CVU	141
	9-N(CH ₃) ₂		−0.443	Pt	DMSO (0.1 M TEAB)	CV	140
	9-CH(CH ₃) ₂	−0.149	−0.133	Au	DMSO (0.3 M TBAB)	CVU	141
	9-(CH ₃) ₃	−0.231	−0.083	Au	DMSO (0.3 M TBAB)	CVU	141
	9-OPh	−0.139		Pt	DMSO (0.1 M TEAB)	CV	140
	9-SCH ₃	−0.019		Pt	DMSO (0.1 M TEAB)	CV	140
	9-SPh	0.143		Pt	DMSO (0.1 M TEAB)	CVU	140
		0.196	0.273	Au	DMSO (0.3 M TBAB)	CV	141
	9-CN	0.544		Pt	DMSO (0.1 M TEAB)	CV	140
	9-CONH ₂	0.480		Pt	DMSO (0.1 M TEAB)	CV	140
	9-OCOCH ₃	0.500		Pt	DMSO (0.1 M TEAB)	CV	140
	9-PhSO ₂	0.683		Pt	DMSO (0.1 M TEAB)	CV	140
	9-(4-PhCH ₃)	−0.142		Pt	DMSO (0.1 M TEAB)	CV	140
	9-(2-PhCH ₃)	−0.051		Pt	DMSO (0.1 M TEAB)	CV	140
	9-(2,4,6-PhMe ₃)	−0.057		Pt	DMSO (0.1 M TEAB)	CV	140
Phenylcyanomethyl	CN•CHC ₆ H ₄ X						
	H	0.056		Pt	DMSO (0.1 M TEAB)	CV	140
	H	−0.54		Au	ACN (0.1 M TBAP)	PM	91
	4-N(CH ₃) ₃	−0.276		Pt	DMSO (0.1 M TEAB)	CV	140
	4-OCH ₃	−0.112		Pt	DMSO (0.1 M TEAB)	CV	140
	4-OCH ₃	−0.73		Au	ACN (0.1 M TBAP)	PM	91
	4-CH ₃	−0.019		Pt	DMSO (0.1 M TEAB)	CV	140
	3-CH ₃	0.062		Pt	DMSO (0.1 M TEAB)	CV	140
	4-F	0.047		Pt	DMSO (0.1 M TEAB)	CV	140
	3-OCH ₃	−0.083		Pt	DMSO (0.1 M TEAB)	CV	140
	4-Ph	−0.092		Pt	DMSO (0.1 M TEAB)	CV	140

(continued overleaf)

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^{\bullet}/R^{-})$ vs SCE	$E^0(R^{\bullet}/R^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
	4-Cl	0.144		Pt	DMSO (0.1 M TEAB)	CV	140
	3-F	0.200		Pt	DMSO (0.1 M TEAB)	CV	140
	4-PhS	0.166		Pt	DMSO (0.1 M TEAB)	CV	140
	3-Cl	0.254		Pt	DMSO (0.1 M TEAB)	CV	140
	3-CF ₃	0.284		Pt	DMSO (0.1 M TEAB)	CV	140
	3-CN	0.296		Pt	DMSO (0.1 M TEAB)	CV	140
	3,4-Cl	0.290		Pt	DMSO (0.1 M TEAB)	CV	140
	3-PhSO ₂	0.317		Pt	DMSO (0.1 M TEAB)	CV	140
	4-CF ₃	0.335		Pt	DMSO (0.1 M TEAB)	CV	140
Phenylmethoxymethyl	CH ₃ O•CHC ₆ H ₄ X						
	H	−1.79		Au	ACN (0.1 M TBAP)	PM	91
	4-CN	−1.13		Au	ACN (0.1 M TBAP)	PM	91
	4-OCH ₃	< −2.0		Au	ACN (0.1 M TBAP)	PM	91
Nitrogen-centered radicals							
Imidazolyl		0.97		Pt	ACN (0.1 M TBAP)	CV	136
Pyrazolyl		1.23		Pt	ACN (0.1 M TBAP)	CV	136
3-Methylpyrazolyl		1.08		Pt	ACN (0.1 M TBAP)	CV	136
4-Nitropyrazolyl		2.01		Pt	ACN (0.1 M TBAP)	CV	136
1,2,3-Triazolyl		1.60		Pt	ACN (0.1 M TBAP)	CV	136
1,2,4-Triazolyl-5-nitro		2.47		Pt	ACN (0.1 M TBAP)	CV	136
1,2,4-Triazolyl		1.67		Pt	ACN (0.1 M TBAP)	CV	136
1,2,3,4-Tetrazolyl		2.45		Pt	ACN (0.1 M TBAP)	CV	136
1,2,3,4-Tetrazolyl		1.93		Pt	ACN (0.1 M TBAP)	CV	136
5-Phenyl							
Indole		1.22		Pt	ACN (0.1 M TBAP)	CV	136
Adenosine		1.80	2.27		W, pH 5	PR	107
Guanosine		1.53	1.82		W, pH 7	PR	107
Adenine		1.70		GC	ACN (0.1 M TBAH)	CV	138
Guanine		1.25		GC	ACN (0.1 M TBAH)	CV	138
Cytosine		1.88		GC	ACN (0.1 M TBAH)	CV	138
Thymine		1.85		GC	ACN (0.1 M TBAH)	CV	138
Uracil		2.13		GC	ACN (0.1 M TBAH)	CV	138
8-Oxo-7,8-dihydro-2'-Deoxyadenosine			0.65		W	PR	139
8-Oxo-7,8-dihydro-2'-Deoxyguanosine			0.55		W	PR	139
8-Oxo-7,8-dihydro-2'-Deoxyguanosine			0.50		W, pH 5	PR	107
Verdazyl, methylene	*NNR ₁ CH ₂ N R ₂ N=CR ₃						
	H, H, H		−0.82		ACN (0.1 M TBAB)	CV	35
	OCH ₃ , OCH ₃ , OCH ₃		−0.92		ACN (0.1 M TBAB)	CV	35
	CH ₃ , CH ₃ , CH ₃		−0.88		ACN (0.1 M TBAB)	CV	35
	H, H, CH ₃		−0.85		ACN (0.1 M TBAB)	CV	35
	Cl, Cl, CH ₃		−0.73		ACN (0.1 M TBAB)	CV	35
	CH ₃ , CH ₃ , OCH ₃	−0.85			ACN (0.1 M TBAB)	CV	35
	CH ₃ , CH ₃ , H		−0.86		ACN (0.1 M TBAB)	CV	35
	CH ₃ , CH ₃ , Cl		−0.85		ACN (0.1 M TBAB)	CV	35
Verdazyl	*NNR ₁ CON R ₂ N=CR ₃						35
	Ph, Ph, Ph		−0.53		ACN (0.1 M TBAB)	CV	35
	CH ₃ , CH ₃ , Ph		−0.87		ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, Ph		−0.94		ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, 2-pyridyl		−0.95		ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, 2-imidazolyl	−0.84			ACN (0.1 M TBAB)	CV	35

Table 1 (continued)

Radical	Structure	$E_{1/2}(R^+/R^-)$ vs SCE	$E^0(R^+/R^-)$ vs SCE	Electrode material	Solvent	Techniques	Reference
	<i>i</i> Pr, <i>i</i> Pr, <i>N</i> -methyl-2-imidazolyl		−0.90		ACN (0.1 M TBAB)	CV	35
Sulfur and selenium-centered radicals							
Methanethiyl	*SCH ₃	−0.40		Au	DMF (0.1 M TBAB)	CV	57
2-Methyl-2-propylthiyl	*SC(CH ₃) ₃	−0.13		Au	DMF (0.1 M TBAB)	CV	57
Phenylthiyl	*SC ₆ H ₄ X						
	4-NH ₂	−0.34		Au	ACN (0.1 M TBAB)	PM	97
	4-OCH ₃	−0.06	−0.035	Au	ACN (0.1 M TBAB)	PM	97
	4-OCH ₃		−0.035	Au	ACN (0.1 M TEAB)	CV	73
	4-CH ₃	0.07	0.040	Au	ACN (0.1 M TBAB)	PM	97
	4-CH ₃		0.040	Au	ACN (0.1 M TEAB)	CV	73
	4-F	0.15		Au	ACN (0.1 M TBAB)	PM	97
	4-H	0.16	0.07	Au	ACN (0.1 M TBAB)	PM	97
	4-H	0.050	0.100	Au	ACN (0.1 M TEAB)	CV	73
	4-Cl	0.23	0.180	Au	ACN (0.1 M TBAB)	PM	97
	4-Cl	0.100	0.180	Au	ACN (0.1 M TEAB)	CV	73
	4-COOCH ₃	0.43		Au	ACN (0.1 M TBAB)	PM	97
	4-CN	0.42		Au	ACN (0.1 M TBAB)	PM	97
	4-NO ₂	0.410	0.455	Au	ACN (0.1 M TEAB)	CV	73
	4-NO ₂	0.81		Au	ACN (0.1 M TBAP)	CV	136
	*SCH ₂ CH ₂ OH	0.12		Au	ACN (0.1 M TBAP)	CV	136
Benzoylthiyl	*SC(O)PhX						
	4-OCH ₃		0.95		W (phosphate buffer)	PR	110
	4-CH ₃		0.93		W (phosphate buffer)	PR	110
	H		0.97		W (phosphate buffer)	PR	110
	4-CF ₃		1.04		W (phosphate buffer)	PR	110
	4-CN		0.99		W (phosphate buffer)	PR	110
Naphthalene-2-thioxy			0.58	Pt	ACN (0.1 M TBAP)	CV	136
Pyridine-2-thioxy			0.45	Pt	ACN (0.1 M TBAP)	CV	136
Phenylselanyl	*SeC ₆ H ₄ X						
	N(CH ₃) ₂	−0.28	−0.34	C	ACN (0.1 M TBAB)	PM	96
	OCH ₃	−0.15	−0.14	C	ACN (0.1 M TBAB)	PM	96
	CH ₃	−0.13	−0.10	C	ACN (0.1 M TBAB)	PM	96
	F	−0.06	−0.03	C	ACN (0.1 M TBAB)	PM	96
	H	−0.06	−0.04	C	ACN (0.1 M TBAB)	PM	96
	Cl	−0.05	0.02	C	ACN (0.1 M TBAB)	PM	96
	Br	−0.02	−0.01	C	ACN (0.1 M TBAB)	PM	96
	CN	0.05	0.17	C	ACN (0.1 M TBAB)	PM	96
	NO ₂	0.09	0.16	C	ACN (0.1 M TBAB)	PM	96
Silicon and germanium-centered radicals							
Triphenylsilyl	*SiPh ₃	−1.39		C	ACN (0.1 M TBAP)	CV	95
Triphenylgermyl	*GePh ₃		−0.61	C	ACN (0.1 M TBAP)	CV	95
Triphenylstannyl	*SnPh ₃	−0.51	−0.54	C	DMSO (0.1 M TBAP)	CV	95
			−0.46	C	ACN (0.1 M TBAP)		
Tributylstannyl	*SnBu ₃	−1.12	−0.93	C	ACN (0.1 M TBAP)	CV	95
				C	DMSO (0.1 M TBAP)		

C, carbon; GC, glassy carbon; Au, gold; Pt, platinum; Hg, mercury; ACN, acetonitrile; DME, dimethoxyethane; DMF, *N,N'*-dimethylformamide; DMSO, dimethylsulfoxide; W, water; TBAB, tetrabutylammonium fluoroborate; TBAP, tetrabutylammonium perchlorate; TBAH, tetrabutylammonium hexafluorophosphate; TEAP, tetraethylammonium perchlorate; LiP, lithium perchlorate; CV, cyclic voltammetry with microelectrode; CVU, cyclic voltammetry with ultramicroelectrode at fast scans; Q, competition Q technique; SHV, second harmonic AC voltammetry; PR, pulse radiolysis; PM, photomodulation voltammetry; LPE, laser photoinjection electron; T, thermochemical cycle.

Table 2 Oxidation and standard potentials of radicals.

Radical	Structure	$E_{1/2}(\text{R}^\bullet/\text{R}^+)$ vs SCE	$E^0(\text{R}^\bullet/\text{R}^-)$ vs SCE	Electrode material	Solvent	Techniques	Reference
Carbon-centered radicals							
<i>tert</i> -Butyl	$\text{C}(\text{CH}_3)_3$	0.09		Au	ACN (0.1 M TBAP)	PM	88
Cyclopropenyl		−0.62		Au	ACN (0.1 M TBAP)	SHV	70
		−0.23		Pt	ACN (0.1 M TBAP)	SHV	70
	Trimethyl	−1.32		Pt	DMSO (0.1 M TBAP)	CV	129
		−1.74		Au	ACN (0.1 M TBAP)	SHV	70
		−1.16		Pt	ACN (0.1 M TBAP)	SHV	70
	Tripropyl	−1.36		Pt	DMSO (0.1 M TBAP)	CV	129
	Dipropylphenyl	−1.16		Au	ACN (0.1 M TBAP)	SHV	70
		−1.17		Pt	ACN (0.1 M TBAP)	SHV	70
	Triphenyl	−0.72		Pt	DMSO (0.1 M TBAP)	CV	129
		−0.72		Au	ACN (0.1 M TBAP)	SHV	70
		−0.85		Pt	ACN (0.1 M TBAP)	SHV	70
	Triphenylmethyl	−0.85		Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''-Cl		0.23	Pt	DMSO (0.1 M TBAP)	CV	129
	4-N(CH ₃) ₂		−0.35	Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''-N(CH ₃) ₂		−0.74	Pt	DMSO (0.1 M TBAP)	CV	129
	4-OCH ₃		0.09	Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''-OCH ₃		−0.07	Pt	DMSO (0.1 M TBAP)	CV	129
	4,4',4''- <i>t</i> Bu	−1.53		Pt	DMSO (0.1 M TBAP)	CV	129
		−1.65		Au	ACN (0.1 M TBAP)	SHV	70
		−1.69		Pt	ACN (0.1 M TBAP)	SHV	70
Cycloheptatrienyl		−0.23		Pt	DMSO (0.1 M TBAP)	CV	129
		−0.16		Au	ACN (0.1 M TBAP)	SHV	70
		−0.18		Pt	ACN (0.1 M TBAP)	SHV	70
1-Naphthylmethyl	4-CO ₂ CH ₂ CH ₃	0.81		Au	ACN (0.1 M TBAP)	PM	84
	3-CN	0.79		Au	ACN (0.1 M TBAP)	PM	84
	4-CN	0.72		Au	ACN (0.1 M TBAP)	PM	84
	3-OCH ₃	0.52		Au	ACN (0.1 M TBAP)	PM	84
	H	0.47		Au	ACN (0.1 M TBAP)	PM	84
	4-F	0.46		Au	ACN (0.1 M TBAP)	PM	84
	4-CH ₃	0.35		Au	ACN (0.1 M TBAP)	PM	84
	2-OCH ₃	0.13		Au	ACN (0.1 M TBAP)	PM	84
	4-OCH ₃	0.04		Au	ACN (0.1 M TBAP)	PM	84
	4,8-OCH ₃	−0.05		Au	ACN (0.1 M TBAP)	PM	84
	4,5-OCH ₃	−0.05		Au	ACN (0.1 M TBAP)	PM	84
	4,7-OCH ₃	−0.06		Au	ACN (0.1 M TBAP)	PM	84
2-Naphthylmethyl	H	0.61		Au	ACN (0.1 M TBAP)	PM	84
9-Hydroxyfluorenyl	$\text{C}_{13}\text{H}_8\text{OH}$	0.38		Au	ACN (0.1 M TBAP)	PM	98
<i>N</i> -Methylacridine		−0.45	−0.41	Au	ACN (0.1 M TBAP)	PM	92
3-Cyano-1,4-dihydro-4-quinolyl							
	<i>N</i> -Methyl	−0.56	−0.53	Au	ACN (0.1 M TBAP)	PM	92
	<i>N</i> -Phenyl	−0.52	−0.49	Au	ACN (0.1 M TBAP)	PM	92
<i>N</i> -Benzyl-1,4-dihydro-4-pyridyl							
	3-CN	−0.84	−0.82	Au	ACN (0.1 M TBAP)	PM	92
	3-C(O)CH ₃	−0.99	−0.97	Au	ACN (0.1 M TBAP)	PM	92
	3-C(O)NH ₂	−1.13	−1.08	Au	ACN (0.1 M TBAP)	PM	92
Cyanobenzyl	4-CN	1.63		Au	ACN (0.1 M TBAP)	PM	91
	H	1.29		Au	ACN (0.1 M TBAP)	PM	91
	4-OCH ₃	0.70		Au	ACN (0.1 M TBAP)	PM	91
Methoxybenzyl	4-CN	0.10		Au	ACN (0.1 M TBAP)	PM	91
	H	−0.33		Au	ACN (0.1 M TBAP)	PM	91
	4-OCH ₃	−0.51		Au	ACN (0.1 M TBAP)	PM	91

Table 2 (continued)

Radical	Structure	$E_{1/2}(\text{R}^{\bullet}/\text{R}^{+})$ vs SCE	$E^0(\text{R}^{\bullet}/\text{R}^{-})$ vs SCE	Electrode material	Solvent	Techniques	Reference
Benzyl	$\text{CH}_2\text{C}_6\text{H}_4\text{X}$						
	4-OCH ₃	0.26		Au	ACN (0.1 M TBAP)	PM	90
	4-OPh	0.45		Au	ACN (0.1 M TBAP)	PM	90
	3-CH ₃	0.70		Au	ACN (0.1 M TBAP)	PM	90
	4-CH ₃	0.51		Au	ACN (0.1 M TBAP)	PM	90
	H	0.73		Au	ACN (0.1 M TBAP)	PM	88, 90
	H	0.74		Au	ACN (0.1 M TBAB)	PM	100
	H	0.63		Au	DMF (0.1 M TBAB)	PM	100
	H	0.73		Au	DMSO (0.1 M TBAB)	PM	100
	4-F	0.73		Au	ACN (0.1 M TBAP)	PM	90
	4-Cl	0.80		Au	ACN (0.1 M TBAP)	PM	90
	4-C(O)CH ₃	0.90		Au	ACN (0.1 M TBAP)	PM	90
	3-CN	1.11		Au	ACN (0.1 M TBAP)	PM	90
	4-CN	1.08		Au	ACN (0.1 M TBAP)	PM	90
Cumyl	$(\text{CH}_3)_2\text{CC}_6\text{H}_4\text{X}$						
	4-OCH ₃	−0.14		Au	ACN (0.1 M TBAP)	PM	90
	4- <i>i</i> Pr	0.02		Au	ACN (0.1 M TBAP)	PM	90
	3- <i>i</i> Pr	0.10		Au	ACN (0.1 M TBAP)	PM	90
	H	0.16		Au	ACN (0.1 M TBAP)	PM	90
	3-OCH ₃	0.28		Au	ACN (0.1 M TBAP)	PM	90
	3-CN	0.34		Au	ACN (0.1 M TBAP)	PM	90
	3-CF ₃	0.41		Au	ACN (0.1 M TBAP)	PM	90
	4-CN	0.46		Au	ACN (0.1 M TBAP)	PM	90
Diphenylmethyl	$\text{CHr}_3\text{CPh}_2\text{X}$						
	4-OCH ₃	0.16		Au	ACN (0.1 M TBAP)	PM	90
	4,4'-(CH ₃) ₂	0.24		Au	ACN (0.1 M TBAP)	PM	90
	2-OCH ₃	0.27		Au	ACN (0.1 M TBAP)	PM	90
	4-CH ₃	0.32		Au	ACN (0.1 M TBAP)	PM	90
	H	0.35		Au	ACN (0.1 M TBAP)	PM	88, 90
	3-OCH ₃	0.38		Au	ACN (0.1 M TBAP)	PM	90
	3-CN	0.56		Au	ACN (0.1 M TBAP)	PM	90
	4-CN	0.72		Au	ACN (0.1 M TBAP)	PM	90
Propyl-2-hydroxyl	$\text{C}(\text{CH}_3)_2\text{OH}$	−0.61		Au	ACN (0.1 M TBAP)	PM	98
	CPh_2OH	−0.25		Au	ACN (0.1 M TBAP)	PM	98
	$\text{PhC}^+\text{CH}_3\text{OH}$	−0.24		Au	ACN (0.1 M TBAP)	PM	98
	$\text{CH}_3\text{C}_6\text{H}_4\text{C}^+\text{CH}_3\text{OH}$	−0.46		Au	ACN (0.1 M TBAP)	PM	98
	PhC^+HOH	−0.30		Au	ACN (0.1 M TBAP)	PM	98
	PhC^+CNOH	0.11		Au	ACN (0.1 M TBAP)	PM	98
	$\text{PhC}^+\text{CF}_3\text{OH}$	0.31		Au	ACN (0.1 M TBAP)	PM	98
	$\text{PhC}^+\text{CH}_3\text{OCH}_3$	−0.11		Au	ACN (0.1 M TBAP)	PM	98
	1,3-Dioxolan-2-yl	0.31		Au	ACN (0.1 M TBAP)	PM	88
	1,3-Dioxolan-4-yl	−0.34		Au	ACN (0.1 M TBAP)	PM	88
1,3,5-Dioxolan-2-yl	$\text{C}_3\text{H}_5\text{O}_3$	0.20		Au	ACN (0.1 M TBAP)	PM	88
Methylbenzyl	CH_2CHPh	0.37		Au	ACN (0.1 M TBAP)	PM	88
Dimethylbenzyl	$(\text{CH}_3)_2\text{CPh}$	0.16		Au	ACN (0.1 M TBAP)	PM	88
Diphenylethyl	CH_2CHPh_2	0.23		Au	ACN (0.1 M TBAP)	PM	88
9-Fluorenyl	C_{13}H_9	0.76		Au	ACN (0.1 M TBAP)	PM	88
Methoxymethyl	CH_2OCH_3	−0.24		Au	ACN (0.1 M TBAP)	PM	88
Ethoxyethyl	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$	−0.45		Au	ACN (0.1 M TBAP)	PM	88
	$(\text{CH}_3)_2\text{C}^+\text{OHC}(\text{CH}_3)_2$	−0.10		Au	ACN (0.1 M TBAP)	PM	88
	$(\text{CH}_3)_2\text{N}^+\text{CH}_2$	−1.03		Au	ACN (0.1 M TBAP)	PM	88
	$(\text{CH}_3\text{CH}_2)_2\text{N}^+\text{CHCH}_3$	−1.12		Au	ACN (0.1 M TBAP)	PM	88
	$(\text{PhCH}_2)_2\text{N}^+\text{CHPh}$	−0.92		Au	ACN (0.1 M TBAP)	PM	88
	$\text{CH}_2(\text{CH}_3)\text{NPh}$	−0.85		Au	ACN (0.1 M TBAP)	PM	88
$t\text{BuNO}^+\text{PhCR}(\text{Me})_2$	$\text{R} = \text{CO}_2\text{CH}_3$		0.87	GC	ACN (0.1 M TBAB)	CV	135

(continued overleaf)

Table 2 (continued)

Radical	Structure	$E_{1/2}(R^+/R^+)$ vs SCE	$E^0(R^+/R^-)$ vs SCE	Electrode material	Solvent	Techniques	Reference
<i>t</i> BuNO [•] PhRtBu	R = 2- CO ₂ CH ₃		0.90	GC	ACN (0.1 M TBAB)	CV	135
	R = 2- CO ₂ ⁻ K ⁺		0.33	GC	ACN (0.1 M TBAB)	CV	135
Perchlorophenalenyl	[•] C ₁₃ Cl ₉	0.97		Pt	ACN (0.1 M TBAH)	CV	33
Nitrogen-centered radicals							
Verdazyl	[•] NNR ₁ CON R ₂ N=CR ₃						
	Ph, Ph, Ph		0.85	GC	ACN (0.1 M TBAB)	CV	35
	CH ₃ CH ₃ Ph		0.68	GC	ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, Ph		0.59	GC	ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, 2-pyridyl		0.61	GC	ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, 2-imidazolyl		0.65	GC	ACN (0.1 M TBAB)	CV	35
	<i>i</i> Pr, <i>i</i> Pr, <i>N</i> -methyl-2-imidazolyl		0.64	GC	ACN (0.1 M TBAB)	CV	35
Verdazyl, methylene	[•] NNR ₁ CH ₂ N R ₂ N=CR ₃						
	H, H, H		0.19	GC	ACN (0.1 M TBAB)	CV	35
	OCH ₃ , OCH ₃ , OCH ₃		0.02	GC	ACN (0.1 M TBAB)	CV	35
	CH ₃ CH ₃ CH ₃		0.10	GC	ACN (0.1 M TBAB)	CV	35
	H, H, CH ₃		0.17	GC	ACN (0.1 M TBAB)	CV	35
	Cl, Cl, CH ₃		0.26	GC	ACN (0.1 M TBAB)	CV	35
	CH ₃ CH ₃ OCH ₃		0.11	GC	ACN (0.1 M TBAB)	CV	35
	CH ₃ CH ₃ H		0.12	GC	ACN (0.1 M TBAB)	CV	35
	CH ₃ CH ₃ Cl		0.15	GC	ACN (0.1 M TBAB)	CV	35
Sulfur and selenium-centered radicals							
Acetylthiyl	[•] SC(O)CH ₃		0.98		W, pH > 8	PR	109
Hydroxyethanethiyl	[•] SCH ₂ CH ₂ OH	-0.36		Pt	ACN (0.1 M TBAP)	CV	136
Phenylthiyl	[•] SC ₆ H ₄ X						
	4-NH ₂	0.35		Au	ACN (0.1 M TBAB)	PM	97
	4-OCH ₃	0.68		Au	ACN (0.1 M TBAB)	PM	97
	4-CH ₃	0.68	-0.035	Au	ACN (0.1 M TBAB)	PM	97
	4-F	0.79	0.040	Au	ACN (0.1 M TBAB)	PM	97
	4-H	0.79		Au	ACN (0.1 M TBAB)	PM	97
	4-Cl	0.90	0.07	Au	ACN (0.1 M TBAB)	PM	97
	4-Cl	0.62	0.180	Pt	ACN (0.1 M TBAP)	CV	136
	4-C(O)OCH ₃	0.86		Au	ACN (0.1 M TBAB)	PM	88
	4-CN	0.98		Au	ACN (0.1 M TBAB)	PM	88
	4-NO ₂		0.455	Pt	ACN (0.1 M TBAP)	CV	136
Phenylselanyl	[•] SeC ₆ H ₄ X						
	N(CH ₃) ₂	0.27		C	ACN (0.1 M TBAB)	PM	96
	OCH ₃	0.61		C	ACN (0.1 M TBAB)	PM	96
	CH ₃	0.62		C	ACN (0.1 M TBAB)	PM	96
	F	0.70		C	ACN (0.1 M TBAB)	PM	96
	H	0.70		C	ACN (0.1 M TBAB)	PM	96
	Cl	0.73		C	ACN (0.1 M TBAB)	PM	96
	Br	0.74		C	ACN (0.1 M TBAB)	PM	96
	CN	0.82		C	ACN (0.1 M TBAB)	PM	96
Silicon and tin-centered radicals							
Triphenylsilyl	[•] SiPh ₃	-0.41		Au	ACN (0.1 M TBAP)	CV	95
Tributylstannyl	[•] SnBu ₃	0.20		Au	ACN (0.1 M TBAP)	CV	95

C, carbon; GC, glassy carbon; Au, gold; Pt, platinum; ACN, acetonitrile; DMF, *N,N'*-dimethylformamide; DMSO, dimethylsulfoxide; W, water; TBAB, tetrabutylammonium fluoroborate; TBAP, tetrabutylammonium perchlorate; TBAH, tetrabutylammonium hexafluorophosphate; CV, cyclic voltammetry with microelectrode; SHV, second harmonic AC voltammetry; PR, pulse radiolysis; PM, photomodulation voltammetry.

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Overview of Radical Initiation

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1 INTRODUCTION

Different fields of chemistry require efficient and convenient methods for the generation of radicals that can be further used as initiating species in various chemical reactions. Radical initiators (RIs) can thus be considered as compounds that can produce free radicals under mild conditions to promote radical reactions. Many chemical approaches using free radical chemistry, as exemplified in the growing number of applications, have been developed for organic synthesis purposes; see also Volume 2 of this encyclopedia.^{1–5} Free radical polymerization reactions are also strongly affected by the nature of the initiators^{6,7} and some selected properties such as the control of the polymerization^{8,9} can be tuned by a careful choice of the initiating system; see also Volume 4 of this encyclopedia. Radicals are also involved in many important biological processes and a clean generation of these intermediates is often required for a better understanding of the associated mechanisms.^{10–20}

The generation of a radical can occur through several routes. The first one is referred to as homolysis and it requires RIs with relatively weak covalent bonds. The activation energy is provided by

1. heating (this is the most classical way),
2. light absorption (this is highly worthwhile for compounds bearing a suitable chromophore),
3. radiolysis (X-ray, γ irradiation, etc.) or sonolysis (these two approaches are not often used).

The second route where radicals are formed by redox reactions is very different. In such processes, an electron is transferred to (or from) a molecule possessing paired electrons, thereby generating a radical anion (or a radical cation); the fragmentation of this latter species leads to a radical and an anion (or a cation). Other routes are also employed: for example, the direct oxidation (or reduction) of an anion (or a cation) by electrochemical methods leading to the formation of a radical. The use of readily oxidizable compounds (e.g., organoboranes) that generate carbon-centered radicals in the presence of molecular oxygen has also been reported (see **Boron in Radical Chemistry**). This latter approach is very useful for low temperature experiments.

Owing to the broad area of free radical chemistry, many reviews or books are already available in the literature.^{1–20} In this article, representative RIs are described according to their different generation pathways. A detailed description of the application of these initiators in radical chemistry is provided in the other articles of this encyclopedia.

2 THERMOLYSIS

Thermolysis of an RI relates to a single bond cleavage upon heating. To operate at a temperature below 150 °C, the RI must not exhibit a dissociation energy exceeding 40 kcal mol^{–1}. This corresponds to a severe criterion for thermal initiators. Indeed, as

Table 1 Bond dissociation energies of representative single bonds.²¹

Single bonds	BDE (kcal mol ⁻¹)
CH₃-H	105
CH₃-CH₃	90.2
PhC(O)-OCH₃	97.9
(CH₃)₂CH-I	56.1
PhS-SPh	51.2
<i>t</i>BuO-OrBu	38.2
CF₃O-OCF₃	47.5

The chemical bond is given by the bold atoms.

shown in Table 1 where some typical representative data for the bond dissociation energy (BDE) of various typical single bonds are provided, it is clearly noted that C–C bonds are usually too strong for thermolysis. Obviously, BDEs are dramatically affected by the substituents so that these data can only be used as a general trend. Therefore, the functional groups that could fit the energy requirement are mainly based on heteroatom–heteroatom or carbon–heteroatom bonds such as in peroxides,

azo compounds, nitrite esters, halogen molecules, *N*-hydroxy-pyridine-2 thione esters, and so on.

RI, as a function of their structure (especially organic peroxides and azo compounds), might be inherently unstable. They are generally stored in a refrigerator and care should be taken while handling these compounds. A good compromise must be achieved for RIs: they must be stable at room temperature but should decompose under mild conditions to generate the targeted radicals.

2.1 Peroxides

The generation of radicals through thermolysis of peroxides has been used for a long time. The RO–OR bond is relatively weak, with a BDE of 35–50 kcal mol⁻¹ depending on the R substituents. This is less than half of the bond strength of the usual C–C, C–H, and C–O bonds (Table 1). The RO–OR bond easily breaks and forms alkoxy radicals (RO[•]):

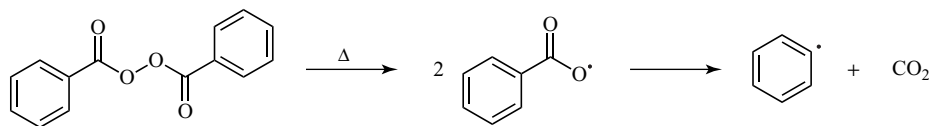
**Table 2** Decomposition rates (k_d in s⁻¹) and 10 hours half-life temperatures for typical commercial peroxides in benzene (except otherwise noted).^{6,7}

	k_d (s ⁻¹) (T , °C)	T for 10 h half-life (°C)
<i>Hydroperoxides</i>		
<i>tert</i> -Butyl hydroperoxide	3.0×10^{-7} (130)	170
Cumene hydroperoxide	4.0×10^{-7} (115)	135
1-Hydroperoxycyclohexyl-1-hydroxycyclohexyl peroxide	—	90
Peracetic acid (hydroperoxide)	—	135 ^a
<i>Peroxides</i>		
<i>tert</i> -Butyl peroxide	7.8×10^{-8} (80)	125
Dicumyl peroxide	—	115
1,1-Bis(<i>tert</i> -butylperoxy)-3,3,5-trimethylcyclohexane	—	85
Bis(1-(<i>tert</i> -butylperoxy)-1-methylethyl)benzene	—	115
2,5-Bis(<i>tert</i> -butylperoxy)-2,5-dimethyl-3-hexyne	—	125
2,5-Bis(<i>tert</i> -butylperoxy)-2,5-dimethylhexane	1.1×10^{-5} (115)	120
2,2-Bis(<i>tert</i> -butylperoxy)butane ^b	—	100
1,1-Bis(<i>tert</i> -butylperoxy)cyclohexane ^b	1.9×10^{-5} (93)	—
<i>Acyl peroxides</i>		
Benzoyl peroxide	2.0×10^{-6} (60)	70
Lauroyl peroxide	4.9×10^{-7} (40)	65
<i>tert</i> -Butyl peracetate ^b	1.2×10^{-6} (85)	100
<i>tert</i> -Amyl peroxybenzoate	—	99
<i>tert</i> -Butyl peroxybenzoate	1.1×10^{-5} (100)	103
<i>tert</i> -Butylperoxy isopropyl carbonate	—	98
<i>Peroxides usable in water</i>		
Potassium persulfate	6.9×10^{-5} (80) ^c	60 ^c

^aIn toluene.

^bCommercial compound often dissolved in a mineral oil.

^cIn water.

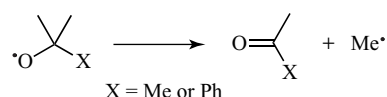


Scheme 1 Decomposition of benzoylperoxide.

A large number of chemical compounds of this type are commercially available. In fact, these structures belong to the most widely used initiators in free radical polymerization (see **Radical Polymerization in Industry**). Representative parameters (half-life temperature and decomposition rate) characterizing the bond cleavage process are gathered in Table 2. As can be seen from the table, there are initiators for basically any temperature regime. To ensure good radical production, a proper initiator has to be chosen in the experiment.

In diacylperoxides (RC(O)OOC(O)R), the formation of acyloxyl radicals is usually followed by a decarboxylation reaction (Scheme 1). These peroxides exhibit lower BDE(O–O) than most dialkylperoxides. This is related to the acyloxyl radicals that are stabilized by resonance, the unpaired electron being delocalized over both oxygen atoms. In diacylperoxides, the substituents have a rather low effect on the decomposition rate constants (Table 2); that is, benzoylperoxide and lauroyl peroxide (which are two of the most commonly employed diacylperoxides) exhibit quite similar decomposition parameters.

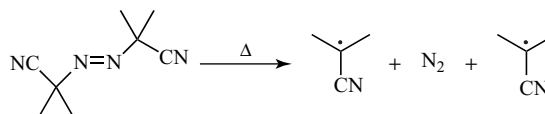
Some fast fragmentations for oxyl radicals can be observed (depending on their structures) because of the formation of a stable ketone; that is, for *t*BuO[•], fragmentation leads to a methyl radical (CH₃[•]) and acetone (Scheme 2). A similar process is also observed for cumyloxyl fragmentation (Scheme 2).^{10–16,22}



Scheme 2 Fragmentation processes for *t*BuO[•] and PhC(CH₃)₂O[•].

2.2 Azo Compounds

Azo compounds R–N=N–R act as precursors for different carbon-centered radicals (R[•]) and release N₂ upon heating (or by irradiation—see below). The formation of N₂ (characterized by a very strong triple bond) is the driving force for this cleavage process. The decomposition rate constant is strongly affected by the substituent (R) as this R-group can strongly stabilize the generated radical, thereby enhancing the efficiency of the dissociation process (Table 3). These compounds are widely used (among them, 2,2'-azobisisobutyronitrile, AIBN) to generate radicals under mild conditions both in organic synthesis and polymer science. For example, AIBN yields isobutyronitrile radicals (Scheme 3).



Scheme 3 Decomposition mechanism of 2,2'-azobisisobutyronitrile.

Table 3 Ten hours half-life temperature and decomposition rates (*k_d*) for typical commercial azo compounds.^{6,7}

Azo compounds	<i>k_d</i> (s ^{−1}) (<i>T</i> , °C)	<i>T</i> for 10 h half-life (°C)
2,2'-Azobisisobutyronitrile	2.2 × 10 ^{−6} (50)	65 ^a
1,1'-Azobis(cyclohexanecarbonitrile)	6.5 × 10 ^{−6} (80) ^a	88 ^a
2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile)	—	30 ^a
4,4-Azobis(4-cyanovaleic acid)	1.9 × 10 ^{−5} (69) ^b	69 ^b
2,2'-Azobis(2-methylpropionamidine)dihydrochloride	—	56 ^b

^a In toluene.

^b In water.

Unsymmetrical azo compounds obviously form two different radicals. Owing to in-cage recombination of the generated radicals, the amount of liberated radicals that are ready for chain initiation is far below the theoretical yield (for further discussion on that issue, see Section 2.6 of this article).

2.3 Initiators for Radical Chain Processes

Radical chain reactions are, meanwhile, frequently used as key steps in organic synthesis.^{1–5,23–26} A detailed description of these reactions is beyond the scope of this article and will be presented in other articles of this encyclopedia devoted to applications in chemical synthesis (see Volume 2).

The radicals generated by thermolysis of peroxides (see Section 2.1) or azo compounds (see Section 2.2) can act as initiating radicals ($\text{In}^\bullet$) for such radical chain processes. A hydrogen abstraction reaction between $\text{In}^\bullet$ and a given H-donor (R-H) that can start the radical chain reaction after H-transfer is required in a primary step as shown in reaction (3) for the reduction of an alkyl halide (R'-X) to the corresponding hydrocarbon (R'-H) (see reactions 4 and 5). The R-H compound must exhibit good hydrogen transfer properties to ensure an efficient reduction step.²⁷



Other useful synthetic reactions (cyclizations, reductions of xanthate, C–C bond formations, hydrosilylations, etc.) can also be conducted by radical chain processes (see **Xanthates and Related Derivatives as Radical Precursors**, **Silanes as Reducing Reagents in Radical Chemistry**, and **Radical Cascade Reactions**).

Tributyltin hydride is probably the most widely used reducing reagent R-H for conducting radical chain reactions (see **Tin Hydrides and Functional Group Transformations**). However, owing to the toxicity of this tin derivative, various promising radical chain reducing reagents have been

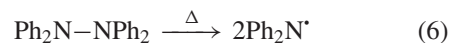
reported.^{28–31} Among them, silicon hydrides or germanium-based compounds appeared as the most interesting, for example, the popular tris(trimethylsilyl)silane, TTMSS (for an in-depth discussion, see **Silanes as Reducing Reagents in Radical Chemistry**). More recently, *N*-heterocyclic carbene–borane complexes were also proposed as tin hydride substitutes.^{32,33} Many kinetic parameters associated with the reduction process are available. For example, the rate constants for reaction (3) with $\text{In}^\bullet = t\text{BuO}^\bullet$ are available at room temperature for different H-donors (see part—hydrogen abstraction reaction).^{33–36}

2.4 Other Heteroatom–Heteroatom or Carbon–Metal Bond Containing Radical Initiators

As mentioned above, the C–C single bond is typically too strong for thermolysis (e.g., 90.2 kcal mol^{−1} for ethane; see Table 1). However, with appropriate substituents, some C–C bonds become susceptible to be cleaved thermally. This can be achieved by installing phenyl groups as substituents. For example, C-radicals can be easily generated by thermolysis of diphenyl(4-triphenylmethyl-2,5-cyclohexadien-1-ylidene)methane ($k_d \sim 3 \times 10^{-3} \text{ s}^{-1}$ at 273 K).³⁷ However, such a cleavage process is only efficient if highly stabilized C-radicals are generated. Therefore, most initiators operate by heteroatom–heteroatom or carbon–metal bond cleavage. In addition to peroxides and azo compounds (as discussed above), some other substance classes have found application as initiators, as discussed below.²⁰

2.4.1 Hydrazine Derivatives

Albeit the N–N bond in $\text{R}_2\text{N-NR}_2$ compounds ($\text{R} = \text{alkyl or H}$) is relatively strong, the BDEs of adequately substituted hydrazines are substantially reduced, allowing them to be used as RIs. For example, through the introduction of phenyl groups, tetraphenylhydrazine becomes an efficient precursor of diphenyl aminyl radicals.³⁸ The rate constant for the thermal decay of tetraphenylhydrazine is about $2 \times 10^{-4} \text{ s}^{-1}$ at 350 K in 1,2-dichlorobenzene:

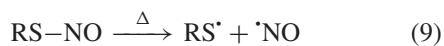


2.4.2 Nitrites and Nitrates (N–O Bond)

The thermolysis of the N–O bond of alkylnitrites and alkylnitrates has been intensively investigated. These compounds exhibit low N–O BDEs ($\sim 37 \text{ kcal mol}^{-1}$) and can generate alkoxyl radicals upon heating. Data on gas phase kinetics are available in the literature.^{39,40} The thermolysis of O-phenyl oxime ethers (through N–O cleavage) was reported as a route to iminyl radicals.⁴¹



Nitrosothiols or nitroso-*N*-acylamines are characterized by weak S–N or N–N bonds, respectively. In analogy to alkylnitrites, these compounds generate $\text{}^\bullet\text{NO}$ upon heating:



2.4.3 *N*-hydroxypyridine-2-thione esters (N–O Bond)

Various *N*-hydroxypyridine-2-thione esters have been applied as sources of carbon-centered radicals.⁴² However, they are generally decomposed by photolysis as they exhibit very suitable light absorption spectra covering the emission spectra of usual UV–visible lamps (i.e., Hg or Hg–Xe or Xe lamp). A more detailed description of the photochemical processes involved is given in Section 4 of this article.

2.4.4 Disulfides (S–S Bond)

The RS–SR' bond is relatively weak (particularly for R=Ar; Table 1) and can be cleaved by heating (reaction 10). The bond strength is strongly affected by the nature of the R/R' substituents. For symmetrical disulfides, only one type of radical is generated (2 equiv of the same thiyl radical).



For *p*-tolyl disulfide or 2,2'-dithiobisbenzothiazole, typical decomposition rate constants lie

in the range of $8 \times 10^{-6} - 2 \times 10^{-8} \text{ s}^{-1}$ at 350 K.⁴³ Under photolysis, a similar S–S bond cleavage process occurs (see Section 4).

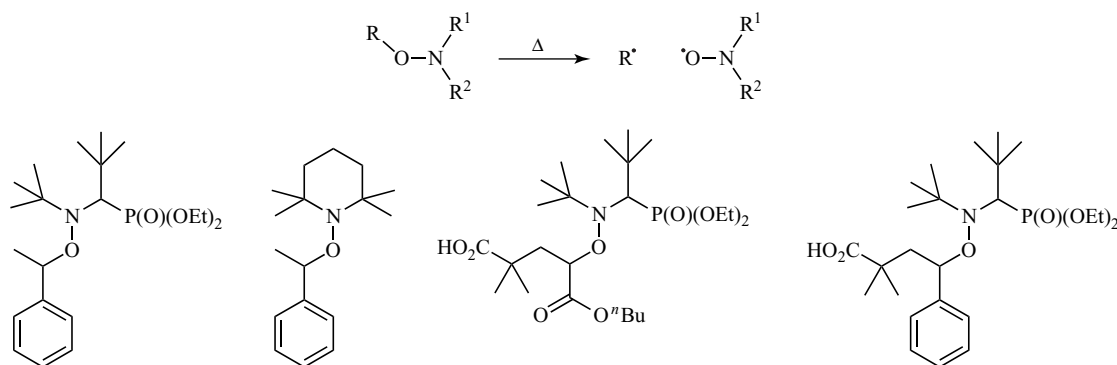
2.4.5 Organometallic Compounds (M–C Bond)

Some organometallic compounds are characterized by relatively weak metal carbon (M–C) bonds. Clean free radical formation is observed for XR_4 or XR_2 (with X = Sn or Hg and R = alkyl for example). However, these reactions mainly occur in the gas phase at a relatively high temperature (typically for $T > 450 \text{ K}$).^{44,45} Therefore, such compounds are generally not used as initiators in synthetic radical chemistry.

2.5 Persistent Radical Initiators

Persistent radicals have meanwhile found many applications in organic synthesis and polymer science. A detailed description of the persistent radical effect is given in other articles of this encyclopedia (see **Nitroxides in Synthetic Radical Chemistry**, **Nitroxide-Mediated Polymerization and its Applications**, and **Fundamentals of Controlled/Living Radical Polymerization**). Controlled polymerization mediated by persistent radicals represents a rapidly emerging field in polymer science. Nitroxides, which are probably the most widely used persistent radicals, play an important role in the well-known nitroxide-mediated polymerization (NMP, see **Nitroxide-Mediated Polymerization and its Applications**).^{8,9}

Nitroxides can be generated by thermolysis of alkoxyamines through an O–C bond cleavage process. The BDE is typically in the 20–35 kcal mol^{-1} range depending on both the alkyl and nitroxide fragments. Some typical compounds are depicted in Scheme 4. 2,2,6,6-Tetramethyl-piperidine-*N*-oxyl (TEMPO), 2,2,5-tri-methyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO), and *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl (SG1) are important members of this substance class. For 1-phenyl-1-(2',2',6',6'-tetramethyl-1'-piperidinyloxy)ethane, the rate constant of thermal C–O bond homolysis is $2.8 \times 10^{-6} \text{ s}^{-1}$ at 350 K



Scheme 4 Decomposition of alkoxyamines.

in cyclohexane. Rate constants for C–O bond homolysis in alkoxyamines are strongly affected by the structures of the alkyl and nitroxide fragments and lie typically in the range of 10^{-3} to 10^{-7} s^{-1} at 350 K.^{46,47}

2.6 The “Cage” Effect

The quantum yield of the thermal dissociation process in solution is usually reduced as compared to thermolysis in the gas phase. In contrast to the gas phase experiment, homolysis of an initiator in the liquid phase leads to the generation of two radicals that exist for a given time as a radical pair (RP) keeping the spin memory. The surrounding solvent molecules create a cage around the RP. In such an RP, where the two radicals have opposite spins, radicals can easily recombine before escaping from the solvent cage (i.e., this recombination occurs inside the solvent cage). The recombination rate constant between the two radicals is usually very high. The cage effect was first recognized in the 1930s by Frank and Rabinowitch.^{48,49} Importantly, this effect is not restricted to thermal processes and is also observed in the solution phase radical generation through photolysis. However, owing to spin considerations on the precursor excited states, evolution of RPs is more complicated in the photochemical process.

Cage effect strongly depends on solvent viscosity and temperature. For an efficient radical initiation, the recombination in the geminate RPs should be as low as possible. This in-cage/out-of-cage ratio is usually non-negligible. A typical value

of about 20% has been reported for the in-cage recombination of radicals during the thermolysis of AIBN, meaning that only about 60% of the radicals escape the cage and are ready for initiating a chain reaction.⁵⁰ This recombination and cage effect is also very important for spectroscopic investigations of radicals, that is, in the chemically induced dynamic nuclear polarization (CIDNP) or in the chemically induced dynamic electron polarization, CIDEP (see **Structures and Reactivity of Radicals Followed by Magnetic Resonance**).^{51–53}

3 ORGANOBORANE INITIATORS

Alkyl radicals can be very efficiently generated from trialkylboranes through interaction with molecular oxygen (organoborane derivatives are generally sensitive to O_2 and must be stored under argon) (Scheme 5). This oxidation reaction is quite efficient.^{54–57}

Trialkylboranes and more especially Et_3B have been intensively used as RIs in organic synthesis (see **Boron in Radical Chemistry**). Indeed, compared to other typical initiators that are activated by thermolysis (such as peroxides or azo compounds), Et_3B can act as an efficient



Scheme 5 Generation of ethyl radicals for the triethylborane/ O_2 system.

radical generator even at very low temperatures (at -78°C).² Low temperature initiation is very important for stereoselective radical chemistry (see **Stereoselective Radical Reactions**). Importantly, these reactions require only traces of oxygen. Processes are easily triggered by supplying oxygen through an air stream. It has been reported that Et_2Zn and 9-borabicyclo(3.3.1)nonane (9-BBN) are also able to initiate radical reactions upon treatment with air.^{58,59}

4 PHOTOCHEMICALLY ACTIVATED RADICAL INITIATORS

4.1 Homolytic Cleavage Process

Homolysis of single bonds can also be induced, at room temperature, by light (particularly by UV light). Radiation allows homolytic cleavage of a σ -bond to generate the corresponding radicals. Cleavage occurs from the excited states (singlet S_1 or triplet T_1) from which the dissociation process is more favorable than from the ground state S_0 . The promotion of an electron usually from the highest occupied molecular orbital (HOMO) (corresponding to a bonding or nonbonding orbital) to the lowest unoccupied molecular orbital (LUMO) (corresponding to an antibonding orbital) is responsible for weakening of bonds in the excited states.

Photoinduced homolysis offers decisive advantages over thermolysis: stronger bonds can be broken, that is, C–C bonds (see Table 4). Moreover, fewer side reactions are generally observed using photochemical activation allowing for cleaner radical generation. In photolysis, two important parameters govern radical formation:

1. The light absorption properties and more specifically the spectral sensitivity. Indeed, an excellent matching of the RI absorption spectrum with the emission spectrum of the irradiation device (light source: Hg lamp, Xe lamp, green fluorescence lamp, laser, LED, etc.) ensures the absorption of a large amount of photons. Different photochemical reactors have been designed to render photochemically induced radical reactions highly efficient.
2. The cleavage quantum yield (Φ_c), which represents the number of bonds broken per photon

absorbed. The cage effect is already included in this particular parameter. A quantum yield of 1.0 means that each absorbed photon leads to a dissociation reaction with the formation of two free radicals. However, Φ_c values less than 1.0 are usually observed because other pathways competing with the dissociation process such as, fluorescence, intersystem crossing, phosphorescence, internal conversion (as considered within the classical Perrin-Jablonski diagram of a single molecule), and excited state oxygen quenching, along with other side reactions are followed in the excited states.⁶⁰

Various compounds containing chemical bonds cleavable under light exposure have been reported in the literature. These initiators will now be briefly reviewed.

Photolysis of peroxides (or acylperoxides) via cleavage of the O–O bond is well established. This process leads to alkoxy (or acyloxy) radicals. However, these molecules mainly absorb at wavelengths $\lambda < 300\text{ nm}$. Since commonly used glassware absorbs all light above $\lambda < 310\text{ nm}$, often special glassware has to be used.

For azo compounds, the same issue must be considered, as a very weak absorption at wavelengths higher than 300 nm is noted, except with AIBN which exhibits a relatively intense absorption band around 340 nm . Starting with AIBN, isobutyronitrile radicals are readily generated by UV irradiation.⁶⁸

Some examples on photolysis of organohalide derivatives exhibiting relatively weak C–halogen bonds have been reported. As alkyl chlorides absorb at very short wavelength ($\lambda < 200\text{ nm}$), only iodides and bromides can be used because of their significant absorption at $200 < \lambda < 350\text{ nm}$. More particularly, alkyl iodides cleave efficiently.^{10–16,69,70}

The photolysis of heteroatom–halogen or heteroatom–heteroatom bonds, for example, in *N*-chloroamines ($\text{R}_2\text{N–Cl}$) and hypochlorites (RO–Cl), also occurs with formation of the corresponding alkoxy and aminyl radicals^{11,71}:



Thiyl radicals can be generated via photolysis of the S–S bond in disulfides, albeit this method suffers from the low light absorption of the precursors at

Table 4 Cleavage quantum yields ϕ_c of various photoinitiators.

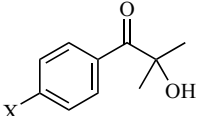
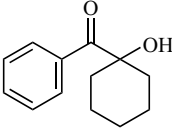
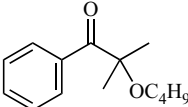
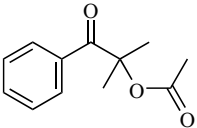
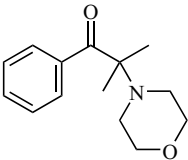
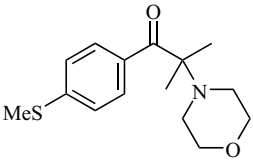
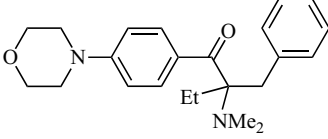
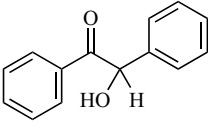
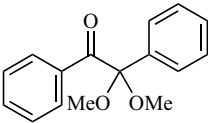
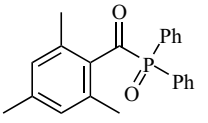
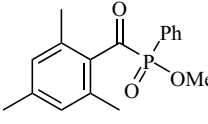
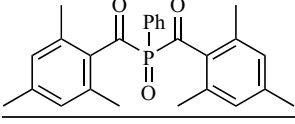
Photoinitiator	Absorption spectral range (nm)	BDE (kcal mol ⁻¹)	Φ_c
			
X=H	<340	69.8	0.8 ^a ; 0.38 ⁶²
X=F	<340	—	0.67 ⁶²
X=Cl	<340	—	0.60 ⁶²
X=OCH ₃	<340	—	0.38 ⁶³
X=SCH ₃	<380	—	0.01 ⁶²
X=N(CH ₃) ₂	<380	—	0.03 ⁶²
	<340	68.9	0.8 ^a ; 1 ^{64,65}
	<340	—	0.33 ⁶²
	<340	—	0.05 ⁶²
	<380	66.8	0.3 ^a
	<380	61.4	0.3 ^a ; 0.13 ⁶⁶
	<380	—	0.24 ⁶⁶

Table 4 (continued)

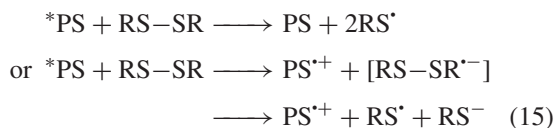
Photoinitiator	Absorption spectral range (nm)	BDE (kcal mol ⁻¹)	Φ_c
	<340	64.8	0.5 ^a
	<340	56	0.95 ^a ; 1.0; 0.52 ^{65,67}
	<400	62	0.7 ^a ; 0.5 ⁶⁴
	<400	—	0.3 ⁶⁴
	<420	—	—

Bond dissociation energies (BDE) calculated at B3LYP/6-31G(d) level.⁶¹^aMeasured by laser induced photoacoustic calorimetry.⁶¹

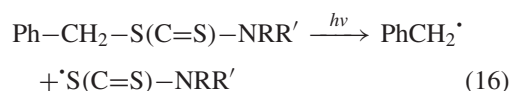
$\lambda > 320$ nm (reaction 13). This is a straightforward way for the formation of thiyl radicals, as in symmetrical disulfides only one kind of thiyl radical is generated. Therefore, this approach has been successfully used in many physical chemistry studies on thiyl radicals.^{72–75}



Bond homolysis can also be induced by energy transfer and/or electron transfer using a photosensitizer, PS, with adjusted light absorption properties⁷⁶:

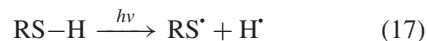


The formation of dithiocarbamyl radicals from the photolysis of benzyldithiocarbamates has also been reported as an efficient process:

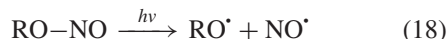


Dithiocarbamyl radicals have been used to control the photopolymerization reaction of different monomers (acrylate, methacrylate, styrene, etc.). In that case, the RI is called a *photoiniferter* (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).⁷⁷

Upon photolysis of thiols, thiyl radicals are also generated; however, the light absorption for these compounds is still worse as compared to disulfides (Ref. 78 and references therein):



More interestingly, nitrites can generate alkoxyl radicals via photochemical O–N bond cleavage (reaction 18). These precursors are interesting as they exhibit quite good light absorption properties owing to the presence of a $n\text{--}\pi^*$ transition at around 360 nm.⁷⁹

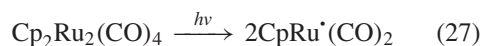
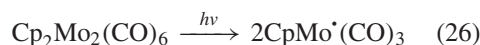
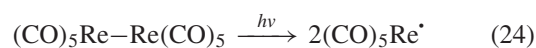
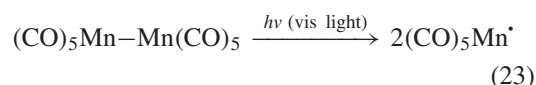
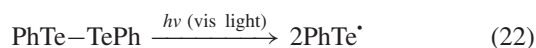
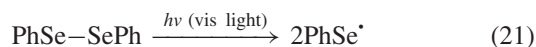


The cleavage of different Si–B bonds with the formation of silyl and boryl radicals under light irradiation were also reported but these precursors suffer from a low light absorption at $\lambda > 300\text{ nm}$ ⁸⁰:

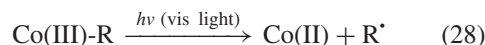


Silyls radicals can be generated by the cleavage of disilane precursors ($\text{R}_3\text{Si--SiR}_3$). This Si–Si dissociation process under light irradiation is well known in polysilanes.³⁴ Some organic precursors that show good light absorption in the more convenient 300– to 400-nm range were more recently proposed.^{81,82}

In organic synthesis, photolysis of alkyliditins has been often applied as an important process for generation of tin radicals, which are highly important in the field of synthetic radical chemistry (see **Tin Hydrides and Functional Group Transformations**). Other photoinduced metal–metal bond cleavage processes for various compounds containing an Se, Te, Mn, Re, Fe, Mo, or Ru atom can be useful in initiating a chain reaction (reactions 20–27).^{10–16,83–89} This is mainly related to the $\sigma\text{--}\sigma^*$ transition, which ensures, after light absorption, formation of a dissociative excited state. Good to excellent light absorption properties are found, that is, the Mn, Mo, and Te derivatives exhibit high absorption coefficients in the visible spectral range; for example, for $\text{Cp}_2\text{Mo}_2(\text{CO})_6$, a significant absorption is found, $750\text{ M}^{-1}\text{ cm}^{-1}$ at 532 nm.



The cleavage of a Co–C bond occurs in Co(III) complexes, which are used, for example, for the radical generation in vitamin B₁₂ (see **Radical Enzymes**)^{90,91}:

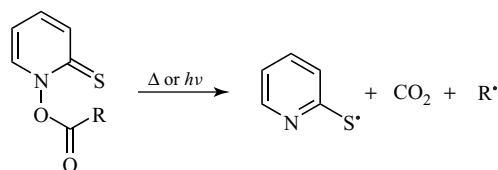


The photolysis of a Hg–C bond is also a very efficient process for clean C-radical generation. Importantly, the BDE for Hg–C bonds is very low:

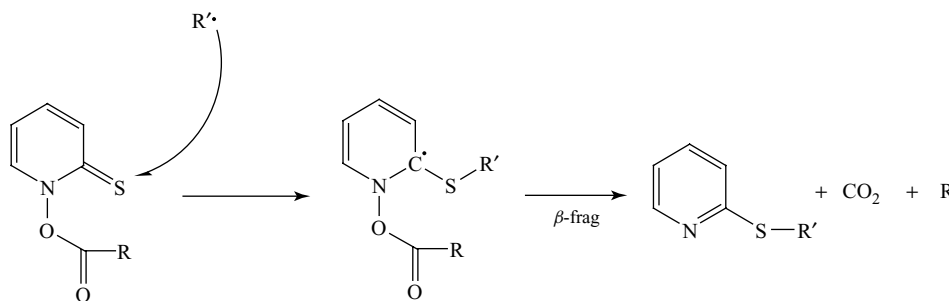


For clean and efficient generation of free radicals in organic synthesis, different classes of organic initiators with absorption spectra matching the emission spectra of classical and common UV–visible lamps have been designed. Particularly, derivatives of *N*-hydroxypyridine-2-thione esters (or *N*-hydroxyquinazoline-4-thiones)^{92–94} and *N*-hydroxypyridine-2-thione carbamates⁹⁵ were proposed as efficient sources of carbon-centered (Scheme 6) and aminyl radicals, respectively. These structures can also be activated by thermolysis.⁴²

N-Hydroxypyridine-2-thione esters are highly interesting reagents since they allow initiation of chain reactions. Propagation is achieved through an addition/ β fragmentation sequence (Scheme 7; see **Xanthates and Related Derivatives as Radical Precursors**). The addition of an $\text{R}'^\bullet$ radical to the C=S bond is usually exothermic and leads to a carbon-centered radical. A favorable β -fragmentation (which corresponds to a monomolecular reaction) occurs with concomitant formation of an aromatic ring; after decarboxylation, a new radical is eventually released ($\text{R}'^\bullet$).



Scheme 6 Radical formation in *N*-hydroxypyridine-2-thione esters.



Scheme 7 Addition β -fragmentation in *N*-hydroxypyridine-2-thione esters.

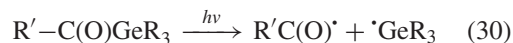
With these precursors that allow generation of radicals in a clean manner, different competitive methods were proposed in kinetic investigations for assessing reaction rate constants of alkyl radicals.⁹⁶ Different radical clocks have been developed using these radical precursors (see **Radical Kinetics and Clocks**).⁹⁷

Many typical organic initiators have been optimized for good light absorption in the UV range and more particularly in the 300–400 nm domain. These compounds are used for organic synthesis, physical chemistry studies, and also as photoinitiators (PI) for free radical photopolymerization (see e.g., Refs 64, 98). UV and visible light-initiated polymerizations have become one of the most important methods used in radiation curing area.^{99–102} In polymer chemistry, compared to thermal initiation processes, several practical advantages of industrial applications of photoinitiation can be listed (see **Radical Polymerization in Industry**): the photopolymerization process is subjected to a strict spatial control; it is easily switched on or off at demand; interestingly, solvent-free systems are employed, meeting the requirements for green chemistry.

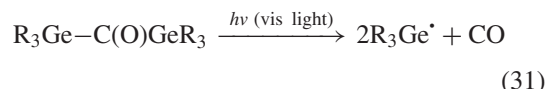
Typical PI structures undergoing efficient photolysis are gathered in Table 4. The PI, usually bearing a carbonyl group, is promoted to its first excited singlet state S_1 by light absorption and then, through intersystem crossing, to its excited

triplet state T_1 . The intersystem crossing quantum yields (Φ_{isc}) are usually high (often close to 1 for ketones).¹⁰³ The α -carbonyl bond cleavage process (often called Norrish I type cleavage) occurs from the T_1 state and corresponds to the frequently encountered primary step (Scheme 8). The spectral absorption range and Φ_c for typical PIs are given if available in the literature; reported Φ_c values often have a large uncertainty and therefore only the more representative values are included. The bond dissociation energies of the cleavable bond (C–C and C–P) are also presented in the table.

Germyl radicals can efficiently be generated from acylgermanes under light irradiation. These compounds show excellent light absorption at $\lambda > 350$ nm^{104–107}:

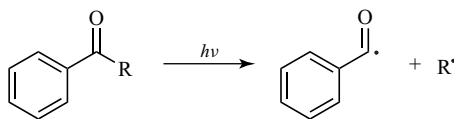


Interestingly, bis(germyl)ketones were reported to be useful Ge-radical precursors that adsorb visible light (with $\lambda_{max} \sim 515$ nm)¹⁰⁸:

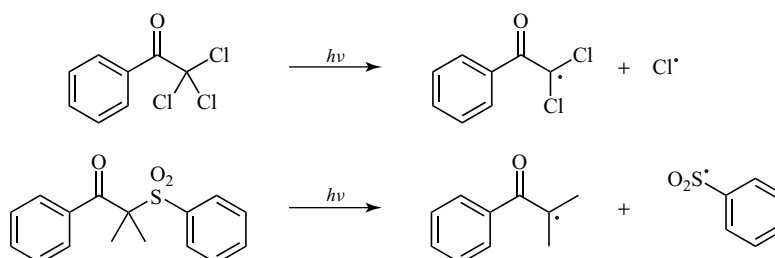


These structures were recently proposed as PIs in free radical polymerization.¹⁰⁹

For some ketones, β -cleavage occurs after irradiation. This can be observed for β -halogenated ketones and also for β -sulfonyl ketones (e.g., bifunctional ketone–sulfonyl ketone derivatives exhibit an interesting absorption around 410 nm) (Scheme 9).^{110–112}



Scheme 8 α -Cleavage process in aromatic ketones.



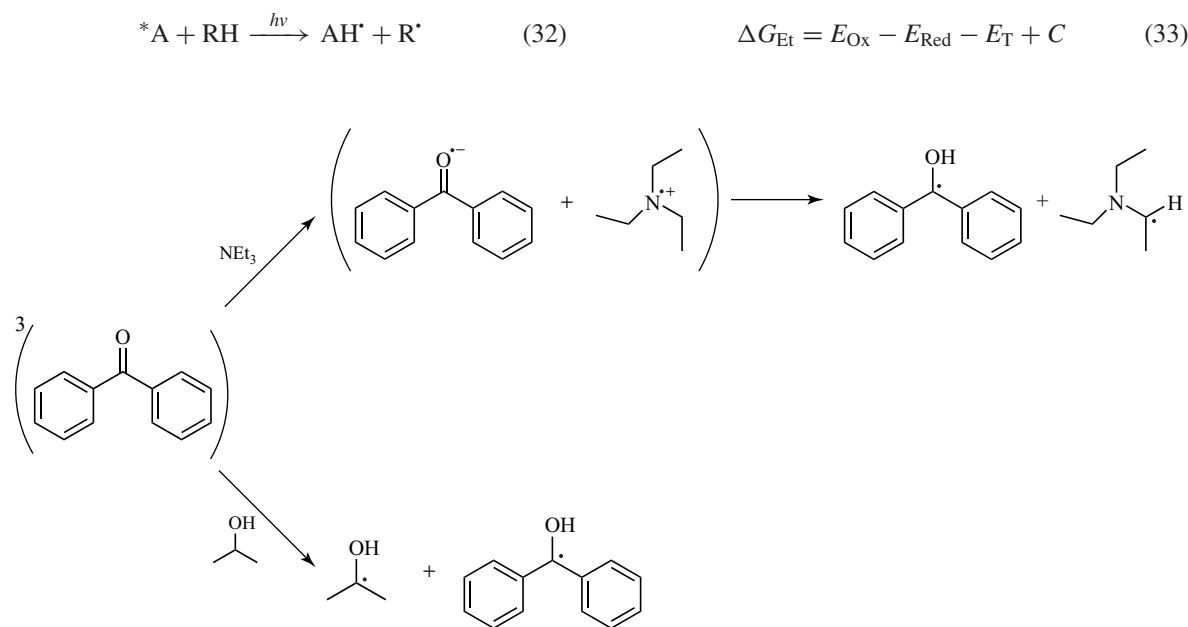
Scheme 9 β -Cleavage process for halogenated ketone derivatives and for sulfonyl ketones.

4.2 Hydrogen Abstraction Reaction

Another route for generation of radicals uses bimolecular hydrogen abstraction reactions. This generally occurs in a molecule (in most of the cases bearing a carbonyl group) in its triplet state T_1 . Using a large range of precursors, the absorption properties can be tuned from the UV (benzophenone) to the near visible (thioxanthone) or the visible wavelengths (camphorquinones, coumarins, dyes, etc.). Hydrogen abstraction usually occurs in the triplet state for ketones or aldehydes (i.e., acetone, acetophenone, benzophenone, thioxanthone, camphorquinone, coumarin derivatives, benzaldehyde, etc.).¹⁰³

This reaction corresponds either to a hydrogen transfer process or an electron transfer followed by a proton transfer (e^-/H^+ mechanism) (Scheme 10).

The competition between these two mechanisms is related to the redox properties of the reactants. The free-energy changes (ΔG_{Et}) for the electron transfer from a donor to an acceptor can be calculated from the classical Rehm–Weller equation (33), where E_{ox} is the oxidation potential of the donor, E_{red} is the reduction potential of the acceptor, E_T is the triplet state energy (or the excited state energy), and C is a coulombic term for the initially formed ion pair (C is often neglected in polar solvents).¹¹³ For systems having a negative ΔG_{Et} , the electron/proton transfer sequence is very favorable.



Scheme 10 Hydrogen transfer and electron–proton transfer sequence for the benzophenone triplet state.

Table 5 Typical hydrogen donors and rate constants for H-transfer to the benzophenone triplet state (^3BP) or the *t*-butoxyl radical ($t\text{BuO}^\bullet$).

Hydrogen donors	$k(^3\text{BP})$ in $10^7 \text{ M}^{-1} \text{ s}^{-1}$	Mechanism	$k(t\text{BuO}^\bullet)$ in $10^7 \text{ M}^{-1} \text{ s}^{-1}$	Generated radicals
Triethylamine	310 (0.94) ^a	$\text{e}^- - \text{H}^+$	$\sim 11\text{--}18^b$	$\text{BPH}^\bullet$; $\text{Et}_2\text{NC}(\bullet)\text{HCH}_3$
Mercaptobenzoxazole	150 (0.5) ^c	$\text{e}^- - \text{H}^+$	100 ^d	$\text{BPH}^\bullet$; $\text{RS}^\bullet$
Isopropanol	0.16 ^e	H	—	$\text{BPH}^\bullet$; 2-hydroxypropyl
Tris(trimethylsilyl)silane $(\text{TMS})_3\text{Si-H}^f$	10.2 (0.95)	H	8.5	$\text{BPH}^\bullet$; $(\text{TMS})_3\text{Si}^\bullet$
Tris(trimethylsilyl)germane $(\text{TMS})_3\text{GeH}^f$	105 (0.81)	H^g	45	$\text{BPH}^\bullet$; $(\text{TMS})_3\text{Ge}^\bullet$
$\text{Ph}_3\text{Sn-H}$	46 (0.74) ^h	H	153 ^h	$\text{BPH}^\bullet$; $\text{Ph}_3\text{Sn}^\bullet$
$\text{Et}_3\text{N} \longrightarrow \text{BH}_3$	9.1 (0.73) ⁱ	H	5.3 ^j	$\text{BPH}^\bullet$; $\text{Et}_3\text{N} \longrightarrow \text{BH}_2^\bullet$

The ketyl radical ($\text{BPH}^\bullet$) quantum yields for the ^3BP /hydrogen donor reaction are given in brackets (column 2).

^aReference 115.

^bReferences 116–118.

^cReference 76.

^dReference 119.

^eReference 120.

^fReferences 34, 36.

^ga minor participation of the $\text{e}^- - \text{H}^+$ mechanism can be expected (see Refs 34, 36).

^hReference 121.

ⁱReference 122.

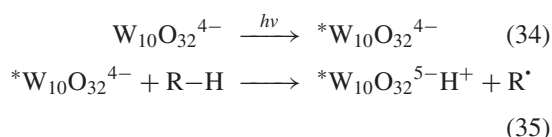
^jReference 123.

Typical hydrogen donors include amines, thiols, alcohols, ethers, silanes, boranes, aliphatic or aromatic hydrocarbons, and so on.^{103,114} For the first two classes (amines and thiols), the process is described by an electron–proton transfer sequence whereas a pure hydrogen transfer is usually expected for the other structures. Typical rate constants characterizing the reactivity of the benzophenone triplet state (^3BP) with different representative hydrogen donors are gathered in Table 5. For triethylamine and mercaptobenzoxazole (which are good representatives of amines and thiols), H-abstraction rate constants lie close to the diffusion limit and are higher than the corresponding rate constants for H-transfers to $t\text{BuO}^\bullet$. This is in agreement with the fulfilled condition $\Delta G_{\text{Et}} < 0$, supporting the e^-/H^+ mechanism. In the ^3BP reaction with alcohols, silanes, germanes, stannanes, or ligated boranes, $\Delta G_{\text{Et}} > 0$ and the e^-/H^+ mechanism is not favorable. The rate constants for H-transfer of these hydrogen donors to ^3BP or $t\text{BuO}^\bullet$ are quite similar. For these processes, ^3BP behaves like an alkoxyl radical.

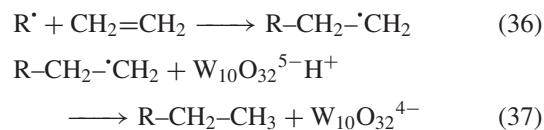
Quantum yields for ketyl radical formation (obviously equal to the quantum yields for the production of the radical derived from the hydrogen donor) are usually quite high (Table 5). The interaction of ketone triplet states with hydrogen donors is an efficient process in the radical photoinitiation step. Many radicals can be generated through this route:

alkyl, aminoalkyl, aminyl, silyl, germyl, stannyl, boryl radicals, and so on.

In addition to ketones discussed above, other compounds have gained great attention to be used in hydrogen abstraction processes. For example, decatungstate acts as an efficient photocatalyst in organic chemistry (reactions 34–37). The excited state of this compound abstracts a hydrogen atom from a large range of donors (R-H)^{124–128}:



This process has been successfully used for radical C–C bond formation via addition of an activated alkane RH to an unsaturated olefin (H-transfer addition reaction):



Decatungstate exhibits high reactivity under visible light; even sunlight can be applied to run these reactions! Interestingly, the use of this photocatalysts in organic synthesis does not require any specific photochemical equipment.

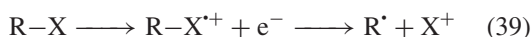
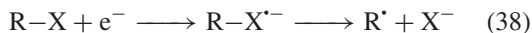
Table 6 Radical initiation through an oxidation process.

Precursor	Oxidizing agent	Expected reaction
Carboxylates	Electrochemical method (Kolbe reaction)	$\text{RCO}_2^- \longrightarrow \text{RCO}_2^\bullet + \text{e}^-$
Phenoxydes	Electrochemical method	$\text{ArO}^- \longrightarrow \text{ArO}^\bullet + \text{e}^-$
Carboxylic acids	Strongly oxidizing metal ions (typically silver II)	$\text{M}^n + \text{RCO}_2\text{H} \longrightarrow \text{M}^{n-1} + \text{RCO}_2^\bullet + \text{H}^+$
Alcohols	Strongly oxidizing metal ions	$\text{M}^n + \text{ROH} \longrightarrow \text{M}^{n-1} + \text{RO}^\bullet + \text{H}^+$
Alkylbenzene derivatives	Ce(IV)	$\text{Ce}^{4+} + \text{PhCH}_3 \longrightarrow \text{Ce}^{3+} + \text{PhCH}_2^\bullet + \text{H}^+$
Carbonyl derivatives (more effective for carbonyl being able to enolize)	Mn(III)(OAc) ₃	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}' + \text{Mn}(\text{OAc})_3 \longrightarrow \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\dot{\text{C}}\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}' + \text{Mn}(\text{OAc})_2 + \text{AcOH}$

The radicals generated appear in bold face.

5 REDOX REACTIONS

Radicals can also be generated via redox processes (see **Electrochemically Initiated Radical Reactions, Organic Electron Donors**) through either reduction or oxidation of an appropriate precursor (RX):



Contrary to the cleavage processes observed in thermolysis and photolysis, the redox process possesses the intrinsic advantage to generate only one radical (instead of a pair of radicals). Within this article, oxidation and reduction reactions will be discussed independently in the following two sections.

5.1 Oxidation

The precursor (R-X) reacts with strongly oxidizing agents such as metal salts of cerium(IV), manganese(III), and silver(II).^{10–16,129,130} These compounds can be used for the oxidation of a large variety of compounds with concomitant formation of free radicals. Some typical examples are gathered in Table 6.

5.2 Reduction

The precursor (R-X) must accept an electron from a reagent that can donate an electron (Table 7). A look at the respective redox potentials of both reactants can indicate the feasibility of such a redox process. Particularly, the addition of an electron to halides is well known as an efficient process for radical generation. The electronegativity of the halogen atom

Table 7 Radical initiation through a reduction process.

Precursor	Reducing agent	Expected reaction
Halides	Sm(II), Co(I), Fe(II), Ru(II)	$\text{M}^n + \text{RX} \longrightarrow \text{M}^{n+1} + \text{R}^\bullet + \text{X}^-$
Peroxides	Co(II), Fe(II), Cu(I), Cr(II), V(II), Ti(III)	$\text{M}^n + \text{RO-OR}' \longrightarrow \text{M}^{n+1} + \text{RO}^\bullet + \text{R}'\text{O}^\bullet$
Arene diazonium salts	Co(I) or strong organic reductants	$\text{M}^n + \text{ArN}_2^+ \longrightarrow \text{M}^{n+1} + \text{Ar}^\bullet + \text{N}_2$
Carbonyl	SmI ₂	$\text{SmI}_2 + \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}' \longrightarrow \text{R}-\overset{\text{O}^-\text{SmI}_2}{\underset{\cdot}{\text{C}}}-\text{R}'$
Persulfate	Silver I	$\text{Ag}^+ + \text{S}_2\text{O}_8^{2-} \longrightarrow \text{Ag}^{2+} + \text{SO}_4^{\bullet-} + \text{SO}_4^{2-}$

The radicals generated appear in bold face.

ensures that X^- will be generated from the corresponding radical anion $RX^{\bullet-}$. Samarium(II) (see **Organic Synthesis Using Samarium Diiodide**), iron, copper, and ruthenium complexes were used for the reductive generation of $R^\bullet$.^{129,130} Some organic single electron transfer reductants were also developed (see **Organic Electron Donors**).^{131–140} The reduction of peroxides via transfer of an electron into the antibonding orbital (σ^*) weakens the RO–OR bond inducing the cleavage of the σ -bond, thereby liberating an anion and the corresponding O-centered radical. This process occurs in the well-known iron(II)/hydrogen peroxide system. This corresponds to the Fenton reaction, which allows generation of hydroxyl radicals. Some cobalt salts in combination with peroxides are also known to initiate a free radical polymerization process at room temperature. Other reductants such as Cr^{2+} , V^{2+} , Ti^{3+} , Co^{2+} , and Cu^+ can also be employed in place of ferrous ions.

5.3 Electrochemical Methods

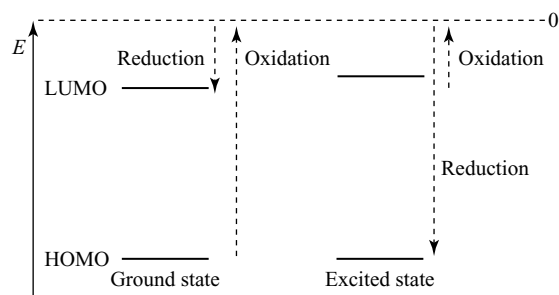
The direct oxidation (or reduction) of an anion (or a cation) by electrochemical methods also leads to radical formation^{141–143}:



Typical examples of electrochemical oxidation/reduction-induced radical generation will be discussed in **Synthetic Electrochemistry**, Volume 2.

5.4 Photoactivated Redox Processes

Redox reactions can also be promoted by light as the excited states (singlet or triplet state) are often better oxidation or reduction agents than the corresponding ground states. This is related to the promotion of an electron from the HOMO to the LUMO. Indeed, in a schematic approach (Scheme 11), the ionization potential is decreased (the electron will be abstracted from the initial LUMO for the excited state instead of the HOMO for the starting molecule). In a similar way, the electron acceptor properties of the excited state are also enhanced, that is, in the case of an



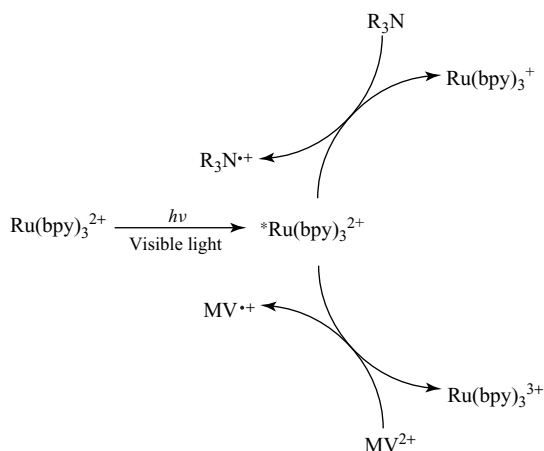
Scheme 11 Orbitals involved in the oxidation or reduction processes for the ground and excited states.

excited acceptor molecule, the donor electron is transferred to the initial HOMO; for a ground state molecule, this occurs in the LUMO (Scheme 11).

The redox process is governed by the Rehm–Weller equation (33), which gives indication about the feasibility of the process. The electron transfer process can be followed by a proton transfer reaction from appropriate hydrogen donors resulting in a net hydrogen transfer process (see Section 4.2). The generation of aminoalkyl radicals by such a light-activated process in ketone/amine systems has been used in some synthetic organic and polymer applications. A detailed description is given in **Synthetic Radical Photochemistry**. (Refs 144, 145 and references therein).

Very recently, photochemically induced electron transfer from transition metals has also gained great attention, particularly for synthetic applications.^{146–152} This process is called *photoredox organocatalysis*. The selected photocatalysts are mainly based on Ru or Ir ($Ru(bpy)_3^{2+}$, $Ir(ppy)_2(dtb-bpy)^+$, etc.) and are characterized by an intense visible light absorption. These catalysts are more efficient than dicyanoanthracene. Very interestingly, with these compounds, very convenient visible light sources—including fluorescent bulbs and ambient sunlight—can be used.

As far as the mechanism is concerned, it is assumed that the excited state of the organocatalyst reacts with a sacrificial quencher through an electron transfer reaction (amine, methyl viologen, enamine, etc.) and generates a strong reductant or oxidant metal complex. For example, $Ru(bpy)_3^{3+}$ (or $Ru(bpy)_3^{3+}$) is generated by reduction (or oxidation) of the $^*Ru(bpy)_3^{2+}$ excited state by an amine (or methyl viologen (MV^{2+})) (Scheme 12). For $Ir(ppy)_2(dtb-bpy)^+$, a strong $Ir(ppy)_2(dtb-bpy)$



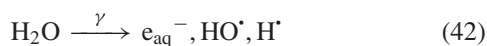
Scheme 12 Formation of Ru(bpy)₃⁺ and Ru(bpy)₃³⁺ in a light-activated process.

reductant is formed by reaction of the corresponding excited state with a sacrificial enamine.^{146–152}

These strong reductants or oxidants can be used to promote radical reactions.^{146–152} For example, CF₃[•] radicals can be generated by a single electron transfer from Ir(ppy)₂(dtb-bpy) to CF₃I.¹⁵² Using Ru-based systems, aryl enones can be reduced to the corresponding radical anions. For electron-rich olefins, the oxidation pathway can be operative to generate the corresponding radical cations. These intermediates can be used in [2+2] cycloadditions.^{146–151}

6 OTHER MODES

Radiolysis (for example, X-ray or γ-radiation) causes the ejection of an electron from the initiating species, leading to the formation of a radical cation that further decomposes to a radical and a cation; see also **Radiation-Induced Radical Reactions**.^{153–156} The associated mechanisms are often quite complex and this mode of activation involving high energy is not really considered as selective. Using water, highly reactive hydroxyl radicals (45%) together with hydrated electrons (45%) and hydrogen atoms (10%) are generated as primary species (reactions 42, 43):



Radiolysis is an important method for radical generation in food applications. Indeed, the irradiation of food generates highly reactive radicals (like OH[•]) that kill the contaminating organisms leading to a food preservation process.

Pulsed radiolysis is a powerful technique to initiate fast reactions. The sample is exposed to a beam of highly accelerated electrons. The transient intermediates can be followed by UV–visible spectroscopy. This method is highly useful to study fast reactions and chemical intermediates (typically in a microsecond–millisecond timescale).^{153–160}

γ-Radiation from ⁶⁰Co has been successfully applied to initiate polymerizations and grafting processes.^{153–156,160,161}

The electron beam induced polymerization (EB curing) belongs to the radiation curing field with important applications (particularly for coatings) in industry.^{162,163}

In sonication with high-intensity ultrasound waves, radical generation results from the effects of cavitation (formation and collapse of cavities in the liquid). High local temperatures and pressures are reached, leading to bond breaking and radical formation.^{164,165}

7 CONCLUSIONS

As shown in this article, the generation of radicals can occur through several different routes. Most of these approaches have been applied as will be presented in many articles of this encyclopedia, in Chemical Synthesis (Volume 2), in Chemical Biology (Volume 3) and also in Polymers and Materials (Volume 4). However, there is still a need for the development of new RIs that allow clean radical generation under mild conditions fulfilling various criteria: low temperature, soft irradiation (sunlight or green fluorescence bulbs), and being highly selective.

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Photo Induced Radical Reactions

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1 INTRODUCTION

Although radicals are very reactive species, owing to their electron deficiency, they can be useful in selective transformations. They are neutral species, and therefore their reactivity is not strongly influenced by solvents. Knowledge of the rate constants for the competing radical reactions permits predictive control of the reactivity. Here, we briefly address free radical processes induced by light, which is one of the most important ways to generate these intermediates (see **Synthetic Radical Photochemistry**). Homolytic cleavage, electron transfer coupled to proton transfer, and electron transfer followed by anion dissociation can occur after light absorption or in the presence of a photosensitizer that absorbs light, finally resulting in the removal of groups or generation of new bonds such as carbon–carbon, carbon–oxygen, carbon–sulphur, carbon–selenium, and carbon–halogen, among others (Scheme 1). In this article, we consider the various photochemical strategies to generate carbon radicals and show examples that underline the interest in these species in synthetic chemistry.

2 ONE-STEP PROCESSES

2.1 Homolytic Cleavage

2.1.1 X–Y Bond Cleavage: C–Y (Y = halogen, C, S, N) and O–Y (Y = I, N, Cl, S)

C-Halogen α -Cleavage of Haloalkanes

The lowest energy transition of haloalkanes involves promotion of one of the electrons of the

halogen to the σ^* orbital of the carbon–halogen (C–X) bond; the wavelength required for excitation depends on the halogen atom and on the substituents attached to the carbon atom.¹ Light absorption causes cleavage of the C–X bond; the relative ease of this process is opposite to the C–X bond strength, that is, C–I > C–Br > C–Cl > C–F. In addition, it also depends on the substituents of the carbon atom. Thus, although direct photolysis of the C–F bond is rare, all benzylic halides undergo light-induced cleavage.

The C–X bond cleavage leads to radical pairs, which can escape from the cage in nonpolar solvents or undergo electron transfer to generate a carbocation and a halide anion (Scheme 2). Chloroalkanes are less prone to generate cationic species than bromoalkanes and these are less prone than iodoalkanes.²

Laser flash photolysis of substituted benzylic halides has allowed the detection of benzylic radicals and cations.³ The homolytic and heterolytic bond fragmentations arise not only from the singlet excited states but also from the triplet excited states, as shown by selective excitation of chlorides in their triplet states by triplet energy transfer from, for example, acetophenone. Carbon–halogen homolysis in (halomethyl)naphthalenes has been postulated to occur also from an exciplex of the halide with a singlet or triplet sensitizer.⁴ This exciplex would cleave heterolytically in a polar solvent but homolytically in a nonpolar solvent such as cyclohexane.

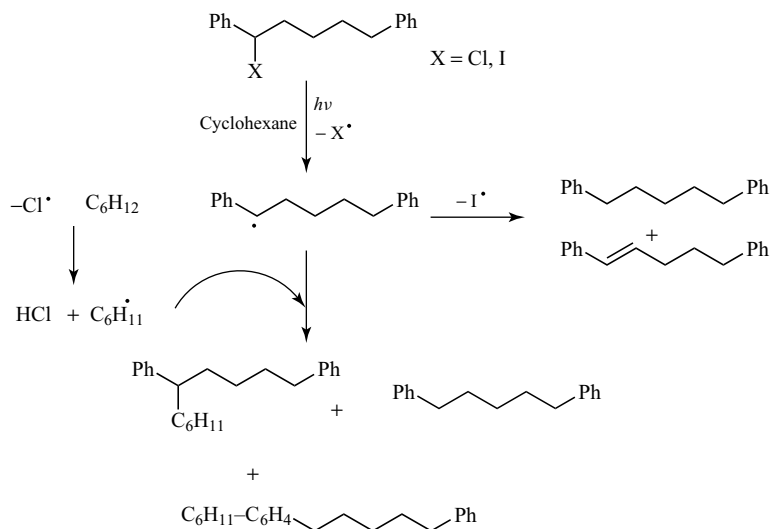
Steady-state irradiation in cyclohexane of a benzylic chloride, such as 1-chloro-1,5-diphenylpentane,



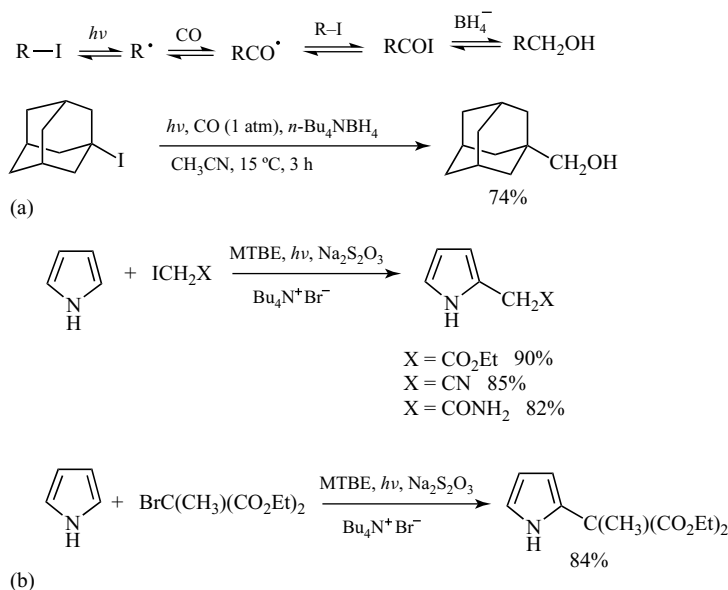
A wide range of benzylic systems, such as benzylic acetates, or benzylic sulphonium, ammonium, and phosphonium salts, have also been investigated.⁷ They follow the reactivity pattern of the more systematically studied benzyl halides.

In addition, photolysis of α -haloesters, α -halonitriles, and α -haloamides (halogen = Br, I) leads to electron-deficient radicals. These radicals have been applied to the radical aromatic substitution of pyrroles and indoles (Scheme 4b).⁹ Carbon-carbon bond formation is followed by addition of the halogen (X) atom and then loss of HX to regenerate the aromaticity. Addition of a reductant, such as $\text{Na}_2\text{S}_2\text{O}_3$, in the presence of a phase-transfer catalyst ($\text{Bu}_4\text{N}^+ \text{Br}^-$) has been used to consume the molecular iodine (bromine) generated as a by-product of the reaction; this methodology avoids the use of distannanes as reductants. Propylene oxide is added to trap the HI (or HBr) produced in the reaction. In the case of iodocycloalkanones bearing an allenyl side chain, the halogen atom remains attached to the final compound.¹⁰

Moreover, 1,*n*-dihaloalkanes ($n \geq 1$) can be precursors of *n*-haloalkyl radicals. Chloroalkyl radicals have the characteristic features of the corresponding



Scheme 3

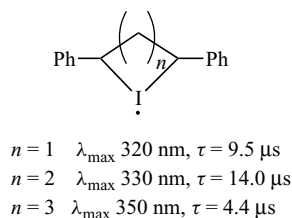


Scheme 4

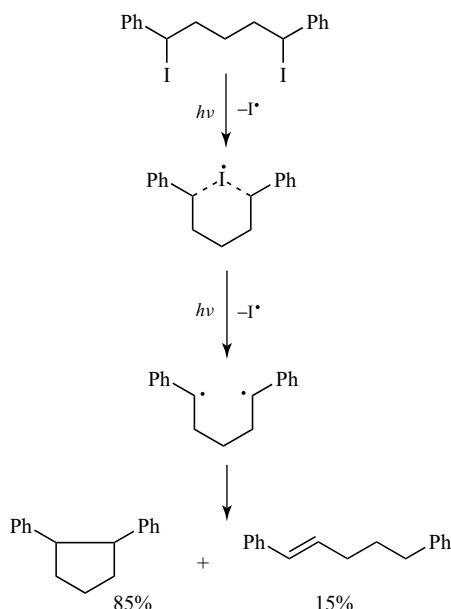
carbon radicals, such as high reactivity toward oxygen (diffusion-controlled quenching) and absorption spectra (λ_{max} at 320 nm for *n*-chloroalkyl phenyl radicals). By contrast, the behavior of *n*-bromo- and *n*-iodoalkyl radicals supports the predominance of a bridged structure, that is, a hypervalent halo

radical, mainly in the case of the iodine species (Scheme 5).^{6–14}

n-Chloro-1,*n*-diphenylalkyl radicals and *n*-iodo-1,*n*-diphenylalkyl radicals have been proved to photolyze to 1,*n*-diphenylalkanedyl biradicals when irradiated at a wavelength matching their optical



Scheme 5



Scheme 6 Two-photon homolysis of 1,5-diiodo-1,5-diphenylpentane.

absorption. The laser drop technique has made it possible to perform product studies under high intensity irradiation conditions while minimizing the amounts of secondary products. Such studies have demonstrated that 1,5-diphenyl-1, n -alkanedyl biradicals mainly cyclize to 1,2-diphenylcyclopentane when photolyzing the iodine-stabilized radical⁶ (Scheme 6), whereas in the case of the chloro-analogs, they mainly undergo disproportionation. This agrees with the cyclic character of iodine radicals.

C-Halogen α -Cleavage of Haloalkenes and Haloarenes

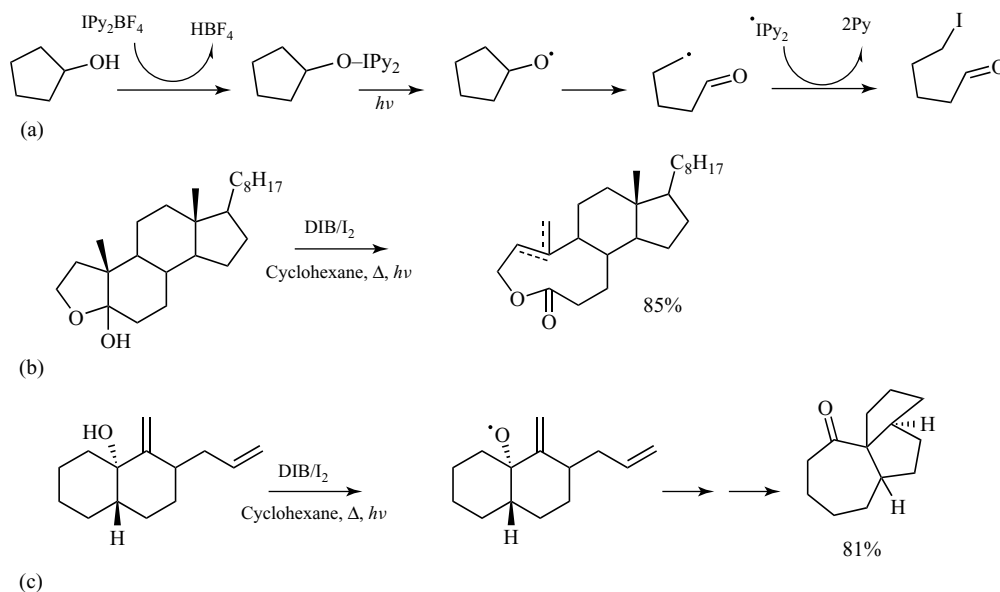
Homolysis of the C–X bond in haloalkenes affords vinyl radicals, whose main reaction is hydrogen or

halogen atom abstraction.¹⁵ Homolytic cleavage of aryl carbon–halogen bonds produces aryl radicals, which can participate in a radical aromatic substitution or abstract hydrogen from a donor.¹⁶ Homolysis requires that the energy of the reactive species be greater than the C–X bond dissociation energy. In simple benzene derivatives, the energy of the excited states is similar to that of many halogen–aryl bonds. However, the process is less likely in polycondensed aromatics because of the lower energy of their excited states.

O–I α -Cleavage of Iodanes

Alkoxy radicals are involved in the photooxidation of hydrocarbons and biological systems. These radicals can be generated photochemically from alcohols by visible light irradiation of dichloromethane solutions containing a hypervalent iodine reagent, such as the (diacetoxy)-iodobenzene (DIB)/I₂ system¹⁷ or bis(pyridine)iodonium tetrafluoroborate (IPy₂BF₄).¹⁸ The O–I cleavage of an iodane intermediate under light excitation leads to an alkoxy radical (Scheme 7a). The C–C β -scission of the alkoxy radicals provides a carbonyl compound and an alkyl radical. This is a reversible reaction, which generally leads to homolysis of the C–C bond belonging to the most significantly strained substructure and produces the most stabilized carbon radical. Therefore, the regioselectivity of this reaction is generally predictable, thus allowing the synthesis of aldehydes and ketones from alcohols under neutral conditions.

An example of the application of C–C β -scission of alkoxy radicals in organic synthesis is the photolysis of steroidal lactols under inert atmosphere, which, after formation of the alkoxy radical, undergo β -fragmentation and provide C-centered radicals; subsequent loss of a hydrogen atom affords medium-sized lactones in good yield (Scheme 7b). Similar fragmentations have been applied to the preparation of a variety of medium-sized ketones and aldehydic biquinanes. In addition, fragmentation of anomeric alkoxy radicals from carbohydrates provides a convenient entry into chiral building blocks (see **Radical Arylations**). Furthermore, ketones have been prepared in high yield by means of cascade radical fragmentation–transannular cyclization sequences (Scheme 7c).



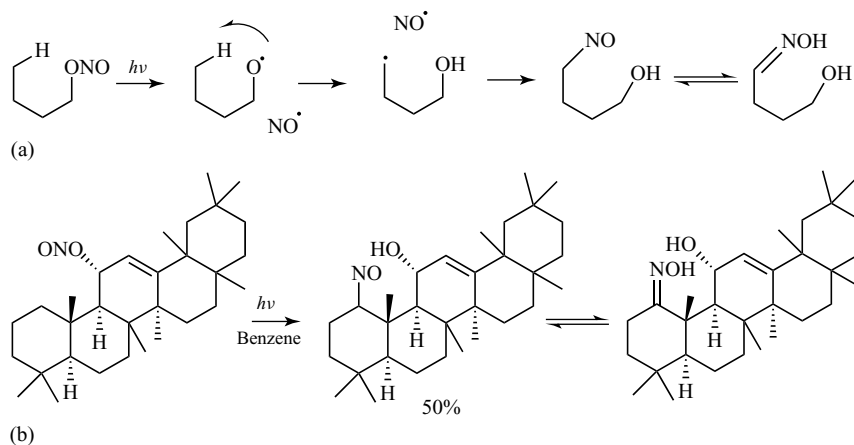
Scheme 7

N-O α -Cleavage of N-Alkoxy Compounds

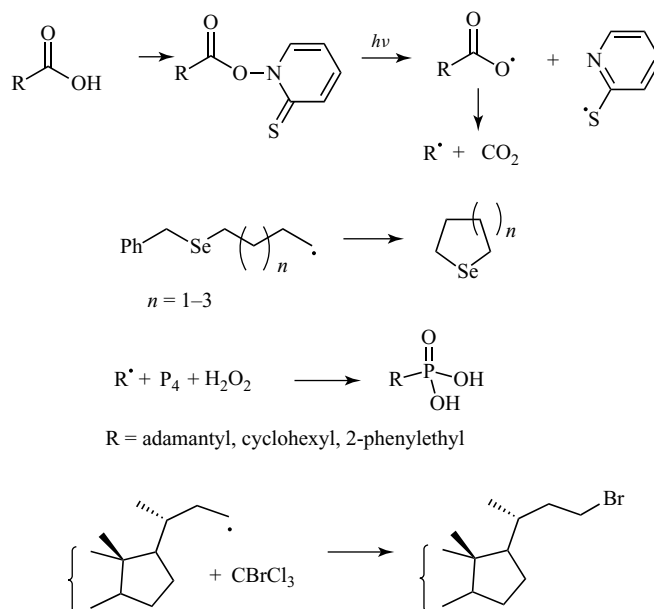
Nitrite esters can be prepared by reaction of alcohols with nitrosyl chloride.¹⁹ The Barton reaction involves photolysis of the N–O bond of a nitrite ester to generate an alkoxy radical, which abstracts a hydrogen atom from an appropriate C–H bond, leading to an alkyl radical (Scheme 8a). Recombination in the solvent cage produces a nitroso alcohol.²⁰ In the presence of oxygen, this can eventually lead to a nitrate ester. The Barton reaction has

allowed the functionalization of remote and nonactivated positions in steroids (Scheme 8b), as well as the synthesis of cyclic alkenes from γ,δ -unsaturated alcohols.

In addition, a carboxylic acid can be converted into a thiohydroxamate ester (Scheme 9).²¹ Homolytic cleavage of the N–O bond leads to a 2-pyridylthiyl radical and an acyloxy radical. After decarboxylation, the alkyl radical reacts with a broad range of compounds, such as alkenes,



Scheme 8



Scheme 9

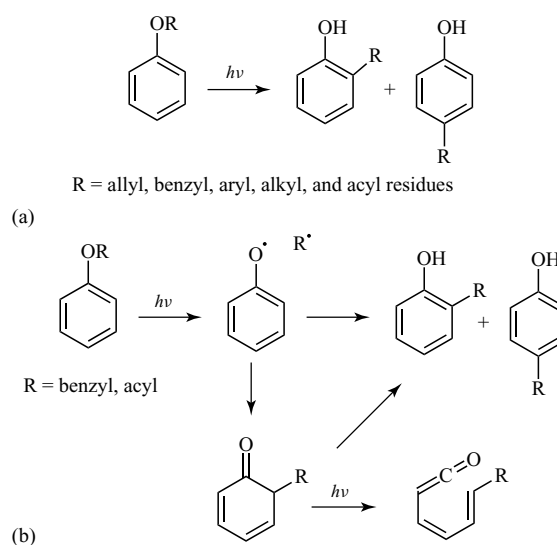
disulfides, seleno compounds, and sulfur dioxide, as well as with phosphorus or other elements (Scheme 9). This reaction has been shown to be versatile for the synthesis of biologically active compounds such as carbohydrates, amino acids, vitamins, and terpenoids.

C–O α -Cleavage of Aromatic Ethers and Esters

The photorearrangement of aromatic ethers (photo-Claisen)²² and esters (photo-Fries)²³ is a classical photochemical process of aromatic molecules, which are mechanistically related (Scheme 10). It consists in the formation of a singlet radical pair (a carbon-centered and an oxygen-centered radical) within a solvent cage after homolysis of an aryloxy–alkyl (photo-Claisen) or an aryloxy–acyl bond (photo-Fries),²⁴ followed by in-cage recombination to *ortho*- and *para*-coupled products. Experimental evidence for this process comprises, among others, (i) detection of phenoxy radicals,^{25,26} (ii) spin trapping of radicals,²⁷ and (iii) measurements of magnetic isotope effects and external magnetic field effects on formation of the resulting products.²⁸

Quantum yields of the photoproducts do not reflect the excited state reactivity. This is because of a predominant C–O versus C–C coupling, which has been demonstrated in an intermolecular approach, where considerable recombination to the

starting material is observed. The quantum yield of the rearranged product is higher in hydroxylic solvents than in cyclohexane; this effect has been explained as being due to stabilization of an intermediate cyclohexadienone (Scheme 10). In fact, laser flash photolysis of benzyl phenyl

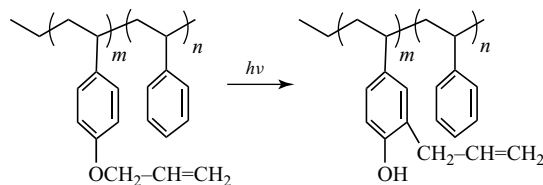


Scheme 10

ethers and phenyl acetate in methylcyclohexane has shown the appearance of a transient signal ($\lambda_{\max}$ at circa 305 nm), ascribed to the corresponding cyclohexa-2,4-dienones. Two-laser two-color laser flash photolysis has made it possible to detect the cyclohexa-2,4-dienone and its subsequent photolysis to a dienic ketene (Scheme 10).²⁹ The first laser (synthesis laser) generates the dienone with 266-nm pulses, whereas the second laser (photolysis laser) with 308-nm pulses matches the absorption of the cyclohexa-2,4-dienone.

These reactions have been chosen as models to study the influence of different media as modifiers of reactivity and selectivity.^{30–32} Studies have been performed in several constrained environments, such as polymers, cyclodextrins, and zeolites. Thus, the influence of medium polarity and polymer relaxation on the motion of the singlet radicals has been studied for the photo-Fries rearrangement of 1-naphthyl (*R*)-2-phenylpropanoate in poly(vinyl acetate) films in their glassy (5 °C) and melted (50 °C) states, and has been compared with the results in ethyl acetate, polyethylene films, and *n*-hexane.³³ These observations indicate that high stereo- and regioselectivities can be obtained if parameters such as the relationship between the rates of in-cage motion and cage-escape or between the rates of radical tumbling and translation are controlled.

Recently, the photo-Claisen reaction has been applied to the formation of micelles from a poly(4-allyloxystyrene)-block-polystyrene diblock



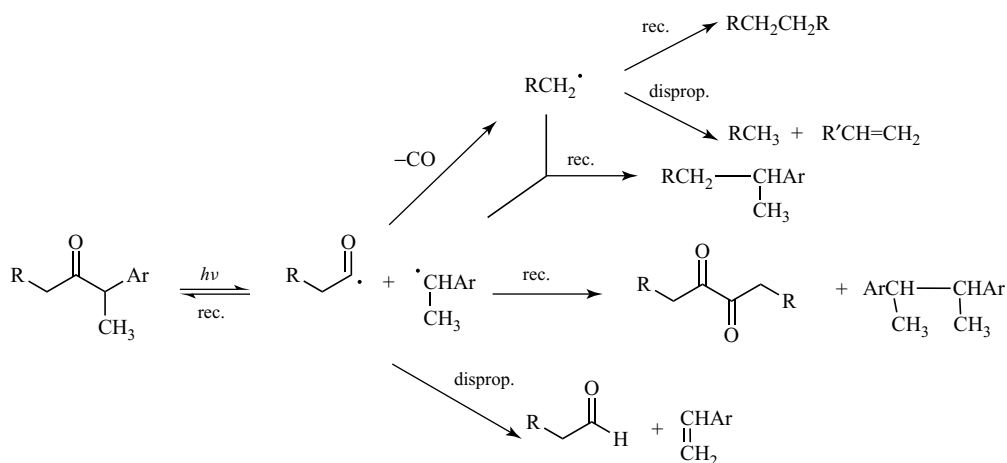
Scheme 11

copolymer in cyclohexane. The conversion of the 4-allyloxystyrene units reaches 90% after irradiation for 24 hours, and the isolated copolymer with a 35-nm hydrodynamic diameter aggregates into micelles with a 98-nm diameter (Scheme 11).³⁴

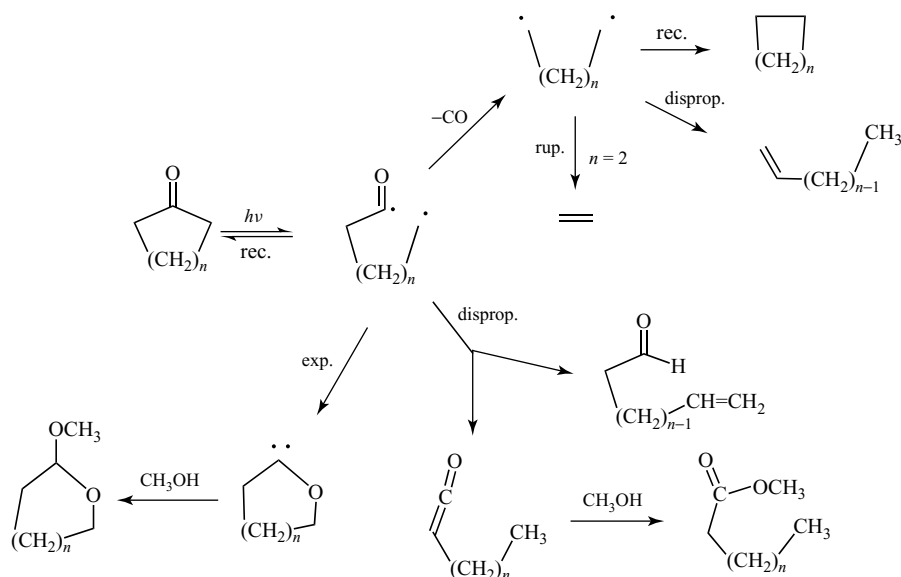
There are many variations of these reactions, which have been extended to other systems, such as anilides, phenoxyacetic acids, aryloxyacetones, sulfonanilides, carbonates, carbamates, sulfonates, benzyl amines, and benzyl alkyl ketones.

C–C α -Cleavage of Ketones

Excitation of alkyl and alkyl aryl ketones induces homolytic bond cleavage at the α -position of the carbonyl group, leading to alkyl acyl radical pairs (Scheme 12). Ketones exhibit reactivity in the excited state analogous to that presented by the alkoxy radicals in the ground state. Thus, the weakest α -bond is cleaved, leading to the most stable radical.^{35–38} In general, the reactivity increases with the stability of the generated radical and with strain release.



Scheme 12



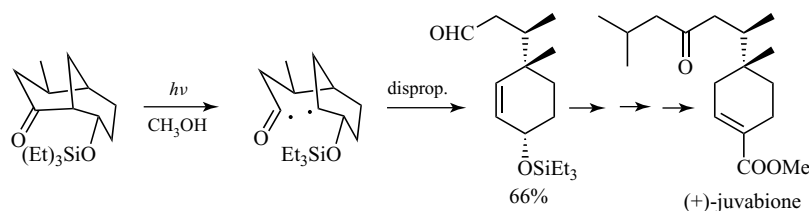
Scheme 13

This reaction, known as the *Norrish type I reaction*, is faster for $n\pi^*$ than for $\pi\pi^*$ excited states, owing to the weakening of α -bond in the former by overlap with the half vacant n -orbital on oxygen. In addition, the α -cleavage reactivity of $n\pi^*$ triplets is circa 100 times higher than that of singlet excited states. As a consequence, the reaction is faster for aliphatic than for aromatic ketones, owing to the more stabilized triplet of the latter.

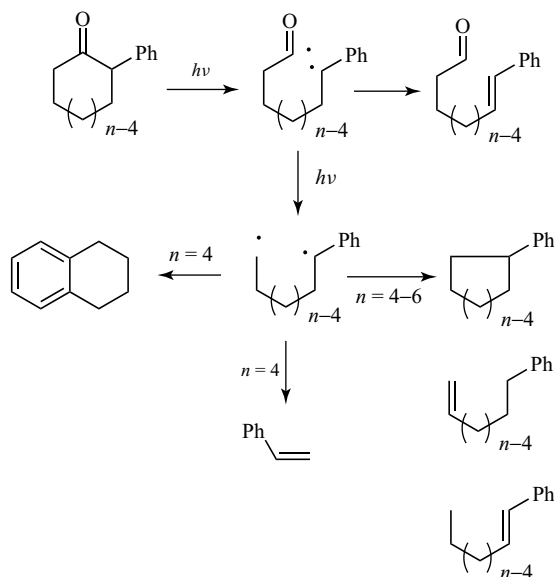
The generated radicals can undergo (i) mutual recombination, which explains that reaction quantum yields are less than unity; (ii) homocoupling; and (iii) disproportionation to an aldehyde and an alkene or a ketene plus an alkane (Scheme 12). In addition, the acyl radical can decarbonylate if a very stable radical is formed, as in the case of dibenzylketones.

In the case of cyclic ketones, new products arise owing to the possibility of secondary intramolecular reactions (Scheme 13). Thus, cyclobutanones can undergo ring expansion (exp.) to produce oxacarbenes, which react with nucleophiles such as alcohols. The product distribution will depend on the relative values of the rate constants of the different competing processes. Decarbonylation can predominate in the presence of radical-stabilizing groups at the α - and α' -positions, if no hydrogen atoms are accessible for disproportionation (disprop.), or when a significant ring strain is released by the loss of CO. Crystalline ketones with radical-stabilizing groups in the two α -positions can efficiently photodecarbonylate and lead to biradicals, which can eventually couple in an almost quantitative yield.³⁹

An example of the application of C–C α -scission of ketones is the synthesis of a precursor of the



Scheme 14



Scheme 15 Photogeneration and photolysis of acyl-alkyl radicals.

sesquiterpene (+)-juvabione by irradiation of an enantiopure bicyclo[3.3.1]nonanone⁴⁰ (Scheme 14). Photolysis of the ketone leads to the acyl-alkyl biradical, which disproportionates mainly to the aldehyde (66% yield).

Acyl-alkyl biradicals exhibit transient UV-absorption spectra, which are practically coincident with those of the corresponding alkyl radicals, since acyl radicals do not absorb at wavelengths longer than 300 nm. Thus, the spectrum of the acyl-alkyl biradical of 2-phenylcycloalkanones compares well with that of the corresponding benzyl radical. These intermediates undergo disproportionation under thermal conditions, while they decarbonylate to biradicals upon further irradiation, eventually leading to products arising from the dialkyl biradicals (Scheme 15).⁴¹ This process has been explained as occurring via light absorption by the benzyl radical, followed by an intramolecular energy transfer to the acyl radical.

C–S α -Cleavage of Thioethers

In general, thioethers undergo homolytic cleavage of the C–S bond from the singlet excited state. The resulting thiyl radicals mainly couple, whereas alkyl radicals stabilize via hydrogen abstraction, loss of a hydrogen atom, or coupling. In the presence

of nucleophilic or electrophilic alkenes, selective trapping of either of the two types of radicals occurs, taking into account the electrophilic or nucleophilic character of the radical partners.⁴²

C–N α -Cleavage of Azo Compounds

Azoalkanes exhibit $n\pi^*$ bands in the 300–400 nm region. This absorption is weak, but it is suitable for the photoextrusion of molecular nitrogen.⁴³ Theoretical and experimental evidence supports the stepwise elimination of nitrogen, via singlet or triplet diazenyl biradicals.

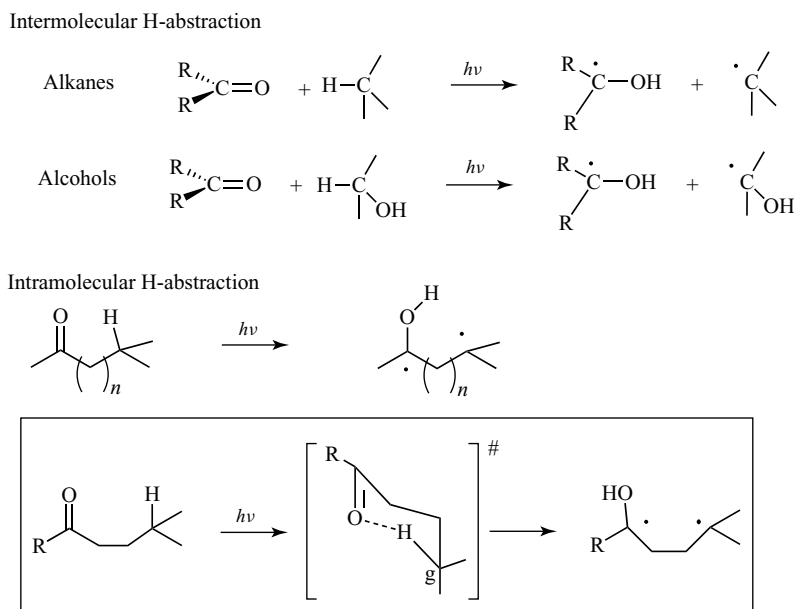
2.1.2 H-Abstraction

H-Abstraction by Ketones

As mentioned earlier, ketones exhibit reactivity in the excited state, which is analogous to that presented by alkoxy radicals in the ground state. The latter can abstract a hydrogen atom from a nearby C–H bond leading to an alkyl radical. Similarly, carbonyl $n\pi^*$ singlets and triplets can abstract a hydrogen atom from good hydrogen donors such as alkanes, alcohols, and ethers, leading to the formation of ketyl/alkyl radical pairs or, in intramolecular processes, ketyl-alkyl biradicals (Scheme 16).^{44,45} The efficacy of the process depends on the C–H bond strength and, in the intramolecular case, on conformational effects. Thus, the reaction generally proceeds through a 6-membered cyclic transition state with a chair conformation, being the Csp^3 –H at the γ -position—the one undergoing homolytic cleavage if it is close to the carbonyl group (Scheme 16). However, H-abstraction can also occur from other positions such as δ , β (if the γ and δ C–H are encumbered), and ε (less frequent).

For the same hydrogen donor, the rate of hydrogen abstraction increases with increasing triplet energy of the ketone; for example, $k_H = 6 \times 10^5$ or $3 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for hydrogen abstraction from isopropanol by benzophenone and biacetil, respectively. This process competes advantageously with α -cleavage of the carbonyl compounds. In addition, aromatic ketones with a low-lying $\pi\pi^*$ triplet excited state do not undergo this reaction, since this type of triplet does not behave as an alkoxy radical.

The alkyl/ketyl radical pairs generated in the intermolecular reactions undergo the typical reactions of radicals, such as homo- and heterocoupling



Scheme 16

recombination, as well as disproportionation (Scheme 17a). In addition, the 1-hydroxy-1,4-biradicals generated by H-abstraction from the γ -position can give rise to (i) cyclobutanols via C–C coupling (Yang reaction), (ii) the starting product via intramolecular disproportionation, and (iii) an enol and an alkene via C–C bond β -cleavage (Norrish II, see Scheme 17b).

The intramolecular disproportionation causes lower reaction quantum yields, but the addition of Lewis bases (alcohols, water, ethers, etc.), capable of forming hydrogen bonds with the hydroxy group of the ketyl radical, makes this undesired reaction less competitive. The fate of Norrish II biradical intermediates strongly depends on stereoelectronic factors, since cleavage requires the overlap between the involved β C–C bond and the p orbitals of the radical centers. Those factors that disfavor this process make the Yang cyclization a more competitive process. There are two limit conformations for the biradicals, namely, the extended and the gauche conformations. Both intramolecular disproportionation and cyclization require the gauche geometry, whereas fragmentation can occur from both conformations.

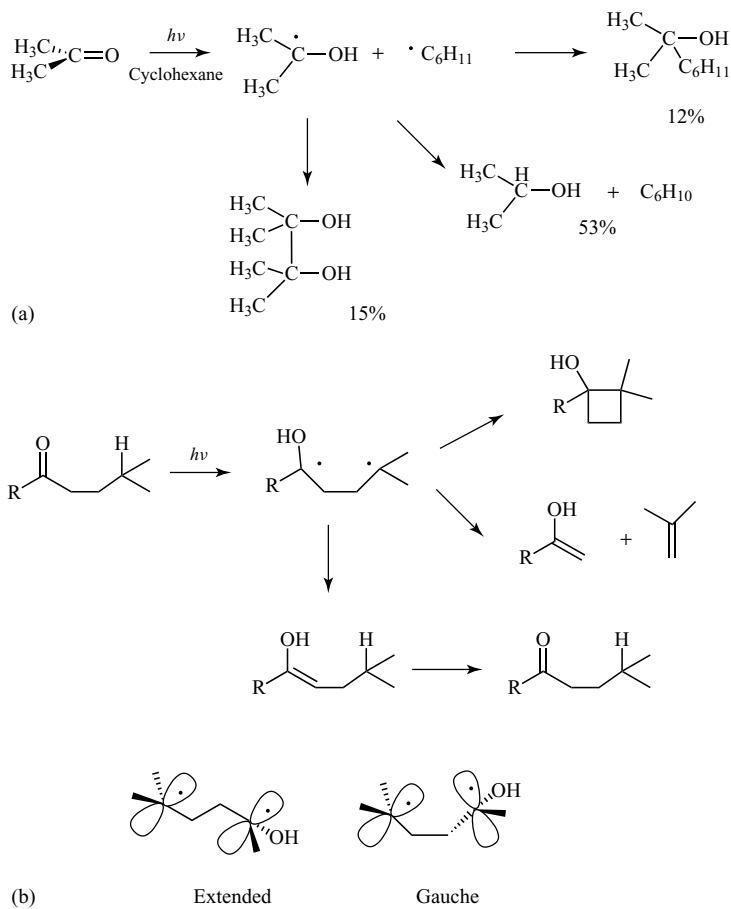
Abstraction from the δ -position may happen if no hydrogen atom is available at γ -position

(Scheme 18). Fragmentation of the resulting 1-hydroxy-1,5-biradicals is not a competitive process and, therefore, cyclopentanol is produced. These processes allow application of the Yang reaction to the synthesis of heterocyclic compounds when a heteroatom is present at the δ -position. In addition, H-abstraction can also occur from the β -position, giving rise to 1-hydroxy-1,3-biradicals.

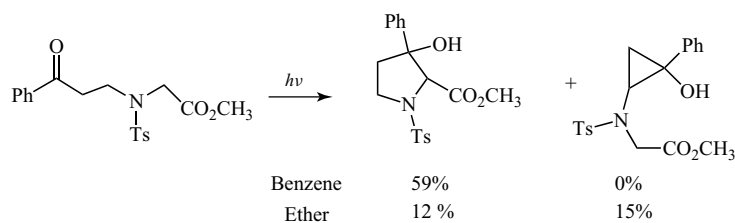
Hydrogen abstraction can also occur at remote positions, and thus the Yang-like cyclization has been used in drug–biomolecules studies,⁴⁶ such as in ketoprofen–cholesterol dyads. This has also been applied with synthetic purposes, for example, in the regio- and stereoselective formation of macrocycles.^{47,48}

Moreover, the C–O bond formation in the course of the Norrish–Yang reaction has also been described in α -mesyloxy- β -keto amides (Scheme 19). Abstraction from the δ -position is followed by a fast loss of methanesulfonic acid to give enolate biradicals. This provides a regioselective cyclization of α -mesyloxy- β -keto amides to 3,4-dihydro-2H-1,3-oxazin-4-ones.

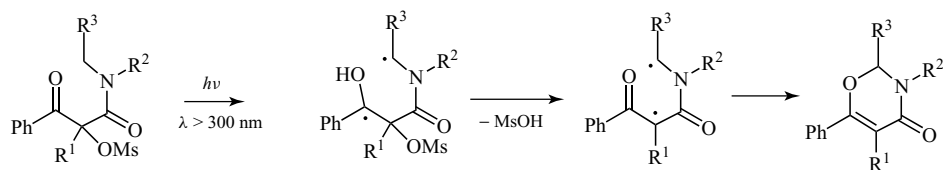
An interesting synthetic application of the intermolecular version is the benzophenone-photosensitized addition of radicals to unsaturated substrates, such as the amidation of α,β -unsaturated



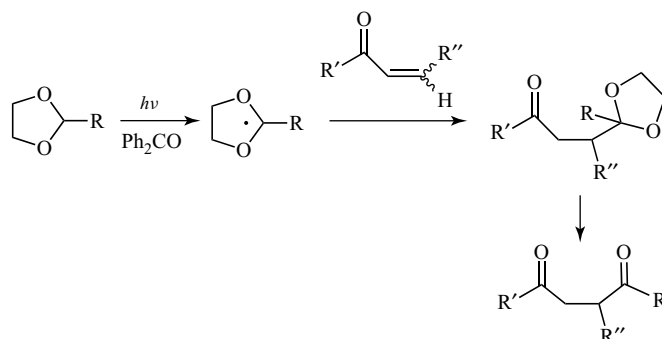
Scheme 17



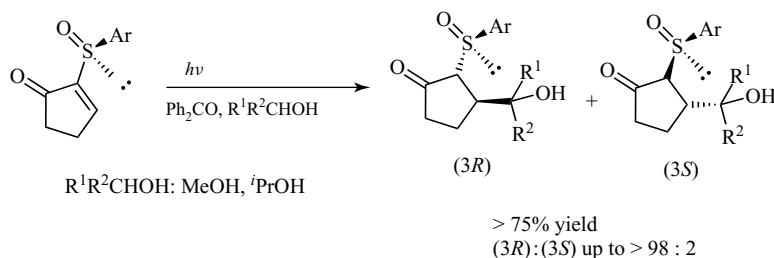
Scheme 18



Scheme 19



Scheme 20

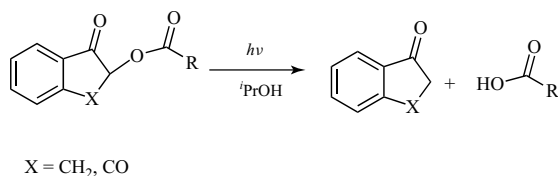


Scheme 21

esters with formamide.⁴⁹ This strategy has been successfully applied to the synthesis of 1,4-diketones; the radical generated after H-abstraction from 2-alkyl-1,3-dioxolanes by benzophenone efficiently adds to α,β -unsaturated ketones (mainly cyclic enones), eventually leading to 1,4-diketones (Scheme 20).

In addition, *O*-stabilized alkyl radicals undergo addition to chiral α -(arylsulfinyl) enones with high diastereoselectivity (Scheme 21).⁵⁰ This strategy can be used for the synthesis of chiral 3-alkylcyclopentanones and 4-alkyl-2-pentanones, owing to the easy removal of the sulfinyl group.

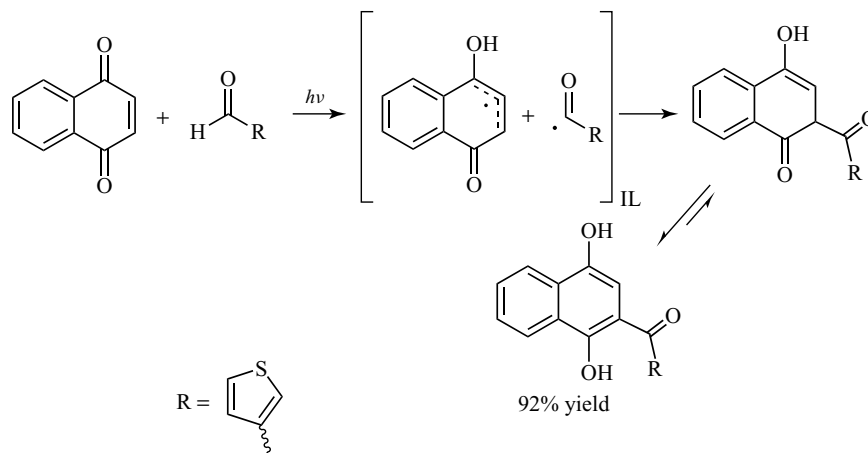
Moreover, the intermolecular H-abstraction reaction has been used as a strategy for the photo-removal of protecting groups. Thus, 1-oxoindan-2-yl and 1,3-dioxoindan-2-yl groups have been shown to be adequate as photoremovable protecting groups of carboxylic acids in the presence of high concentration of hydrogen donors (Scheme 22).⁵¹ The use of 1,3-diones can be beneficial, mainly in the presence of other potentially photolabile groups, owing to their improved absorption properties.



Scheme 22

H-Abstraction by Quinones

The photo-Friedel–Crafts reaction is one of the methods of photoinduced acylations.⁵² It is based on the hydrogen abstraction from aliphatic and aromatic aldehydes by the 1,4-quinone triplet excited state to generate a radical pair, which combines within the solvent cage⁵³ and/or escapes (Scheme 23). In the latter case, the free acyl radical can subsequently add to a second quinone in a free radical chain reaction.⁵⁴ The operating mechanism depends on the specific reaction conditions. The photoproduct, an acylated hydroquinone, can then be oxidized, leading to the corresponding acylated quinone.⁵⁵ This reaction



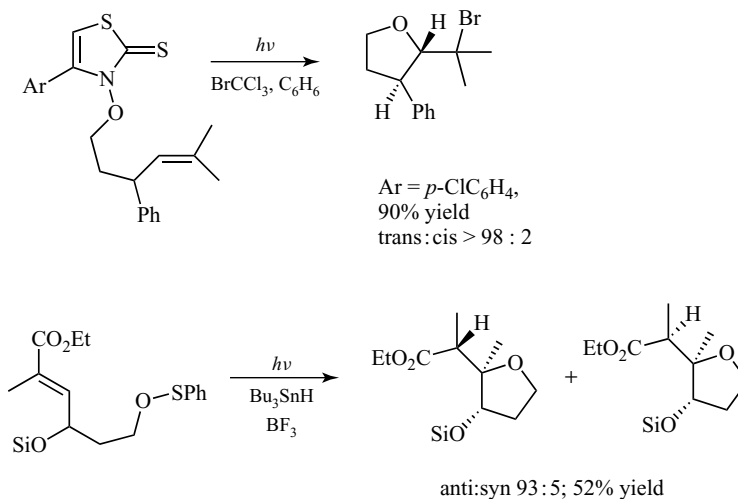
Scheme 23

can be performed on a large scale as demonstrated by Mattay *et al.* in the photoinduced acylation of 1,4-quinone and 1,4-naphthoquinone with aliphatic and aromatic aldehydes using sunlight.^{56,57} Moreover, the photo-Friedel–Crafts acylation of 1,4-naphthoquinone with various aldehydes has been performed at room temperature in ionic liquids,⁵³ leading to high conversions and selectivities. This methodology avoids the use of hazardous solvents, such as benzene and acetonitrile, which are commonly used for this transformation, and has been applied in the preparation of heteroacylhydroquinones, with a high yield under sunlight.⁵⁸

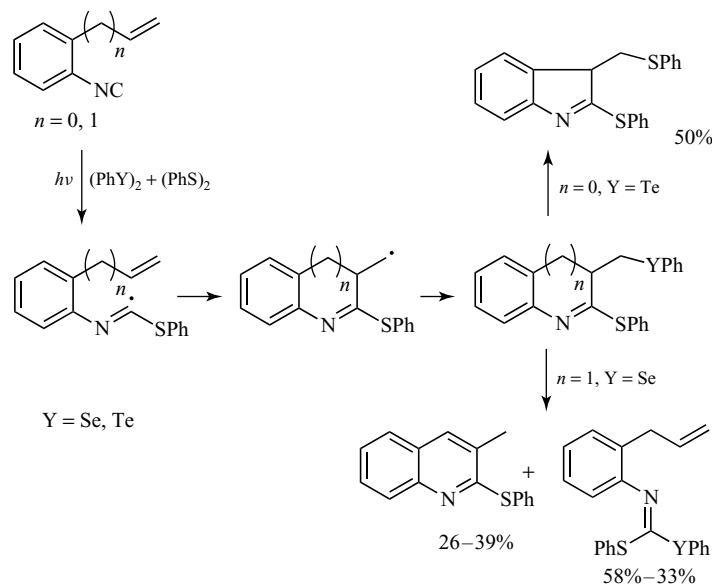
2.2 Radical Addition

The X–Y homolytic cleavage of several substrates followed by addition of the resulting radicals to unsaturated compounds can be a useful strategy for the generation of alkyl radicals. Subsequent trapping by hydrogen (Bu_3SnH), chlorine (Cl-CCl_3), bromine (Br-CCl_3), or iodine ($\text{I-C}_4\text{F}_9$, $\text{I-C(CH}_3)_2\text{CO}_2\text{Et}$) atom donors affords β -functionalized oxacycles, which can be used as building blocks for further reactions.

Thus, as mentioned earlier, alkoxyl radicals can be generated by means of N–O α -cleavage of



Scheme 24



Scheme 25

N-alkoxy compounds; then, these radicals can undergo addition to olefinic π -bonds, which has been applied to the synthesis of substituted oxacycles (Scheme 24). The 5-exo-trig-cyclization is the most studied O-radical addition reaction, which proceeds under kinetic control. Similarly, the photochemical S–O α -cleavage of sulfenates with an appended olefinic chain can lead to tetrahydrofurans in the presence of Bu_3SnH .

Moreover, the visible light-absorbing diphenyl ditelluride ($PhTeTePh$) can be used for a smooth photo-thiotelluration of isocyanides in the presence of diphenyl disulphide ($PhSSPh$).⁵⁹ This reaction has been applied to the radical cyclization of *ortho*-vinyl and *ortho*-allyl substituted phenylisocyanides and leads to the formation of bithiolated indole and quinoline derivatives, respectively, in moderate yields (see **Unusual Radical Acceptors**) (Scheme 25).

3 ELECTRON-TRANSFER PROCESSES

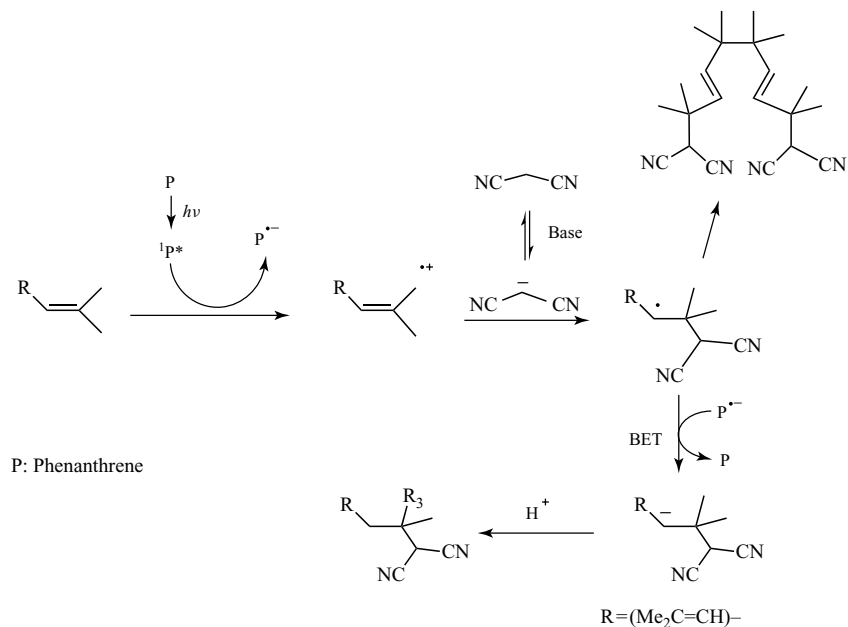
Photoinduced electron transfer (PET) reactions have been extensively applied as an interesting route in synthetic organic photochemistry. Light excitation is an adequate strategy for generating radical ions in solution, since molecules are

more easily reduced and oxidized in the excited state. Carbonyl chromophores (ketones, aldehydes, quinones, amides, imides) and aromatic compounds with electron-withdrawing groups (aromatic nitriles, pyridinium, and pyrylium salts) are strong electron acceptors in their excited states and can oxidize substrates such as alkenes, aromatic compounds, amines, thioethers, and carboxylates, among others. In addition, other excited states, such as aromatic compounds with electron-donating groups, can act as reductants. The generated radical cation (radical anion) can act as a secondary electron acceptor (electron donor) in a photocatalytic process; in addition, it can combine with a nucleophilic (electrophilic) species or eliminate an electrophilic (nucleophilic) species to generate radical intermediates.

3.1 Oxidation Followed by Coupling with Nucleophiles

3.1.1 Photosensitized Alkylation of Alkenes

A light-absorbing compound may act as an electron acceptor and play the role of a photosensitizer.⁶⁰ PET from alkenes or dienes to the singlet excited state of the photosensitizer affords radical cations,



Scheme 26

which have to escape from the solvent cage to avoid coupling to the photosensitizer radical anion (Scheme 26). The substrate radical cation reacts with the anion of an active methylene compound (the nucleophile) to form radical intermediates. Back electron transfer from the photosensitizer radical anion followed by protonation produces the anti-Markovnikov adduct of the mono-olefin. In the case of the dienes, the allylic radical dimerizes. Single electron transfer (SET) from the nucleophile is a competitive reaction, but it represents a minor reaction when the nucleophile concentration is maintained low by using a weak base. These reactions represent a green strategy for C–C bond formation, since they require weak bases, such as alkaline metal carbonates, they occur at room temperature, and they do not use noble metals or halogens.

3.2 Reduction Followed by Coupling with Electrophiles

3.2.1 Addition of Ketyl Radicals to Alkenes

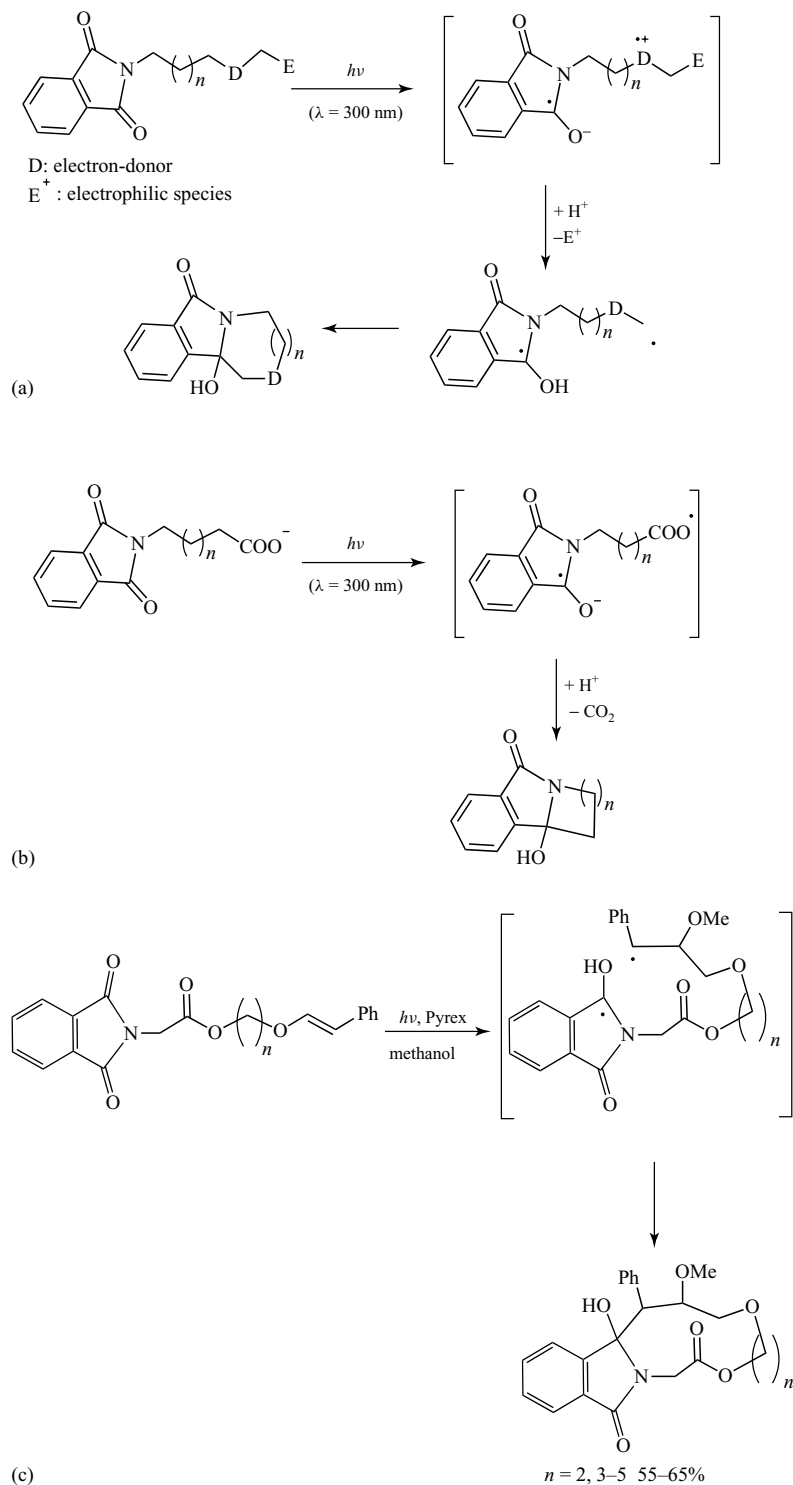
PET from tertiary amines to acetophenones and nonaromatic ketones followed by proton transfer

leads to α -aminoalkyl/ketyl radical pairs.⁶¹ The nucleophilic ketyl radical can add to electron-deficient alkenes, such as furanones, in a stereoselective manner (see **Synthetic Radical Photochemistry**).

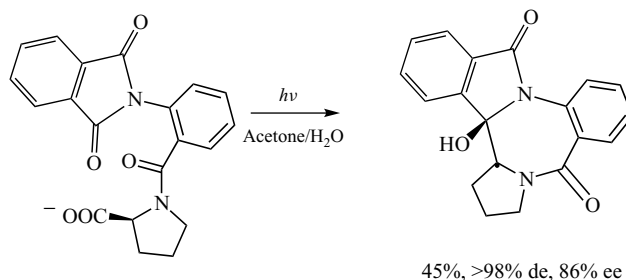
3.3 Inter- and Intramolecular Electron Transfer Followed by Elimination or Addition of a Neutral Species

3.3.1 Phthalimides

The phthalimide chromophore (reduction potential circa -1.4 V vs the saturated calomel electrode (SCE) in dimethylformamide (DMF) is a strong electron acceptor in the singlet and triplet excited states that can oxidize tethered carboxylate, thioether, and alkene groups, in carboxyalkyl-, thioalkyl-, and alkenyl-*N*-substituted derivatives, respectively. Subsequent protonation of the phthalimide anion and loss of a charged (proton, trimethylsilylmethyl cation) or a neutral (CO_2) electrophilic species generates a biradical, which eventually recombines to a cyclic compound (Scheme 27). The removal of a charged species



Scheme 27



Scheme 28

from the radical ion is termed *mesolytic cleavage* and this type of reactions will be discussed in Section 3.4.

Oxidation of the tethered carboxylate in carboxyalkyl-*N*-substituted derivatives leads to an acyloxy radical in addition to the phthalimide ketyl anion. This process is followed by the loss of CO₂ and protonation of the ketyl anion by the solvent to generate a biradical that recombines (Scheme 27b). Remarkable chiral memory has been detected in triplet-photosensitized reactions such as that shown in Scheme 28, where the radical generated after decarboxylation cyclizes to a pyrrolobenzodiazepine with 86% ee.⁶²

In addition, styrylalkyl-*N*-substituted phthalimides undergo medium- to macro-ring photocyclization via electron transfer between the arylalkenyl and the imide moieties separated by 6–13 bonds (Scheme 27c). This reaction occurs with solvent (methanol) incorporation to the double bond.⁶³ Similar intermolecular reactions have been observed for phthalimides with various olefins.

Mechanistic studies of sulfur-substituted *N*-alkylphthalimides have been performed using time-resolved UV–Vis spectroscopy. The low quantum yield of the cyclization is in accordance with the photoinduced charge separation occurring not in the phthalimide low-lying $\pi\pi^*$ excited state but in the spectroscopically undetectable higher lying $n\pi^*$ state.⁶⁴

3.4 Mesolytic X–Y Bond Cleavage

PET between neutral donors and acceptors leads to the generation of radical ion pairs. The unimolecular cleavage of radical ions into a radical and an

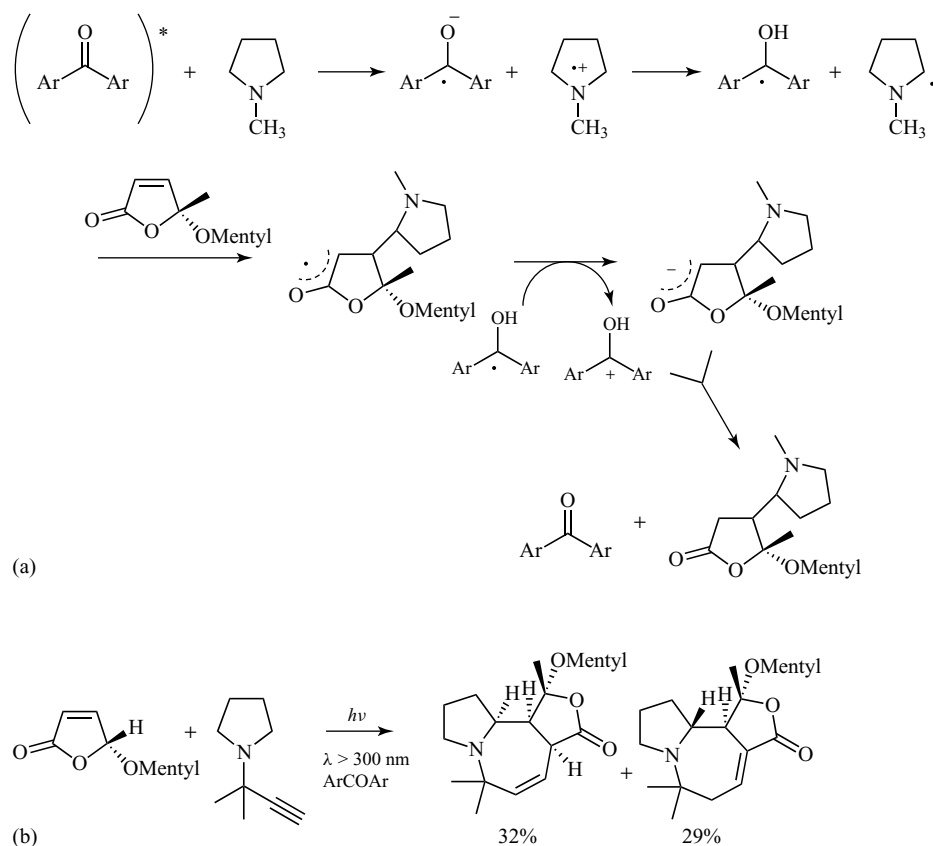
ionic species is termed *mesolytic cleavage*.⁶⁵ Photoinduced SET followed by radical cation fragmentation is a mild and selective strategy for generating radicals from neutral substrates. It has been demonstrated that the more difficult it is to oxidize a substrate, the more energy is accumulated in the radical cation, and therefore the bond cleaves more easily. Thus, fragmentation of strong σ bonds (C–C, C–H, C–Si) can be achieved. The preferred fragmentation can be predicted taking into account the electrofugacity of the leaving cation.⁶⁶

In the case of radical anions, their reactivity depends on the nature of the acceptor. Though, the number of examples of the applicability of radical anions to the generation of organic radicals is fewer than that of radical cations, there are interesting reports on their potential in selective organic synthesis. Some examples are presented in the following sections.

3.4.1 C–H Mesolytic Cleavage

Radical Addition of Tertiary Amines to Alkenes

PET from tertiary cyclic amines to electron-donor-substituted aromatic ketones (photocatalysts) leads to amine radical cations, which after loss of a proton, produce alkyl radicals (Scheme 29).⁶⁷ The nucleophilic character of alkyl radicals permits their trapping by electron-withdrawing substituted alkenes (unsaturated nitriles, esters, lactones, and ketones). The reaction has been carried out in gram scale and applied to asymmetric synthesis using enantiomerically pure 2-(5*H*)-furanones. In addition, in the presence of thiocarbonyl compounds, this strategy has been successfully applied to the addition of acyclic amines to alkenes. Moreover, in the presence



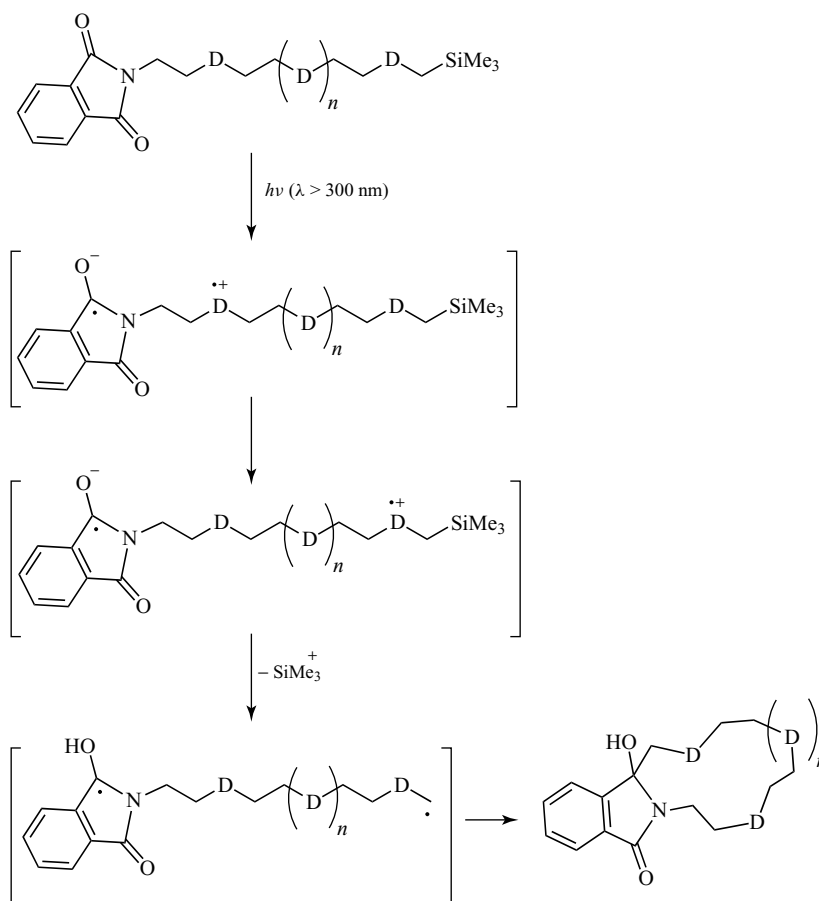
Scheme 29

of cyclic amines with a pendant unsaturated chain, a radical tandem addition–cyclization reaction has been used in the preparation of bicyclic and tricyclic derivatives. An intramolecular version of this reaction in the presence of a chiral sensitizer has also been reported.⁶⁸

3.4.2 C–Si Mesolytic Cleavage

N-Phthalimides linked to a polydonor chain, which contain C-terminal α -amidotrimethylsilyl groups, undergo macrocyclization reactions via sequential SET processes.^{69,70} Thus, electron transfer from the neighboring donor to the excited phthalimide chromophore leads to a radical cation generating an intermediate zwitterionic biradical. Intrachain SET would produce mixtures of interconverting zwitterionic biradicals, a process that

is fast when the polydonor radical cations have similar energies. Finally, hole migration to the α -amidotrimethylsilane center is followed by fast desilylation to form a $1,\omega$ -biradical intermediate, which recombines to the macrocyclic peptide (Scheme 30). Evidence for the involvement of SET processes in linked acceptor–polydonor systems has been found by means of pico- and nanosecond transient absorption measurements in naphthalimide–phenothiazine dyads.⁷¹ In addition, comparison between the photocyclization reactions in phthalimides and 2,3-naphthalimides linked to (trimethylsilyl)methyl ether donors via polyethylenoxy versus polymethylene chains has shown the higher chemical yields and quantum efficiencies of the polyethylenoxy-tethered substrates. This reaction has been applied to the preparation of crown ethers or cyclic oligopeptides. In general, medium- to macrocycles are accessible by this method.^{63,72}



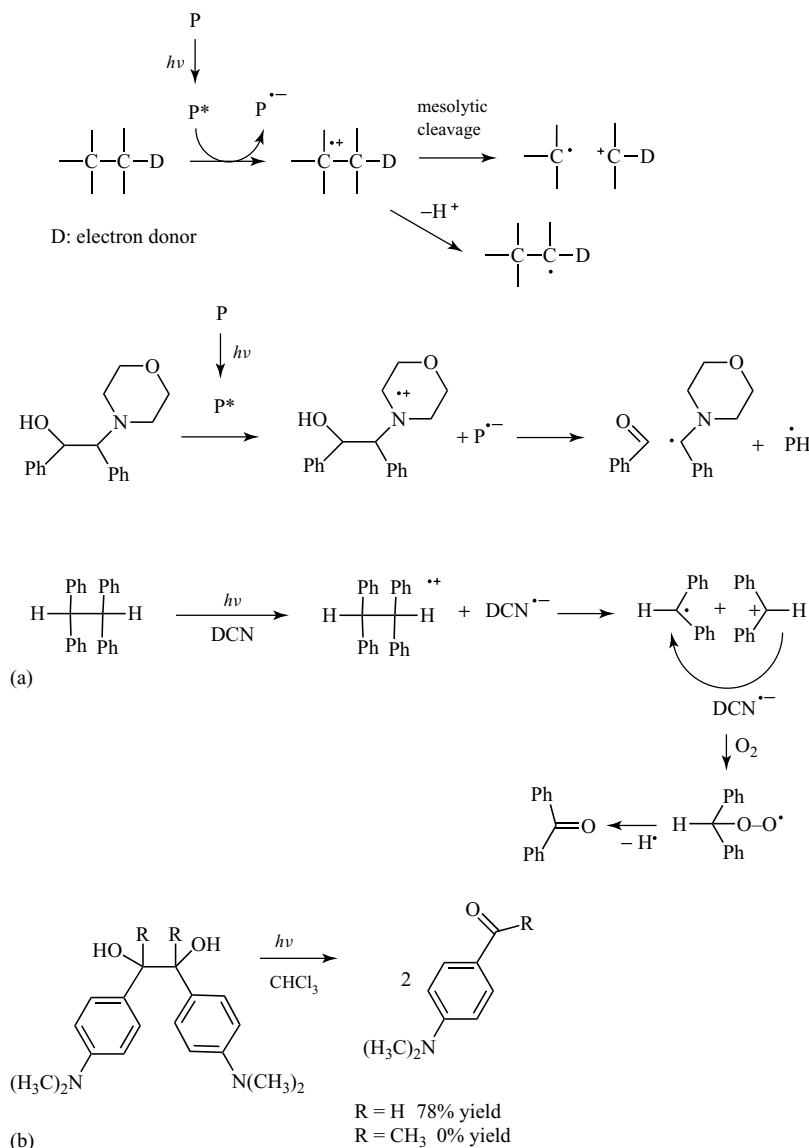
Scheme 30

3.4.3 C–C Mesolytic Cleavage

Mesolytic C–C bond cleavage (Scheme 31) is easier in carbocyclic compounds, where strain release provides the driving force for bond scission. In addition, unstrained C–C bond cleavage can occur mostly in aromatic substrates with aliphatic side chains. The presence of alkyl, aryl, hydroxyl, alkoxy, and siloxy groups at the α -position of the C–C bond lowers the barrier to the mesolytic cleavage, owing to the stabilization of the resulting cation via electron donation.⁶⁶ Deprotonation can be a competitive process to the C–C bond rupture in heteroatom-centered $\text{C}_\beta\text{--C}_\alpha\text{--X}^+$ radical cations, since removal of an electron from the heteroatom lone pair reduces the bond order of the geminal bonds (C–C, C–H, etc.).

In this reaction, radicals are generated in the presence of radical anions, and the cross-coupling can be fast. Thus, in the case of aromatic nitriles as photosensitizers, the radical anions are persistent and non-nucleophilic; as a consequence, they can further react with the radicals arising after the mesolytic cleavage. This results in an unconventional strategy for aromatic alkylation or formation of alkylidihydro derivatives.⁷³

Pinacols derived from benzophenones bearing dimethylamino substituents undergo C–C fragmentation via PET with chloroform followed by mesolytic C–C cleavage.⁷⁴ The fast dechlorination of the chloroform radical anion inhibits the back electron-transfer reaction (radical anion to radical cation)⁷⁵ and makes pinacol fragmentation feasible.



Scheme 31

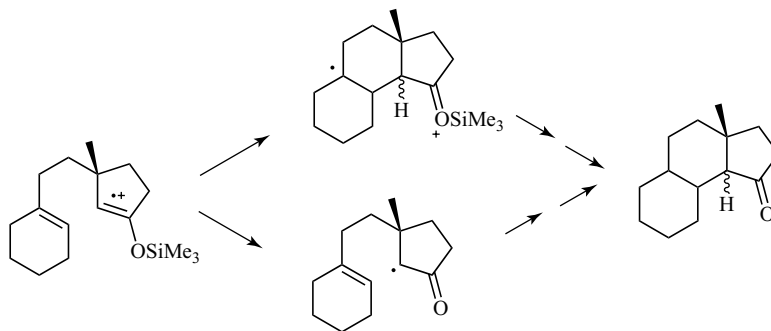
3.4.4 O-Si Mesolytic Cleavage

Electron-rich double bonds such as silyl enol ethers are easily oxidized by the excited state of electron-deficient aromatic compounds (dicyanoanthracene or dicyanonaphthalene). Cyclization reactions of the initially formed silyloxy radical cation in cyclic silyl enol ethers tethered to an olefinic or an electron-rich aromatic ring can produce bicyclic and tricyclic ketones (Scheme 32).^{76,77} The desilylation

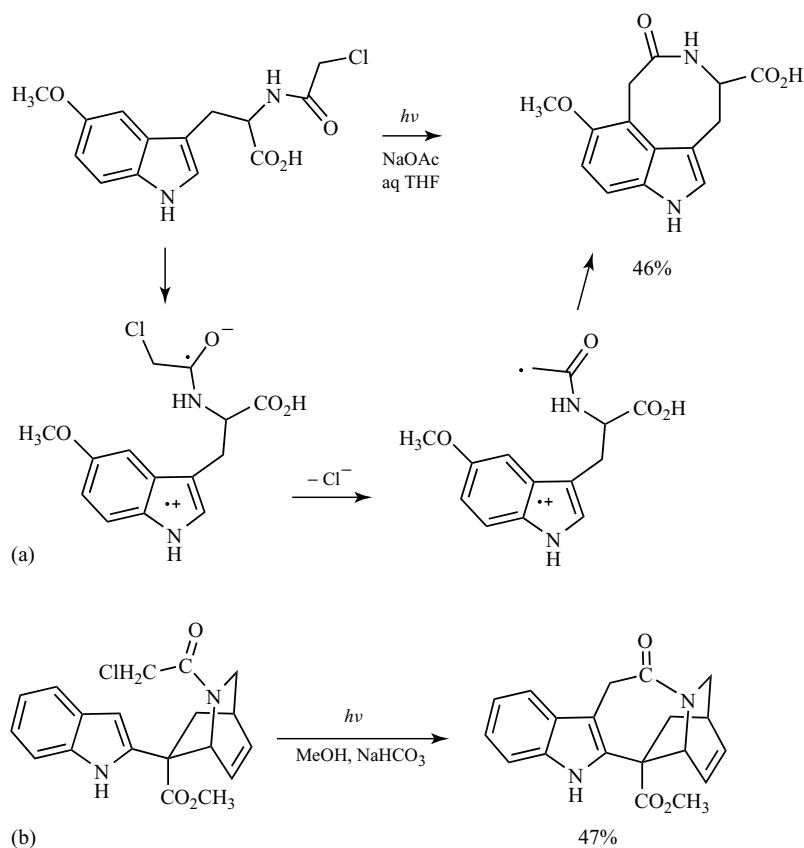
step can occur before or after the cyclization step.⁷⁸

3.4.5 C-Halogen Mesolytic Cleavage

Photoelectron transfer to the σ^* orbital of a carbon-halogen bond leads to σ -radical anions, which subsequently undergo mesolytic fragmentation to produce radicals and halide anions.



Scheme 32

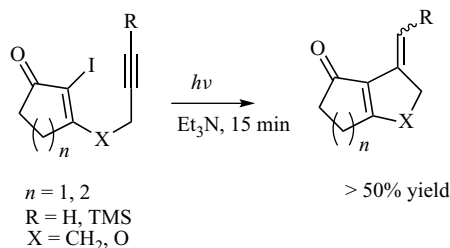


Scheme 33

Aromatic α -Chloroacetamides

The acetamide group can act as electron acceptor versus an appended excited aromatic moiety (Scheme 33).^{79–81} This step is followed by loss of the chloride ion to give an electrophilic alkyl

radical, which reacts with the aromatic ring and eventually leads to the aromatic substitution product. This reaction has been applied to the preparation of azepine derivatives, which are not easily accessible by ground state reactions.



Scheme 34

α -Iodo Enones

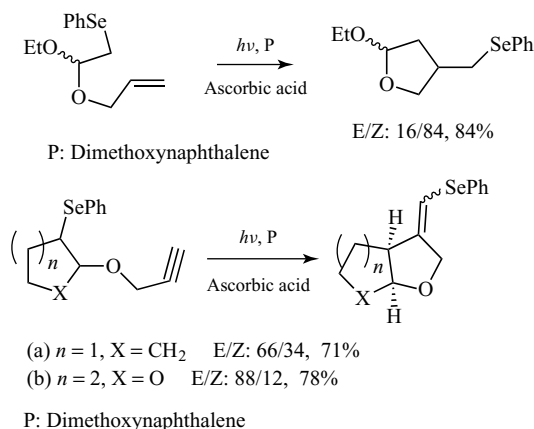
PET from triethylamine to α -iodo enones bearing an alkynyl moiety easily affords cyclization products in yields ranging from 50% to 75%, via the α -enone radical generated from mesolytic cleavage of the C–I bond (Scheme 34).⁸²

Electron Transfer to Chloroaromatics

Inter- or intramolecular electron transfer from amines to chloroaromatics, followed by mesolytic cleavage of the C–Cl bond, leads to aromatic radicals, which abstract a hydrogen atom from the medium.⁸³ Redox photosensitization has been used to reduce polychlorobenzenes with electron-donor photosensitizers such as *N, N, N', N'*-tetramethyl-*para*-phenylenediamine and 2-methoxyphenol.⁸⁴ However, when a chloropyridine residue is attached to an enaminone, mesolytic cleavage of the C–Cl bond leads to pyridyl radicals, which can proceed to cyclization products (Scheme 35).⁸⁵

3.4.6 C–Se Mesolytic Cleavage

Reductive activation of carbon–selenium bonds in $\text{R}_2\text{CH–SePh}$ compounds can be photosensitized by electron-rich aromatic compounds, such as

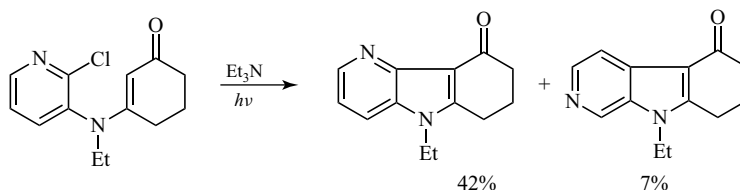


Scheme 36

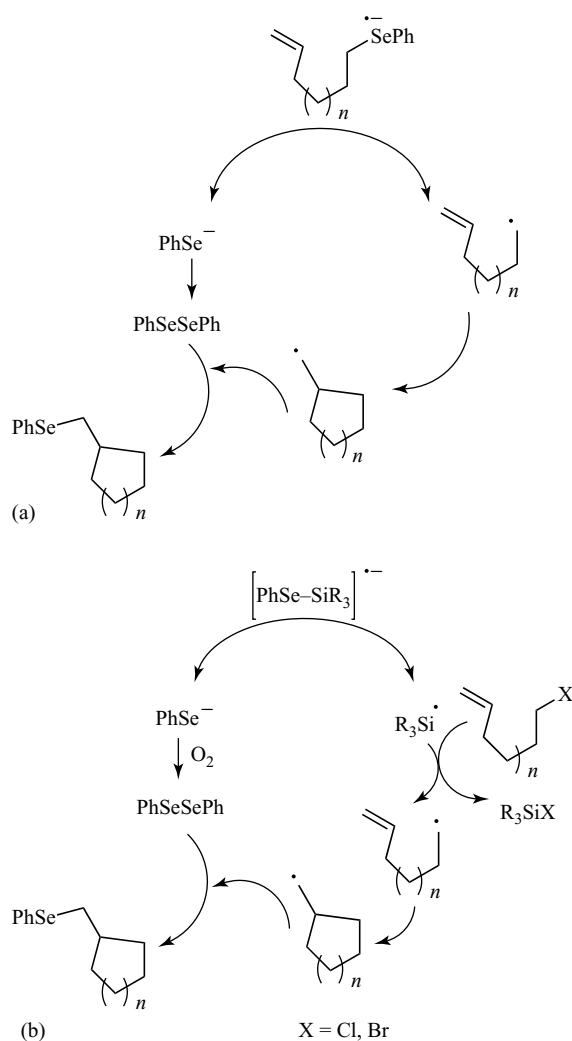
dimethoxynaphthalenes, in the presence of ascorbic acid as co-oxidant. The C–Se radical anions cleave to the carbon-centered radicals and PhSe radical.⁸⁶ This strategy has shown applicability as in the unimolecular phenylselenenyl group transfer reactions shown in Scheme 36.

3.4.7 Se–Se and Si–Se Mesolytic Cleavage

An interesting alternative to the use of hydride reagents to initiate radical additions is that of one-electron reductive PET activation of Se–Se and Si–Se bonds of PhSe–SePh and PhSe–SiR₃ seleno-organic compounds, respectively (Scheme 37). This bond activation is performed by using electron-rich aromatic photosensitizers, such as 1,3-dimethoxynaphthalene and dimethoxyanthracene, in the presence of ascorbic acid as the sacrificial electron donor.⁸⁷ In the case of PhSe–SiR₃, trialkylsilyl



Scheme 35



Scheme 37

radicals are generated; the alkylsilyl radical is more halophilic than alkyl- or aryl-substituted tin radical.

Moreover, taking into account the high rate constant ($9.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$) for the reaction of R₃Si radical with alkyl phenylselenides and the fast oxidative dimerization of PhSe anion to PhSe-SePh, a catalytic strategy for phenylselenenyl group transfer-based radical reaction has been developed from seleno-organic compounds as precursors.⁸⁸ The generality of the reaction has been demonstrated by carrying out model cyclizations, intermolecular additions, and tandem annulations.

3.4.8 N-S Mesolytic Cleavage

The N-S bond of *N*-tosyl amides undergoes cleavage after PET from 2-phenyl-*N*, *N*'-dimethylbenzimidazole to the amide, owing to the remarkable weakening of the N-S bond in the radical anion. This is a simple, mild, and chemoselective desulfonylation of *N*-tosyl amides.⁸⁹

4 SPECIAL TECHNIQUES FOR THE CHARACTERIZATION OF PHOTOCHEMICALLY GENERATED RADICALS

4.1 Flash Photolysis Spectroscopy

Throughout this chapter, we have mentioned examples in which the flash photolysis technique has been applied in the detection of radicals generated after irradiation of different types of substrates.⁹⁰ It uses a short and intense flash of light (pump source), often from a laser, to generate the reactive species in high concentration, allowing spectroscopic detection. The absorption changes can be recorded, for example, using a spectrally continuous xenon lamp (probe source). Probe sources in a pulsed mode can be used to enhance the photon flux for measurements in short-time ranges.

Both spectral and kinetic data can be obtained; in the spectral mode, complete transient absorption spectra are measured at a specific time after excitation using a time-gated array detector. In the kinetic mode, the transient absorption, generated by the light pulse, is recorded at a given wavelength as a function of time by using a photodetector and a digital storage oscilloscope. In general, transient absorption features can be measured with temporal resolutions from picoseconds to milliseconds in pulsed mode, and milliseconds to seconds in continuous mode.

In addition, the application of the *two-photon two-color laser flash photolysis* to study the photoreactivity of photogenerated radicals has been mentioned above. A first laser pulse (referred to as *synthesis* laser) produces the radical, whereas the second laser pulse from the *photolysis* laser excites it.⁹¹ The wavelength of the photolysis laser is selected so as to match the optical absorption of the radical.

In laser flash photolysis, a problem may arise when the photogenerated radicals do not absorb in the available analyzing wavelength range so as to be optically detected. This problem can be circumvented by using other time-resolved detection techniques, such as *time-resolved infrared (IR) spectroscopy*. This technique also uses a pump-probe methodology; the pump pulse is often generated by a pulsed laser, whereas the probe beam is in the IR region. Thus, alkoxycarbonyl radicals generated after laser excitation can be characterized in this way, monitoring the characteristic highly intense carbonyl stretching bands.⁹²

4.2 Other Spectroscopic Techniques

Photoacoustic Spectroscopy

Photoacoustic spectroscopy is based on the monitoring of heat evolved from nonradiative deactivation of the transient species obtained after the excitation of an absorbing molecule.⁹³ The rapid nonradiative relaxation of the generated transient species causes a local heating in the medium. This causes a density change of the solvent, inducing a change in the refractive index, which leads to a thermal wave monitored by a probe laser. Intersystem crossing, internal conversion, and photochemical reactions are detectable with this technique, which can provide important kinetic and thermodynamic information on metastable species produced directly or indirectly in the system and can be of particular interest for the study of nonoptically detectable species. Regarding radicals, photoacoustic spectroscopy has allowed the determination of the enthalpy of formation of the benzophenone ketyl radical from the reaction of the benzophenone triplet excited state and benzydrol. In addition, it has been applied to the determination of the α (C–H) bond dissociation energy of amines by monitoring the H-abstraction by triplet benzophenone.

Time-Resolved Fluorescence Spectroscopy

Time-resolved fluorescence spectroscopy of radicals is also a useful tool in radical research. Thus, a radical can be generated after a laser pulse and its emission can be measured after excitation with a second pulse. In the *time-resolved IR emission spectroscopy*, the precursor molecule dissociates upon irradiation, and the transient radical is generated

with high vibrational excitation; IR emission of these excited species is then detected.⁹⁴

Photochemically Induced Dynamic Nuclear Polarization (photo-CIDNP) Technique

Photochemically induced dynamic nuclear polarization (photo-CIDNP) technique holds all the advantages of NMR spectroscopy and in addition allows the analysis of processes occurring in a nanosecond timescale.⁹⁵ It is a powerful tool for the study of radical cage reactions. When radical pairs are formed by excitation of a molecule, they are spin correlated. The population of energy levels is not at thermal equilibrium and electron spin transitions may be fully polarized. Part of the polarization is transferred to nuclear spins via the hyperfine interaction, which leads to strong absorption or emission signals. Transient free radicals⁹⁶ have been characterized, and their reaction mechanisms studied using this powerful technique.

Thus, it has been used to confirm the radical nature of the photo-Fries rearrangement.⁹⁷ In addition, the absence of polarization in the photolysis of 1-naphthyl acetate protons indicates an insignificant recombination of the naphthoxyl and acyl radicals to the initial compound and, hence, that recombination is not responsible for the difference from unity of the quantum yield of this rearrangement. In agreement, flash photolysis experiments show formation of the 1-naphthyl acetate triplet excited state, whose main deactivation channel is the triplet–triplet annihilation.

5 CONCLUSION

A wide variety of organic radicals can be photochemically generated from suitable precursors. These reactive intermediates may follow different secondary pathways, giving rise to a vast array of photoproducts. Hence, photoinduced radical reactions may be of preparative interest, provided that the product yields and selectivities are sufficient. A large body of experimental mechanistic evidence has been obtained by laser flash photolysis or related time-resolved techniques; this constitutes a valuable contribution to the field of physical organic chemistry.

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Radiation-Induced Radical Reactions

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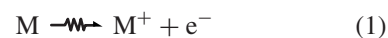
1 INTRODUCTION

Radiolysis, the initiation of reactions by high-energy radiation, is a very valuable and powerful chemical tool for inducing and studying radical reactions in gases, liquids, and solids. The chemical changes that commonly involve radiation-induced radical reactions are the consequences of the absorption of the energy of high-energy radiation by matter.^{1–7} The mechanisms by which the radiation energy is deposited in matter depend on the type of radiation. There are three types of ionizing radiations: (i) charged particles (electrons and heavy positive ions), (ii) neutral particles (neutrons), and (iii) electromagnetic radiation (X- and γ -rays). The mode of interaction of the three classes of ionizing radiation with matter is summarized in Scheme 1.

The relative importance of these three main processes, that is, emission of radiation “bremsstrahlung,” and inelastic and elastic collisions by which charged particles interact with matter, depends on the energy of the particles and also on the nature of the material they passed through. Only the first two of them reduce the energy of the particle and give rise to ionization and excitation of the medium. In the case of neutrons, there are four main processes by which they interact in collisions with atomic nuclei: elastic and inelastic scatterings, nuclear reactions, and capture. γ -Rays are produced by inelastic scatterings and capture. Protons and other positive ions are produced by elastic scattering and nuclear reactions. There are three important processes by which electromagnetic

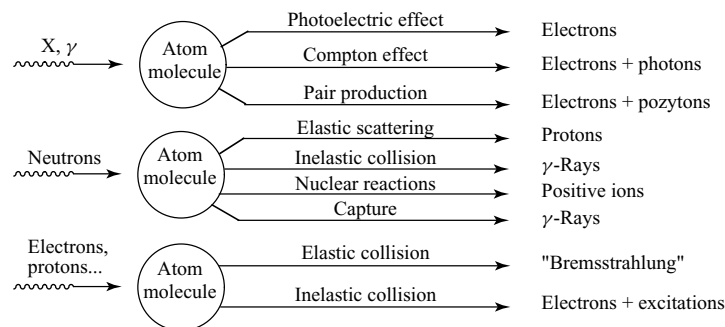
radiation interacts with matter. These processes are the photoelectric and Compton effects, pair production whose probabilities varied with the energy of radiation, and the atomic number Z of the material involved.^{1–7}

As the overall effects of all three types of high-energy radiation are ionization and excitation of the molecules of the medium through which they pass, the chemical effects of the various high-energy radiation are qualitatively similar. These processes may be generally represented by the following equations:



where M is a molecule of the absorbing medium and M^+ and M^* are the ionized state and the excited state of the molecule, respectively. The symbol “ $\xrightarrow{\text{high-energy radiation}}$ ” used informs that a reaction is initiated directly by a high-energy radiation. The electrons produced in ionization (1) can cause further ionization and excitation. Thus, the primary effect of any type of ionizing radiation on matter is the production of ions, excited states, and electrons. These species subsequently react in a number of ways leading to the production of free radicals.

Radiation energy deposition is spatially inhomogeneous and creates sites of dense ionization, called *spurs*. The mean rate of energy loss by the particle per unit path length, called *linear energy transfer* (LET), increases in the sequence electron, proton, and α -particle, for the same particle energy (E). This is, according to the Bethe equations,³ because



Scheme 1 Interaction of high-energy electromagnetic radiation, neutrons, and charged particles with matter.

the value of LET increases with decreasing particle velocity (v), which decreases with increasing particle mass M for the same E and because LET increases as the square of the particle charge Z . The average distance between *spurs* along a track can be roughly calculated as 10^2 eV/LET . Considering particles with $E = 10 \text{ MeV}$, ~ 500 , 12, and 1 nm distances between spurs along electron, proton, and α -particle tracks are obtained, respectively. At subpicoseconds time scales, local inhomogeneous distribution of ions, excited states, and electrons in *spurs* produced by high-energy electromagnetic radiation or by the charged particles (including electrons) results in high local concentration of reactive species promoting their geminate recombination. Inhomogeneity of such type does not take place in photolytic methods, where photolysis generates excitations and in some cases ionizations, with a spatial distribution determined by the distribution of the absorbing species (solute) (see **Photo Induced Radical Reactions**).⁸

An important feature of high-energy radiation is that it is absorbed in matter nonselectively, which means that molecules are ionized according to their relative abundance in the medium irradiated. In another words, for both high-energy photons and high-energy charged particles, partition of energy among the components of a sample is controlled by the contribution of each component to the density of electrons. This leads to the concept of a *direct effect* of the radiation on the solute and an *indirect effect*, in which excited species and ions derived from the solvent subsequently react with the solute. Therefore, in studies on dilute solutions, it is the solvent that absorbs most of the energy. Any direct effect on the solute molecules will be negligible in comparison with the indirect effect. The radical reactions observed will be essentially

those resulting from the interactions of excited states and/or ions from the solvent with themselves or with any solute that is present. Therefore, the knowledge of the radiolysis mechanism of the solvent is of paramount importance for radical reactions initiated by high-energy radiation. One potential disadvantage of the latter situation is that the limiting rate of intermediate formation derived from the solute is usually controlled by its concentration. In photolysis, the energy of quanta is transferred directly to the chromophore producing radical intermediates directly. On the other hand, high-energy radiation allows studies on radical reactions that cannot be studied by photochemistry, due to differences in the fundamental physical processes connected with absorption of energy. For instance, absorption of high-energy radiation permits initiation of radical reactions in systems that do not contain a chromophore or an excited state that would be amenable to photolytic methods. High background absorption of the system, low quantum yields, or the lack of suitable photosensitizers also limits the application of photolytic techniques to initiate certain radical reactions.⁸

Two main types of approaches are commonly used in applying high-energy radiation for inducing radical reactions. First, radiolysis can involve exposure to a steady radiation source, usually a ^{60}Co source for a desired amount of time, and the stable products resulting from the radical reactions are analyzed after the end of the radiolysis period. Modern analytical techniques are necessary to measure and identify the products. These include high-performance liquid chromatography for separation of products, with spectrophotometric, fluorescence, electrochemical, mass spectrometric, or nuclear magnetic resonance (NMR) detections as appropriate. The second approach is required

where it is desired to generate sufficient concentration of radicals in a short time to follow radical reactions directly. This technique, pulse radiolysis, has been the main source of quantitative information concerning reaction kinetics of free radicals in solutions.^{9–13} For radicals in solutions, the most commonly used technique is time-resolved UV-vis spectroscopy,^{11,12,14} but time-resolved conductivity,^{12,15–17} electron paramagnetic resonance,¹⁸ vibrational resonance Raman spectroscopy,¹⁹ microwave absorption spectroscopy,^{20,21} polarography,²² circular dichroism,²³ and very recently infrared spectroscopy,^{24,25} although less widely employed, can and do provide kinetic, spectral, and mechanistic details that are not accessible via optical measurements.

The above introduction is supposed to serve as a brief summary of specific features of high-energy radiation and its interaction with matter for those researchers who are new to the field of radiation chemistry. Owing to space limitations, a comprehensive overview of basics of radiation-induced phenomena cannot be given here. There are many excellent and comprehensive chapters in books^{1,4,6,26–28} and books,^{2,5,7,29–33} which present and discuss the topics above in a more detailed manner.

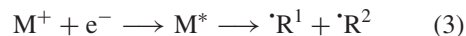
2 RADIATION-INDUCED RADICAL REACTIONS IN GASES

2.1 Basic Considerations

Radiolysis of gases differs from radiolysis of the condensed phases because of differences in the electron density of the absorbing medium and variations in the related freedom of the excited and ionized species. For the above reasons, the transient species diffuse faster, have longer lifetimes, and therefore the track effects are less important. Radiation chemical yields of transients are less dependent on the LET of radiation and their distribution is more uniform in gases than in liquids and solids.

The radiolysis of a simple gas generates many primary products, including excited states, positive ions, and low-energy electrons. These processes may be visualized by (1 and 2) (*vide supra*). The resulting positive ions and electrons recombine rapidly to produce neutral species with very high internal energy (molecular or atomic). They

can subsequently undergo rapid decomposition generating free radicals (3) or transfer their excess energy to other species in the gas mixture (4), which then undergo decomposition to give radicals (5), respectively:



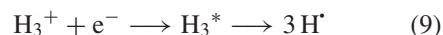
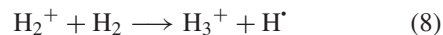
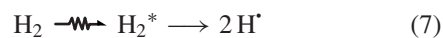
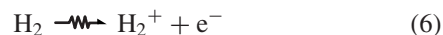
The literature concerned with radiation-induced radical reactions in gas phase is extensive. A full account of this topic is outside the scope of this article. A few systems only can be presented here to illustrate the different types of reactions observed for different molecules. Therefore, the reader is referred to several excellent reviews, which address them in more details (see **Radical Chemistry in the Gas Phase**).^{34–37}

2.2 Selected Gaseous Systems

Generally, high yields of radicals can be obtained by irradiation of various bath gases, including hydrogen (H₂), ammonia (NH₃), nitrous oxide (N₂O), H₂O (in form of water vapor), sulfur hexafluoride (SF₆), halogenated hydrocarbons, and noble gases with additives.

2.2.1 Hydrogen and Hydrogen/Chlorine Systems

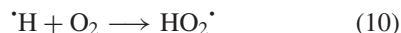
The radiation-induced reactions in gaseous hydrogen can be summarized by the following reactions: ionization (6), excitation and dissociation (7), ion molecule reaction (8), and neutralization-decomposition (9)²:



Once the main radical product (H[·]) is formed, in the presence of small amounts of additives in the bath gas, it can be used to produce other

radicals. Using such systems, a variety of free radical reactions have been studied.

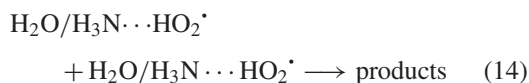
For example, in presence of oxygen (O_2), formation of $HO_2^{\cdot}$ was observed:



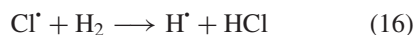
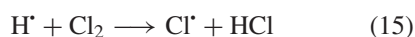
Moreover, it was found that the gas-phase self-reaction of $HO_2^{\cdot}$ radicals (11) was markedly enhanced in the presence of NH_3 and H_2O ^{38,39}:



This phenomenon was rationalized in terms of the formation of hydrogen-bonded transient complexes between the $HO_2^{\cdot}$ and NH_3 or H_2O ³⁸:

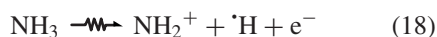
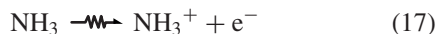


Irradiation of gaseous hydrogen (H_2) and chlorine (Cl_2) mixture is a good example, where formation of hydrogen chloride occurs via chain reactions where chlorine and hydrogen atoms take part in the propagation step:



2.2.2 Ammonia

The primary processes that should be considered in mechanisms for radiolysis of gaseous ammonia are ionization and excitation⁴⁰:



There is considerable experimental support that ions and excited molecules produced in reactions (17)–(21) lead principally to $^{\cdot}NH_2$ and $^{\cdot}H$

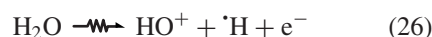
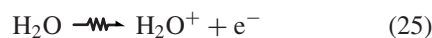
atoms (21–24):



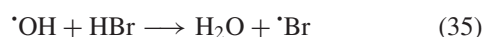
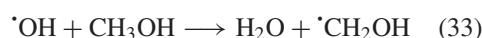
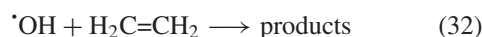
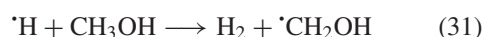
Since the relative importance of various elementary processes involved in radiolysis of gaseous NH_3 depends on dose rate, temperature, and pressure, it is not possible to formulate a mechanism that will be applicable under all conditions.

2.2.3 Water Vapor

Primary ionization processes in water vapor can be described by the following ionization reactions³⁵:

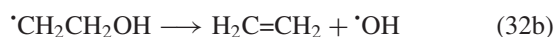


The primary radicals produced ($^{\cdot}H$ and $^{\cdot}OH$) in the source reactions (26 and 27) can react with a wide range of molecules to produce secondary radicals.^{35,37} For example, in the presence of olefinic (e.g., C_2H_4) and hydrogen atom-donating scavengers (e.g., CH_3OH and HBr), the alkyl (30) and hydroxyalkyl radicals (31–33) and bromine atoms (34 and 35) can be formed:



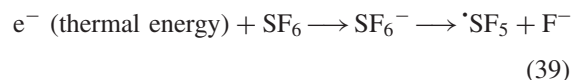
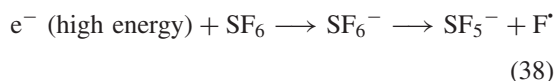
The reaction of $^{\cdot}OH$ radicals with ethylene (32) represents interesting mechanistic case. The results revealed three kinetically separate temperature

regions: 343–563 K, where the disappearance of $\cdot\text{OH}$ radicals is dominated by the addition of $\cdot\text{OH}$ radicals to the double bond of ethylene (32a); 563–748 K, where concurrent reactions of addition, the reverse reaction of addition (32b), and H-atom abstraction are dominant (32c); and 748–1173 K, where H-atom abstraction is likely the main reaction (32c).⁴¹

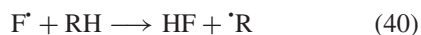


2.2.4 Sulfur Hexafluoride (SF_6)

Irradiation of gaseous sulfur hexafluoride (SF_6) enables production of radicals ($\cdot\text{F}$ atoms and sulfur pentafluoride radicals $\cdot\text{SF}_5$) (36–39). The former radicals ($\cdot\text{F}$) are very difficult to make via other techniques:



$\cdot\text{F}$ atoms produced in reactions (37) and (38) are capable of abstracting H atoms from alkanes (RH) and halogenated hydrocarbons ($\text{R}^{\text{X}}\text{H}$) forming alkyl ($\cdot\text{R}$) and halogenated alkyl ($\cdot\text{R}^{\text{X}}$) radicals, respectively (40 and 41)^{42–47}:

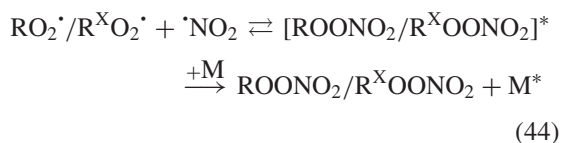
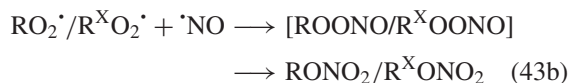
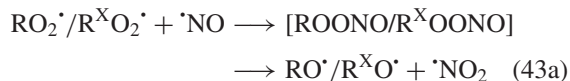


where $\text{X}=\text{Cl}, \text{Br}, \text{I}, \text{and F}$. In the presence of oxygen, this system enables easy generation of peroxy radicals:



Since peroxy radicals ($\text{RO}_2\cdot/\text{R}^{\text{X}}\text{O}_2\cdot$) play a key role in the chemistry occurring in the atmosphere, their reactions with $\cdot\text{NO}$ and $\cdot\text{NO}_2$ (43 and 44)

are of great importance and have been extensively studied using pulse radiolysis technique by several groups.^{47–66} $\text{RO}_2\cdot$ and $\text{R}^{\text{X}}\text{O}_2\cdot$ reactions with $\cdot\text{NO}$ and $\cdot\text{NO}_2$ constitute a reliable data bank of rate constants and activation energies for environmental studies:

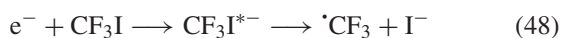
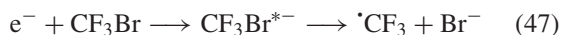
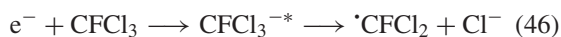
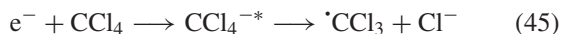


The reactions (43a and 43b) involve a short-lived complex, which can either decompose (43a) or rearrange to the nitrate (43b).⁶⁴ It was found that the reactivity increased with the degree of halogenation on the carbon atom attached to the $\text{OO}\cdot$ group and decreased with increasing size of the peroxy radical.^{48,55} There was little or no effect of β -halogenation to the $\text{OO}\cdot$ group on reactivity.⁶⁴

Reaction (44) is complex, with the initial formation of an excited adduct, which can either decompose back to the reactants or be deactivated by collision with a “third body”.⁶⁴

2.2.5 Halogenated Hydrocarbons

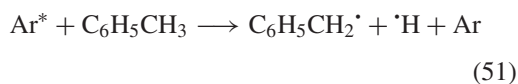
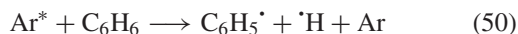
Halogenated hydrocarbons reacting with thermal electrons undergo dissociative electron attachment forming respective halogenated hydrocarbon radicals via temporary excited negative ions^{37,67}:



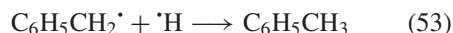
Studies on the electron attachment to halogenated hydrocarbons demonstrated the extreme fragility of these compounds toward low-energy electrons. The rate constants of thermal electron attachment increase in the order $\text{F} < \text{Cl} < \text{Br} < \text{I}$ and with the number of halogen atoms in the molecule.⁶⁸

2.2.6 Argon (Ar) Mixtures

A large number of radiation-induced radical reactions have been studied in gaseous Ar mixtures. For example, the radiolysis of Ar/aromatic hydrocarbon mixtures produces excited metastable argon atoms (49), which on collision with benzene (50) or toluene^{69–72} (51) generate phenyl or benzyl radicals, respectively:



Using these systems, the recombination reactions of phenyl/benzyl radicals (52 and 53) and of monosubstituted benzenes (54)⁷⁰ with hydrogen atoms and of phenyl radicals with nitric oxide (NO) (55) have been studied:

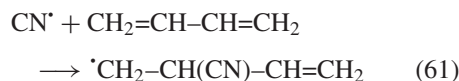
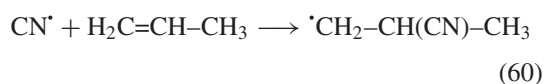


The rate constants for the reaction (54) were correlated with the Hammett σ -values of the X-substituents, showing that hydrogen atoms ($\cdot\text{H}$) are electrophilic in these reactions.⁷⁰

The gas-phase pulse radiolysis of argon (Ar)/carbonitridic cyanide (C_2N_2) mixture has been used for the generation of cyanide radicals (49 and 56),



and subsequently to study their reactions with selected alkanes (methane and ethane) (57 and 58) and alkenes (ethylene, propylene, and 1,3-butadiene) (59–61) and benzene (62)⁷³:



The measured rate constants for the reactions (59–62) approach the collisional limit and reflect the extremely electrophilic nature of $\cdot\text{CN}$ radicals.⁷³

The gas-phase radiolysis of argon (Ar)/carbon tetrachloride (CCl_4) mixture has been used as a source of $\cdot\text{CCl}_3$ radicals (49 and 63):



Their reaction with nitric dioxide ($\cdot\text{NO}_2$) has been subsequently studied by following the kinetics of production of CCl_3NO_2 (64)⁷⁴:



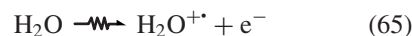
3 RADIATION-INDUCED RADICAL REACTIONS IN LIQUIDS

3.1 Radiolysis of Water

3.1.1 Basic Considerations

The radiolysis of water has been studied intensively since the beginning of radiation chemistry. Therefore, water is the most thoroughly characterized solvent as far as the knowledge about the properties of primary radiolysis transients is concerned. Most of the radiation-induced radical reactions have been studied in aqueous solutions because it is relatively easy and convenient to produce enormous variety of highly reactive radical species, which otherwise cannot readily be generated by thermal or photochemical methods. Excellent critical reviews of the spectral and kinetic properties, methods of production, and compilations of reaction rate constants of the primary radiolysis transients with inorganic and organic substrates have been written over the years.^{5,75–89}

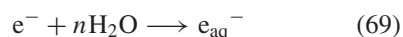
The current state of knowledge can be summarized by the following reactions^{88,89}:



Equations (65 and 66) represent ionization and electronic excitation of water molecules, respectively, and these processes occur in $\sim 10^{-16}$ s. The water radical cation (H_2O^+) is a very strong acid and immediately loses a proton (in $\sim 10^{-14}$ s) to neighboring water molecules forming hydroxyl radical ($\cdot\text{OH}$) (67):

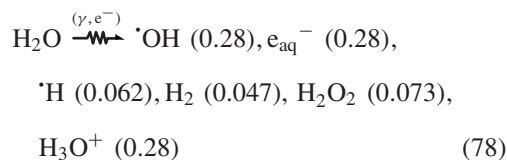


The electronically excited water molecules (H_2O^*) undergo homolytic dissociation (68) in $\sim 10^{-13}$ s and the electron ejected in an ionization process (65) undergo, after thermalization, hydration by $\sim 10^{-12}$ s (69):



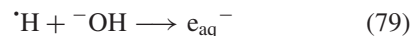
At this time, for low LET radiation (γ -rays from ^{60}Co source and fast electrons from an accelerator), the products of reactions represented by (67–69) are distributed inhomogeneously and located together in small widely separated *spurs*. Fraction of them interacts with one another within *spurs* forming molecular and secondary radical products. The complete set of spur reactions in water (70–77) together with the respective rate constants is listed in Table 1.^{81,89}

The remaining fraction of primary and secondary products diffuses into the bulk solvent and becomes homogeneously distributed and may react with added solutes (acting as radical scavengers). The spur processes and diffusion of reactants outside *spurs* are completed within $\sim 10^{-7}$ s. For the purposes of this article, the radiolysis of water (for low LET radiation $\sim 0.23 \text{ eV nm}^{-1}$) can be summarized by the following equation⁸⁹:

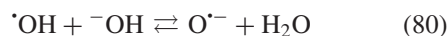


The numbers in parentheses represent radiation chemical yields (known as G values) in units of $\mu\text{mol J}^{-1}$.

$\cdot\text{H}$ atoms and hydrated electrons (e_{aq}^-) exist in an acid/base equilibrium with $\text{p}K_{\text{a}}(\cdot\text{H}) = 9.1$, and hence, at $\text{pH} < 4$, the diffusion-controlled reaction of e_{aq}^- with bulk protons becomes important ((72) in Table 1) resulting in a pH-dependent increased yield of $\cdot\text{H}$ atoms. On the other hand, in very basic solutions, $\cdot\text{H}$ atoms are converted into e_{aq}^- (79), with $k_{79} = 2.2 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁸³



In basic solutions, $\cdot\text{OH}$ radical is converted to its conjugate base, oxide radical ion ($\text{O}^{\cdot-}$), with $\text{p}K_{\text{a}}(\cdot\text{OH}) = 11.8$ (80), with $k_{80\text{f}} = 1.3 \times 10^{10} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $k_{80\text{r}} = 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁹⁰



Redox properties of the primary radicals from water radiolysis can be summarized as follows⁸³: the hydrated electron (e_{aq}^-) is a powerful reductant in neutral and alkaline solutions with a reduction potential of $E^0 = -2.87 \text{ V}$ versus normal hydrogen electrode (NHE). The hydrogen atom ($\cdot\text{H}$) becomes the major reductant in acidic solutions with a reduction potential of $E^0(\text{H}^+/\cdot\text{H}) = -2.31 \text{ V}$ versus NHE. The hydroxyl radical ($\cdot\text{OH}$) is a powerful oxidant with a reduction potential of $E^0(\cdot\text{OH}/\cdot\text{OH}) = 1.90 \text{ V}$ versus NHE in neutral solutions and with a reduction potential of $E^0(\text{H}^+, \cdot\text{OH}/\text{H}_2\text{O}) = 2.72 \text{ V}$ versus NHE in acidic solutions.

Table 1 Spur reactions in water.^{81,89}

Reaction	Number	$k \text{ (dm}^3 \text{ mol}^{-1} \text{ s}^{-1}\text{)}$
$\text{e}_{\text{aq}}^- + \text{e}_{\text{aq}}^- \rightarrow \text{H}_2 + 2\text{OH}^-$	(70)	5.4×10^9
$\text{e}_{\text{aq}}^- + \cdot\text{OH} \rightarrow \text{OH}^-$	(71)	3.0×10^{10}
$\text{e}_{\text{aq}}^- + \text{H}_3\text{O}^+ \rightarrow \cdot\text{H} + \text{H}_2\text{O}$	(72)	2.3×10^{10}
$\text{e}_{\text{aq}}^- + \cdot\text{H} \rightarrow \text{H}_2 + \text{OH}^-$	(73)	2.5×10^{10}
$\cdot\text{H} + \cdot\text{H} \rightarrow \text{H}_2$	(74)	1.3×10^{10}
$\cdot\text{OH} + \cdot\text{OH} \rightarrow \text{H}_2\text{O}_2$	(75)	5.3×10^9
$\cdot\text{OH} + \cdot\text{H} \rightarrow \text{H}_2\text{O}$	(76)	3.2×10^{10}
$\text{H}_3\text{O}^+ + \text{OH}^- \rightarrow 2\text{H}_2\text{O}$	(77)	1.4×10^{11}

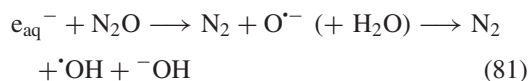
3.1.2 Selective Generation of Primary Radicals

The primary radicals formed in the radiolysis of aqueous solutions possess both oxidative ($\cdot\text{OH}$) and reductive (e_{aq}^- , $\cdot\text{H}$) properties. In most cases, it is desirable to study the reactions of individual radicals since interpretation of experiments will be easier

when dealing with only one type of radical. This can be achieved via appropriate chemical additives to design solutions that largely contain a single radical species.⁸⁹

Oxidizing Conditions

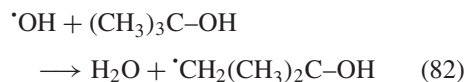
In order to study the reactions of $\cdot\text{OH}$ radicals without a contribution of e_{aq}^- , the reaction solution is saturated with nitrous oxide (N_2O). Hydrated electrons are rapidly scavenged by the N_2O generating additional amount of $\cdot\text{OH}$ radicals (81), with $k_{81} = 9.1 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁹¹



The radiation chemical yield of $\cdot\text{OH}$ radicals is thus the sum of the primary yields of $\cdot\text{OH}$ radicals and e_{aq}^- , that is, $0.56 \mu\text{mol J}^{-1}$. The hydrogen atoms react only slowly with N_2O ($k = 2.1 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$).⁸⁹ Therefore, the only other radical present is the $\cdot\text{H}$ atom, which represents $\cong 10\%$ of the total radical yield at neutral solutions.

Reducing Conditions

A good approach to study hydrated electron reactions without a contribution of $\cdot\text{OH}$ radicals is irradiation of Ar/N_2 -saturated aqueous solutions containing high concentration ($>0.1 \text{ M}$) of 2-methyl-2-propanol (*tert*-butanol). The alcohol is added to remove the highly reactive $\cdot\text{OH}$ radical by transferring the radical site to a 2-hydroxy-2,2-dimethylethyl radical (82), with $k_{82} = 6.0 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁸³



Under these experimental conditions, the yield of $\cdot\text{H}$ atoms is almost not affected since their rate constant with 2-methyl-2-propanol is low ($k = 1.7 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$)⁹² and recently revised at $1.15 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁹³ The $\cdot\text{CH}_2(\text{CH}_3)_2\text{C}-\text{OH}$ radical is largely unreactive mostly to steric hindrance. Moreover, its optical absorption spectrum is located to the UV below 270 nm and therefore does not interfere with other radical spectra located at $>270 \text{ nm}$. After removal of $\cdot\text{OH}$ radicals, only e_{aq}^- and H atoms are present, with $G(e_{\text{aq}}^-) = 0.28$ and $G(\cdot\text{H}) = 0.062 \mu\text{mol J}^{-1}$ in neutral solution.

The cleanest way to study $\cdot\text{H}$ atom reactions without the contribution of $\cdot\text{OH}$ radicals is irradiation of acidic aqueous solutions saturated with H_2 . However, due to the low solubility of H_2 under normal pressure conditions, this requires a special pressure cell. The hydroxyl radicals react with H_2 generating additional amount of $\cdot\text{H}$ atoms (83), with $k_{83} = 4.2 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.⁸³



For the above reason, $\cdot\text{H}$ atom reactions, without contribution of $\cdot\text{OH}$ radicals and hydrated electrons, can be conveniently studied by irradiation of highly acidic Ar/N_2 -saturated aqueous solutions containing high concentration ($>0.1 \text{ M}$) of 2-methyl-2-propanol (*tert*-butanol). The $\cdot\text{OH}$ radicals are removed in reaction (82) and e_{aq}^- are converted to $\cdot\text{H}$ atoms via neutralization with H^+ ((72) in Table 1).

3.1.3 Generation of Selective Secondary Radicals

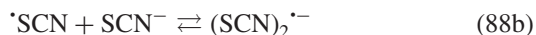
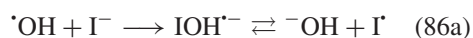
Oxidizing Radicals

Since the $\cdot\text{OH}$ radical is a very strong oxidant, it reacts very fastly with almost all compounds and thus is not selective. Moreover, in one-electron oxidation reactions, the $\cdot\text{OH}$ radical reacts with formation of a primary intermediate adduct. Therefore, there was a strong need for a generation of more selective radicals that react by a direct electron transfer (ET).^{86,89} In aqueous solutions, a large variety of oxidizing inorganic radicals have been generated and their reaction rates and spectra obtained have been compiled.^{79,84,94}

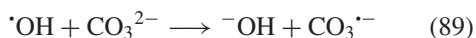
Reactions leading to generation of the most common oxidizing selective inorganic radicals from the primary $\cdot\text{OH}$ radicals are presented by (84a–93).^{82,84,88}

Hydroxyl radicals react with many halide (pseudohalide) ions forming a three-electron-bonded adduct radicals that further decompose into ${}^-\text{OH}$ and the halide (pseudohalide) radicals (84a–88a). The latter radicals form the weak $\sigma\sigma^* 2c-3e$ bond complexes, dihalogen (pseudohalogen) radical anions, with another halide (pseudohalide) ions (84b–88b).^{95–104} In basic and neutral solutions, $\cdot\text{Cl}$

radical is a stronger oxidant than $\cdot\text{OH}$, and the formation of $\text{Cl}_2^{\cdot-}$ (84b) can only proceed in acidic solutions (84a).⁹⁷



Equilibrium constants of reactions presented by (84b–88b) are compiled in Table 2.



A very useful way of generating oxidizing radicals, particularly when they are more powerful than $\cdot\text{OH}$ in neutral solution (e.g., $\text{SO}_4^{\cdot-}$), is via the following reactions⁸²:



Table 2 Equilibrium constants of selected dimeric radical anions.

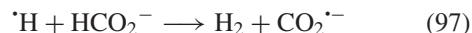
Dimeric radical anion	Number	Equilibrium constant K ($\text{dm}^3 \text{mol}^{-1}$)
$\text{Cl}_2^{\cdot-}$	(84b)	6.0×10^4 ¹⁰³ ; 1.4×10^5 ⁸⁸
$\text{Br}_2^{\cdot-}$	(85b)	3.9×10^5 ¹⁰⁴
$\text{I}_2^{\cdot-}$	(86b)	1.1×10^5 ^{95,101}
$\text{N}_6^{\cdot-}$	(87b)	0.33 ¹⁰⁰
$(\text{SCN})_2^{\cdot-}$	(88b)	2.0×10^5 ^{95,102}

Compilation of the reduction potentials of selected oxidizing inorganic radicals formed in reactions (84a)–(95b) is presented in Table 3.

Radiolysis of water provides a very convenient source of one-electron oxidizing radicals characterized by a very broad range of reduction potentials.^{86,105} These radicals are useful for studying redox changes in metalloproteins and organometallic complexes since they more likely attack the metal centers. However, they are particularly useful for studying long-range electron transfer (LRET) processes in biological systems such as synthetic and native peptides and native, mutant or modified proteins since they could selectively attack amino acid residues.^{5,85,106–108}

Reducing Radicals

Since both e_{aq}^- and H atoms are very strong reductants, they do not react in a selective way. Carbon dioxide radical anion ($\text{CO}_2^{\cdot-}$) is an efficient reducing agent, rapidly reducing a large number of aqueous metal ions and metal complexes without formation of intermediate adducts.⁸⁸ Reactions leading to generation of this most common reductive selective inorganic radical from the primary $\cdot\text{OH}$ and $\cdot\text{H}$ radicals are presented by the following equations:



Reduction of O_2 by $\text{CO}_2^{\cdot-}$ is commonly used to produce superoxide radical ions (98) for study of its reactions⁸⁴:



The less negative reduction potential of $\text{CO}_2^{\cdot-}$ relative to that of e_{aq}^- is illustrated by its ability

Table 3 Reduction potentials of selected inorganic radicals.¹⁰⁵

One-electron oxidants		One-electron reductants	
Redox couple	<i>E</i> (V) vs NHE	Redox couple	<i>E</i> (V) vs NHE
SO ₄ ^{•−} /SO ₄ ^{2−}	+2.47		
Cl ₂ ^{•−} /2Cl [−]	+2.30		
Br ₂ ^{•−} /2Br [−]	+1.66		
N ₃ ^{•−} /N ₃ [−]	+1.33	CO ₂ /CO ₂ ^{•−}	−1.90
(SCN) ₂ ^{•−} /2SCN [−]	+1.33	SO ₂ /SO ₂ ^{•−}	−0.28
I ₂ ^{•−} /2I [−]	+1.04		
NO ₂ ^{•−} /NO ₂ [−]	+1.00		
ClO ₂ ^{•−} /ClO ₂ [−]	+0.93		
SO ₃ ^{•−} /SO ₃ ^{2−}	+0.63		

to reduce aromatic compounds only if they contain electron-withdrawing substituents. Rate constants of the ET reactions of CO₂^{•−} are sufficiently below the diffusion-controlled range where correlations between rate constants and reduction potentials can be made.

3.1.4 Radical Reactions Involving Primary Radicals from Water Radiolysis

The Hydroxyl Radical

The electrophilic ($\rho = -0.41$) hydroxyl radical ([•]OH) is a very reactive radical, which reacts at close to diffusion-controlled rates.^{85,88,109} Rate constants for over 3500 reactions have been compiled, including reactions with molecules, ions, and radicals derived from inorganic and organic solutes.^{83,110} The [•]OH radical undergoes the following types of reactions: (i) ET, (ii) hydrogen abstraction, (iii) addition to C–C, C–N, and S–O double bonds, (iv) addition to aromatic rings, and (v) addition to electron-rich functional groups.⁸⁸

In most ET reactions involving [•]OH radicals, an intermediate complex is formed in the first step, preceding the actual ET reaction:

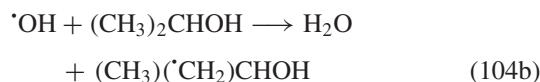
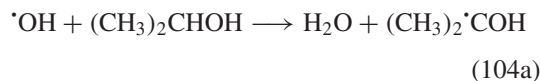
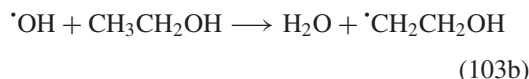
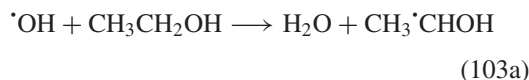


Since the HO–H bond dissociation energy (BDE) is very high, while the BDE of the C–H and S–H bonds are much weaker, there is a considerable

driving force for H-abstraction reactions by [•]OH radicals:

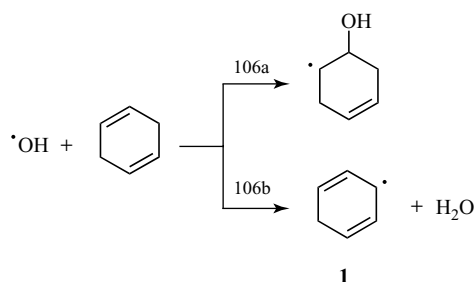


Moreover, since the BDE for primary hydrogens (–CH₃) is higher than that for secondary (–CH₂–) and tertiary (–CH–) ones, a remarkable selectivity is observed:



The yields (in percentage) of H-abstraction reactions (103a and 104a) are equal to 84.3 and 85.5%, respectively. On the other hand, the yields of H-abstraction reactions (103b and 104b) are both equal to 13.3%.¹¹¹

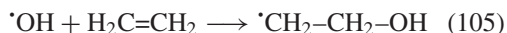
Since the neighboring substituents can affect the rate constants of H-abstraction reactions and thus the yield of the respective radicals, a high regioselectivity was observed. The electron-donating substituents (e.g., –OR or –NR₂) favor abstraction of a hydrogen and the electron-withdrawing groups



Scheme 2 Reactions of $\cdot\text{OH}$ radicals with 1,4-cyclohexadiene.

(e.g., $>\text{C}=\text{O}$) decrease the rate of H-abstraction. Combination of electron donation and electron withdrawal favors additionally H-abstraction.¹¹² This effect was observed in the series of amino acid anhydrides where H-abstraction by $\cdot\text{OH}$ radicals occurs at the peptide carbon.¹¹³

Addition of $\cdot\text{OH}$ radicals to C–C double bonds is very fast and occurs close to diffusion-controlled rates (e.g., for ethylene $k_{105} = 4.4 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$):

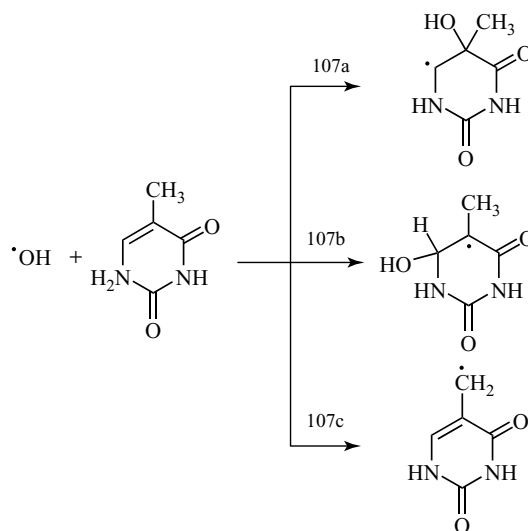


For molecules in which both addition to C–C double bonds and H-abstraction reactions are possible, addition will be the generally preferred route, even for molecules having weakly bound hydrogens, such as four pentadienyl hydrogens in 1,3- and 1,4-cyclohexadienes. For instance, in 1,4-cyclohexadiene, addition to C–C double bonds occurs to an extent of 75% (Scheme 2, reaction (106a)), while H-abstraction yielding allylic radicals (**1**) occurs to an extent of only 25% (Scheme 2, reaction (106b)).¹¹⁴

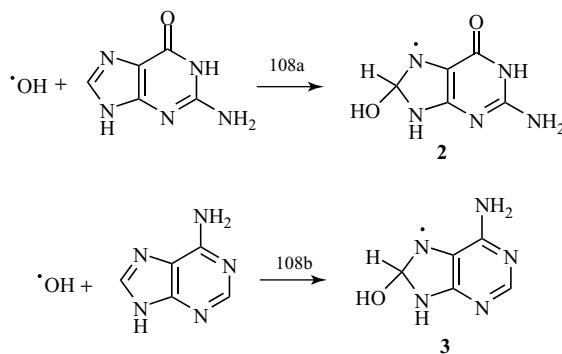
Even more pronounced is the situation in the case of thymine (Scheme 3), where $\cdot\text{OH}$ addition to the C(5)–C(6) double bond is much preferred (90%) (107a and 107b) over an abstraction of allylic hydrogens at the C(5) methyl group (10%) (107c).^{5,88,115–117}

Addition of $\cdot\text{OH}$ radicals to C–N double bonds occurs in purines (guanine and adenine) (Scheme 4, reactions (108a) and (108b)). The C(8)–OH adducts (**2** and **3**) have reducing properties and their yields have been determined at 17 and 37% in guanine and adenine, respectively.^{5,88,117}

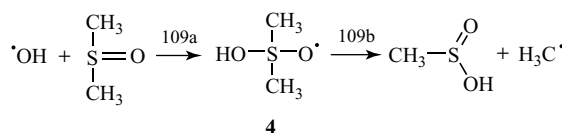
Addition of $\cdot\text{OH}$ radicals to S–O double bonds has been observed in sulfoxides (109a). The resulting



Scheme 3 Reactions of $\cdot\text{OH}$ radicals with thymine.



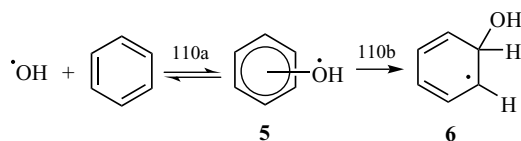
Scheme 4 Reactions of $\cdot\text{OH}$ radicals with purines.



Scheme 5 Reactions of $\cdot\text{OH}$ radicals with dimethylsulfoxide.

radical **4** undergoes a very rapid β -fragmentation (109b) to give the carbon-centered radical as shown in Scheme 5.¹¹⁸

Addition of $\cdot\text{OH}$ radicals to aromatic rings is probably in equilibrium with a short-lived π -complex **5** (110a) prior to transform in a



Scheme 6 Addition of $\cdot\text{OH}$ radicals to benzene.

σ -complex **6** (110b), where the OH group bounds tightly to the C-atoms (Scheme 6).¹¹⁹ A high regioselectivity is observed in these reactions: electron-donating substituents direct $\cdot\text{OH}$ radicals into the *ortho*- and *para*-positions, while electron-withdrawing substituents mostly into *meta*-position.^{120–127}

Addition of $\cdot\text{OH}$ radicals to electron-rich functional groups has been observed in disulfides **7** (111)^{109, 128–134} and sulfides **8** (112)^{109, 130–135} as shown in Scheme 7. The $\cdot\text{OH}$ adduct **9** undergoes fragmentation (113a and b) and dissociation (114). Various radical and molecular products are formed, including radicals **10** and **11** and radical cations **12**. The $\cdot\text{OH}$ adduct **13** (hydroxysulfuranyl radicals) undergoes dissociation (115a) or proton-catalyzed hydroxide ion (OH^-) elimination (115b) resulting in the formation of radical cations **14**.^{135–139} These radical cations can be stabilized by 2c–3e bonding with other heteroatoms (e.g., S, N, and O) present in sulfide molecules or undergo deprotonation at neighboring carbon atoms forming α -(alkylthio)alkyl radicals.^{134, 138–156}

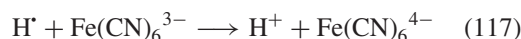
The Hydrogen Atom

Radical reactions of $\cdot\text{H}$ atoms are very similar to those involving $\cdot\text{OH}$ radicals.^{77,85,86,88,109,157} Rate

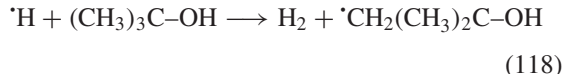
constants for their reactions have been also compiled including reactions with molecules, ions, and radicals derived from inorganic and organic solutes.^{83,158}

The $\cdot\text{H}$ atoms undergo the following types of reactions⁸⁸: (i) ET, (ii) hydrogen abstraction, (iii) addition to C–C double bonds, (iv) addition to aromatic rings, (v) addition to electron-rich functional groups, and (vi) homolytic substitution.

In ET reactions, $\cdot\text{H}$ atoms are capable of reducing transition metal ions (116) and inorganic anions (117)^{159,160}:

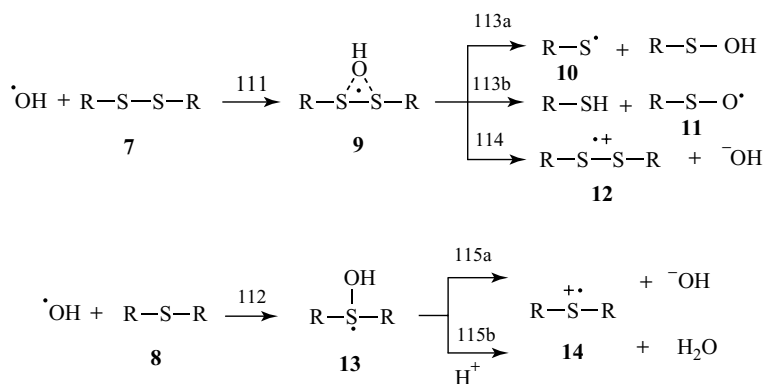


$\cdot\text{H}$ atoms also undergo H-abstraction reactions, however, with much lower rate constants than $\cdot\text{OH}$ radicals. This is particularly reflected in a substantially lower rate constant of $\cdot\text{H}$ atoms with 2-methyl-2-propanol (118) (*vide* reaction with $\cdot\text{OH}$ (82))⁸³:

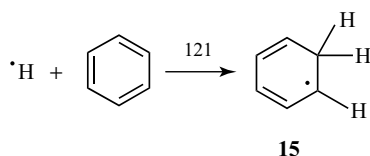


$$k_{118} = (1.7 - 11.5) \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \ll k_{82} = 6.0 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}.$$

H/D isotope effects are better pronounced in H-abstraction reactions as was seen in reaction of $\cdot\text{H}$ atoms with 2-propanol and 2-propanol- d_2 ,

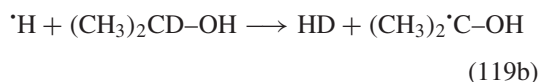
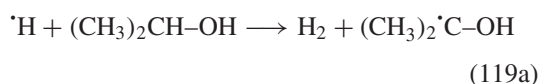


Scheme 7 Addition of $\cdot\text{OH}$ radicals to disulfides and sulfides and consecutive reactions.



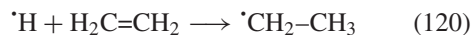
Scheme 8 Addition of $\cdot\text{H}$ atoms to benzene.

respectively:



The ratio $k_{\text{H}}/k_{\text{D}} = 7.5$ was measured for $\cdot\text{H}$ atoms in comparison with the $k_{\text{H}}/k_{\text{D}} = 1.5$ for $\cdot\text{OH}$ radicals.¹⁶¹

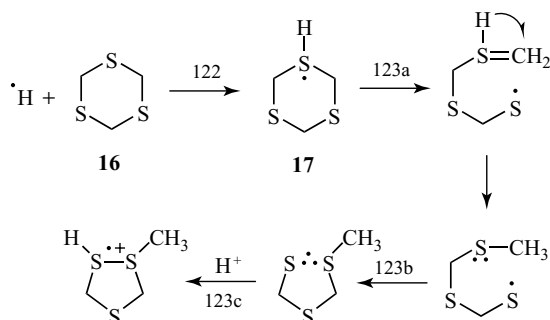
Addition of $\cdot\text{H}$ atoms to C–C double bonds is very fast and occurs close to diffusion-controlled rates (e.g., for ethylene $k_{120} = 3.0 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ^{83,158}).



Owing to their pronounced electrophilicity ($\rho = -0.45$), $\cdot\text{H}$ atoms show a high regioselectivity in addition reactions.¹⁵⁷ If there is a competition between addition and H-abstraction, the former reaction is always preferred.⁸⁸

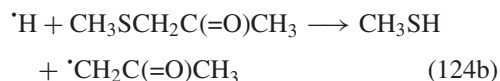
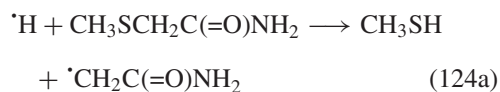
Addition of $\cdot\text{H}$ atoms to aromatic rings (Scheme 8, reaction (121)) leads to a σ -complex **15**, the H-atom bounds tightly to the C-atoms.

With trithianes containing three thioether groups **16** (Scheme 9), $\cdot\text{H}$ atoms react by addition to the sulfur atom (122).¹⁶² The resulting adducts **17** have not been detected because they decompose very rapidly by the ring opening followed either by α - or β -scissions (123a), further intramolecular sulfur–sulfur coupling (constituting a ring contraction) (123b), and further stabilization of the S $\cdot$ S bond thus formed by protonation (123c).



Scheme 9 Addition of $\cdot\text{H}$ atoms to trithianes and consecutive reactions.

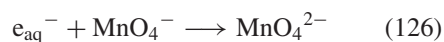
$\cdot\text{H}$ atoms can also undergo bimolecular homolytic substitution ($\text{S}_{\text{H}}2$) with α (alkylthio) carbonyl compounds (reactions 124a and 124b).^{163,164}



The respective acetamide- and acetone-derived radicals were identified by time-resolved electron spin resonance. The above-mentioned reaction is driven by the strong S–H bond formation, while only breaking a relatively weak C–S bond, which was supported by density functional theory calculations.

Hydrated Electrons

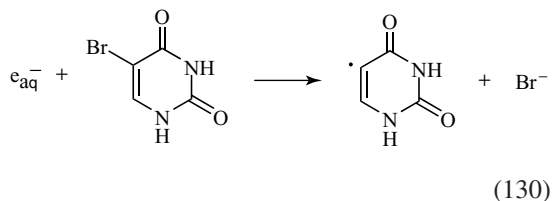
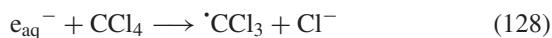
The hydrated electron is the most powerful reductant and therefore similar to $\cdot\text{H}$ atom is capable of reducing metal ions (125) and inorganic anions (126).^{80,81,86,89,165}



Hydrated electrons react with many compounds by a dissociative electron attachment. Some selected examples of such reactions are presented:



where X=Cl, Br, and I.



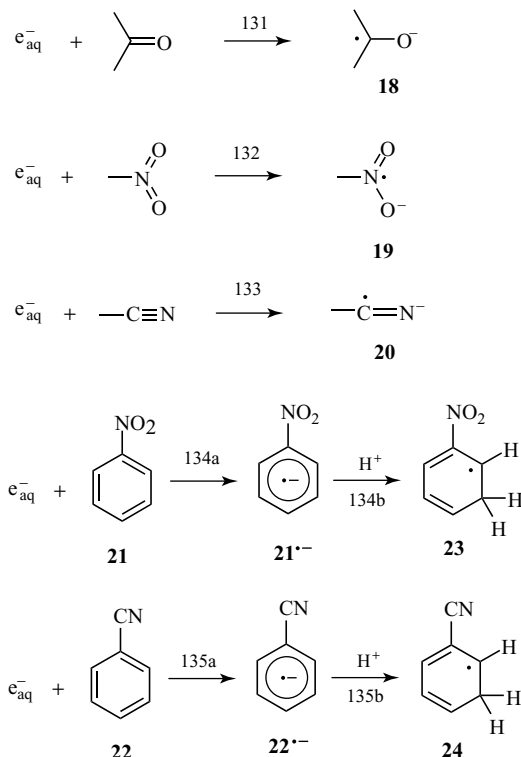
Hydrated electrons react with a large number of compounds containing carbonyl, nitro, and cyano groups and with high electron affinity at diffusion-controlled rates by forming the corresponding radical anions **18–20** (Scheme 10, reactions (131)–(133)).^{83,166,167}

Hydrated electrons do not react with benzene with an appreciable rate ($k \sim 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$),¹⁶⁸ however, with benzene-containing electron-withdrawing substituents ($-\text{NO}_2$ **21**, $-\text{CN}$ **22**), the rate constants are at diffusion-controlled limit (Scheme 10, reactions (134a) and (135a)). The resulting radical anions **21**^{•−} and **22**^{•−} undergo a very rapid protonation by water, yielding the same species as expected for the reaction with $\cdot\text{H}$ atoms **23** and **24** (Scheme 10, reactions (134b) and (135b)).

Radical reactions involving primary radicals from water radiolysis have been successfully applied for generation, identification, and spectral and kinetic characterization of a large variety of radicals and radical ions in amino acids (see **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**),^{5,85,106,108,154,156} peptides,^{85,108,154,156} proteins,^{108,169} nucleobases, nucleosides, nucleotides, poly-nucleotides, and DNA (see **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA**).^{5,88,117,170,171}

3.1.5 Radical Reactions Involving Selective Secondary Radicals from Water Radiolysis

Selective secondary inorganic radicals (Section 3.1.3) are efficient one-electron oxidizing and/or reducing agents.^{86,88} They can be used for a generation of a particular radical for study and they

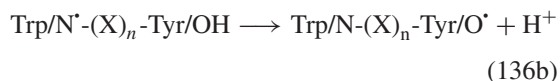
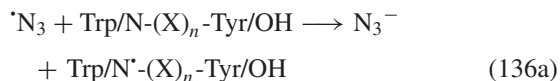


Scheme 10 Reactions of hydrated electrons with aliphatic and aromatic compounds containing carbonyl, nitro, and cyano groups.

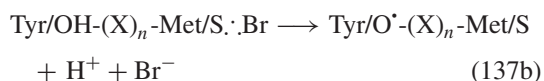
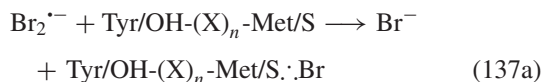
usually react without formation of intermediate adducts (such as $\cdot\text{OH}$ or $\cdot\text{H}$ adducts). For instance, the azide radical ($\cdot\text{N}_3$) was found to oxidize aromatic systems such as aniline and phenoxide ions and their derivatives at a rate constant of $(3\text{--}5) \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ primarily via ET, whereas benzene, toluene, and anisole are not observably oxidized by N_3 .¹⁷² Since the majority of the above radicals are selective one-electron oxidants, they have been used in biological systems such as peptides or proteins to generate radical site primarily at aromatic and sulfur-containing amino acid side chains.^{5,85,107,108,169} The azide radical ($\cdot\text{N}_3$) shows great selectivity for tryptophan (Trp) residues.^{173–175} Similar selectivity was also shown by dichloride radical anions ($\text{Cl}_2^{\cdot-}$) and carbonate radical anion ($\text{CO}_3^{\cdot-}$). The Trp residue, the cysteine residue in the form of an anion (Cys^-), and the methionine residue in the form of monoanion (Met^-) are the preferential sites for dithiocyanate radical anion ($(\text{SCN})_2^{\cdot-}$). Dibromide radical anion ($\text{Br}_2^{\cdot-}$) reacts rapidly with

Trp, Cys, and Met residues and Cys^{•-} and tyrosine residues in the form of an anion (Tyr^{•-}).⁸⁵ These radicals were particularly useful for studying redox changes in amino acids, peptides, and proteins that were coupled very often with intramolecular LRET processes.^{85,107,173,175–179}

Intramolecular LRET reactions involving radicals located on the side chains of aromatic (Trp and Tyr), sulfur (Met and Cys), and His residues proceed on ground-state potential energy surfaces, making pulse radiolysis an effective and unique tool for these studies (see **Electron Transfer in Peptides and Proteins**). The advantage of pulse radiolysis is that using either an oxidizing or a reducing radical can generate the donor–acceptor complex.¹⁷⁸ The typical LRET pulse radiolysis experiments begin with the rapid selective oxidation or reduction of one redox site on a peptide or protein molecule, which is followed by the intramolecular LRET. Pulse radiolysis of simple model synthetic and natural peptides and native and mutant proteins have induced the following radical transformations: Trp/N[•] → Tyr/O[•] (136a and 136b),^{176,180–203} Met/S[•]:Br → TyrO[•] (137a and 137b),^{175,191,204–207} Met/S[•]:Br → Trp/N[•] (138a and 138b),^{175,191,205} CysS[•] ⇌ TyrO[•] (139a and 139b),^{175,189,206} His/N^{•+} → TyrO[•] (140a and 140b),²⁰⁸ and [CysS-SCys]^{•-} → Cu⁺ (141a and 141b)^{179,209–216};

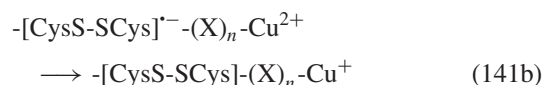
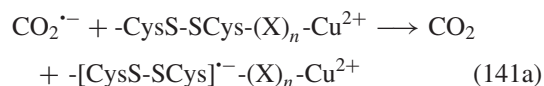
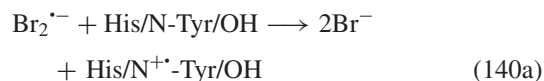
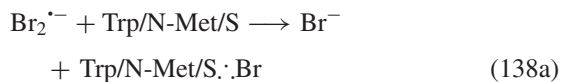


where X = glycine (Gly) or proline (Pro) residues, $n = 0–5$, in synthetic peptides or the respective oligopeptide backbone separating Trp and Tyr residues in native peptides and proteins;



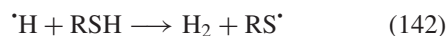
where X = proline (Pro) residues, $n = 0–4$, in synthetic peptides or the respective oligopeptide backbone, separating Met and Tyr residues in native

peptides and proteins;



where X is the respective oligopeptide backbone separating CysS-SCys and Cu²⁺ cation in native and mutant proteins (see **Electron Transfer in Peptides and Proteins**).

Biologically relevant thiyl radicals (RS[•]) have been considered for a long time as rather unreactive species. They are formed as a result of hydrogen abstraction from thiols (RSH) by primary radicals from water radiolysis: [•]OH (102) and [•]H (142), and by a dissociative attachment of hydrated electron (e_{aq}⁻) to disulfides (RSSR) (143)^{130–134}:



More recently, several reactions of RS[•] induced radiolytically have been characterized and kinetically described: H-atom abstraction from the αC–H bonds,²¹⁷ from amino acid side chain C–H bonds²¹⁸ in model peptides, and from bisallylic methylene groups in polyunsaturated fatty acid (PUFA),²¹⁹ intramolecular addition to aromatic rings,²²⁰ reversible intramolecular hydrogen transfer in peptides,^{221,222} addition to the C5–C6 double bond in pyrimidines,²²³ and catalyzed

cis/trans isomerization of lipid double bonds in mono-²²⁴ and polyunsaturated fatty acids (see **Lipid Isomerization**).^{225–230} All these reactions have been recently reviewed.¹⁵⁶

3.2 Radiolysis of Organic Solvents

The advantage of organic solvents over water is the broad range of solvent polarities available. Therefore, compounds that are insoluble in water can be studied in a suitable solvent or mixture of solvents. Moreover, depending on the solvent used, radiolysis offers a convenient method of generation of radical ions and excited states or preferentially one of them. Therefore, one may, by choice of a solvent, and in addition, of a saturating gas, exercise some control over the nature of the ionic species and excited states formed in the irradiated solvents and thus selectively generate radical ions and/or excited states derived from the solutes. There is a large variety of organic solvents that have been used for inducing radical reactions by means of high-energy radiation.²³¹ Owing to space limitations, only selective and most popular solvents are given in the following sections.

3.2.1 Radiolysis of Alcohols

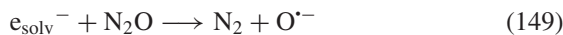
Radiolysis of neat alcohols leads to the formation of the alcohol positive ions and solvated electrons (144).^{232–236} In protic polar solvents such as methanol and 2-propanol, radical anions of a solute are formed through the attachment of solvated electron to the solute molecules (145). Solute radical cations, however, are not formed since the alcohol-derived radical cations disappear rapidly producing ketyl and alkoxy radicals according to reactions depicted in (146 and 147), respectively:



Reductive ketyl radicals formed in reaction (146) can also generate radical anions of a solute according to the following reaction:



In order to study the reduction reactions of ketyl radicals without a contribution of e_{solv}^- , the alcohol solution is saturated with nitrous oxide (N_2O). Solvated electrons are rapidly scavenged by N_2O generating oxide radical ions ($\text{O}^{\bullet-}$) (149), which subsequently react with alcohol molecules forming ketyl radicals (150):

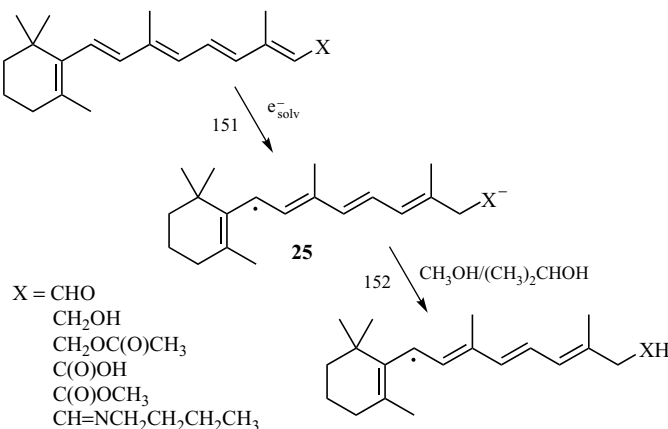


Since in alcohols mainly reductive radicals are formed, solvated electrons and ketyl radicals (144 and 146), these solvents have been used to induce selectively the one-electron reduction of solute molecules.^{237–244}

A few systems can be presented here to illustrate the generation of solute radical anions via reactions of solvated electrons and ketyl radicals with solute molecules and subsequent reactions of radical anions in alcohol solutions.

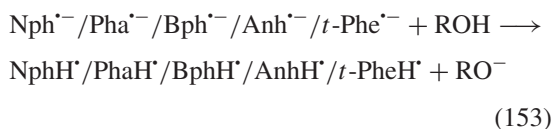
Radical anions **25** derived from (i) retinyl polyenes derivatives^{245–247} (retinal, retinol, retinol acetate retinoic acid, methyl retinoate, and *n* butylamine Schiff base of retinal) (Scheme 11, reaction (151)), (ii) retinal homologues^{245,247,248} (β -cyclocitral, β -ionone, C_{17} , C_{22} , C_{24} , and C_{30} aldehydes), and (iii) carotenes (septapreno- β -carotene, all-*trans*- β -carotene, 15,15'-*cis*- β -carotene, and all-*trans*-lycopene),^{245,249,250} astaxanthin, and canthaxanthin^{250,251} have been generated and studied in methanol and 2-propanol.

Radical anions derived from naphthalene ($\text{Nph}^{\bullet-}$), phenanthrene ($\text{Pha}^{\bullet-}$), biphenyl ($\text{Bph}^{\bullet-}$), anthracene ($\text{Anh}^{\bullet-}$), *p*-, *o*-, *m*-terphenyls (*t*- $\text{Phe}^{\bullet-}$) undergo protonation by alcohol molecules. The rate constants for reaction (153) depend on the



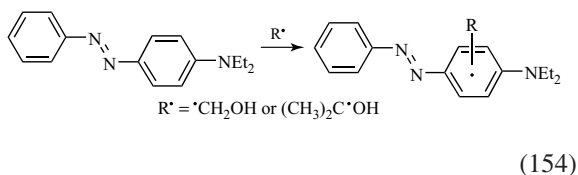
Scheme 11 Formation of radical anions derived from retinyl polyenes and their subsequent protonation.

properties of alcohols (acidity of the hydroxyl proton)²⁵² and the nature of the aromatic radical anion²⁵³:



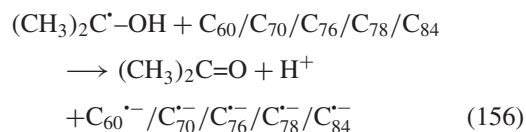
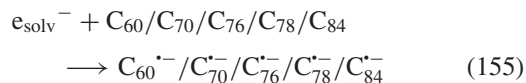
Radical anions derived from retinal, retinoic acid, methyl retinoate **25**, and retinal homologues undergo protonation by alcohol molecules (Scheme 11, reaction (152)).²⁵⁴ The rate constants for protonation of radical anions in alcohols decrease on increasing the polyene chain length.²⁴⁷

Fast protonation of radical anions derived from azobenzene^{255,256} and 4-(diethylamino)-azobenzene²⁵⁶ has been observed in irradiated methanol and 2-propanol. Moreover, both ketyl radicals undergo a very fast addition with 4-(diethylamino)azobenzene²⁵⁶:

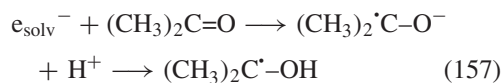


Radical anions derived from fullerenes (C_{60} , C_{70} , C_{76} , C_{78} , and C_{84}) have been generated (155 and 156) and their spectral and kinetic properties

have been characterized in 2-propanol (see **Radical Chemistry on Fullerenes**)^{257–262}:



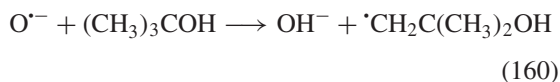
The reduction reactions of ketyl radicals derived from 2-propanol with fullerenes (C_{60} , C_{70} , C_{76} , C_{78} , and C_{84}) (156), without a contribution of e_{solv}^- (155), have been studied in a toluene/2-propanol/acetone (8 : 1 : 1 v/v) solvent mixture.^{259–262} The $(\text{CH}_3)_2\text{C}^{\bullet}\text{-OH}$ radicals were formed in a reaction depicted in (146) and by a sequence of the following reactions: solvated electron capture by acetone followed by subsequent protonation of ketyl radical anions (157):



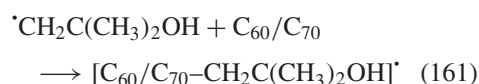
Alkyl radical (•CH_3) addition reaction to C_{60} has been studied in 2-propanol containing methyl iodide (CH_3I) as an electron scavenger^{257,258}:



The β -hydroxy alkyl radical ($\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$) addition reaction to C_{60} and C_{70} has been studied in N_2O saturated 2-methyl-2-propanol (*tert*-butanol) solutions.^{259,260} The $\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$ radical is formed in reaction (160) analogous to reaction depicted in (150):

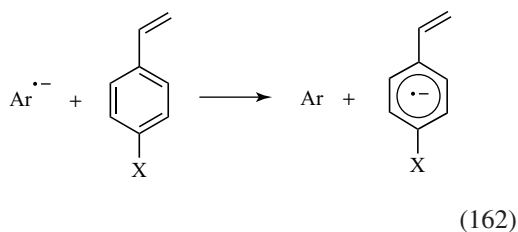


Since $\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$ radicals are practically redox inert, they form only adduct radicals:



Spectral parameters of radicals derived from fullerenes and absolute rate constants for reactions depicted in (155, 156, 159, and 161) have been reported.^{257–262} Radical chemistry of fullerenes has been addressed in a more detailed manner (see **Radical Chemistry on Fullerenes**).

ET reactions from radical anions of biphenyl, anthracene, and pyrene ($\text{Ar}^{\cdot-}$) to styrene (St) and *para*-substituted styrenes (*p*-X-St; X = OCH_3 , CH_3 , and Cl) have been induced in 2-propanol.²⁶³ The respective radical anions ($\text{Ar}^{\cdot-}$) formed in reactions (145 and 148) subsequently react with styrene and substituted styrenes (St) (162):



The rate constants for reactions depicted in (162) are in the range 10^6 – $10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.

3.2.2 Radiolysis of Tetrahydrofuran

Tetrahydrofuran (THF) is another example of the solvent in which selective generation of radical anions can be achieved. Pulse irradiation of a neat THF leads to formation of the THF radical cations and solvated electrons (163) and triplet states

formed by solvent radical ion recombination (164). The yield of solvated electrons in THF was found ($G \sim 0.53$) as the average of reported values. Low yields for $^3(\text{C}_4\text{H}_8\text{O})^*$ were measured. The yield of radical cations have not been measured since solvent radical cations ($(\text{C}_4\text{H}_8\text{O})^{+\cdot}$) decompose very fastly to solvated protons and radicals (165):

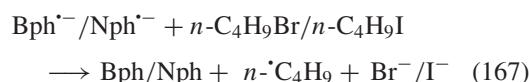


In this solvent, similar to alcohols (Section 3.2.1), only radical anions of solute molecules are formed:



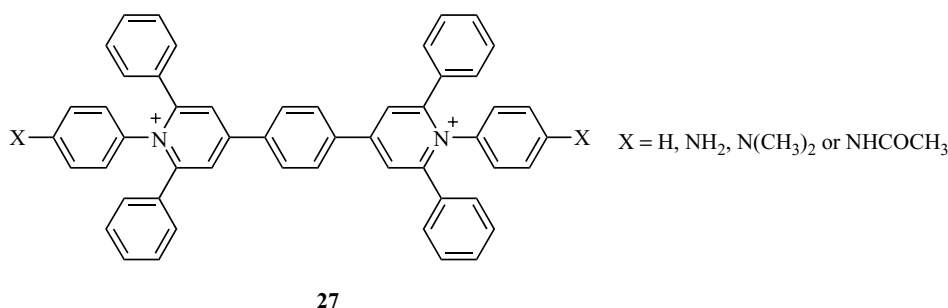
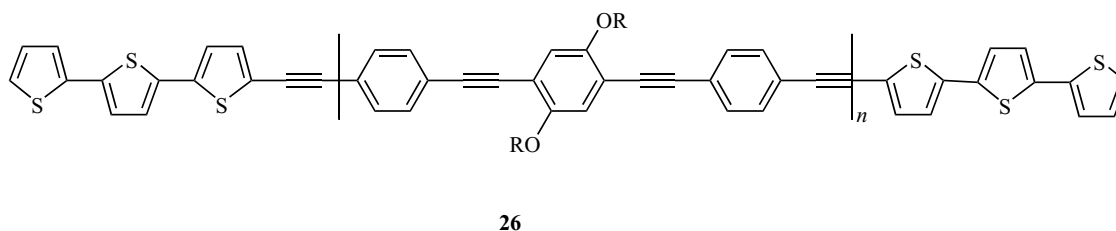
The formation of solute radical anions or radicals in THF has been reported by many workers using a variety of solutes: organomercury compounds,^{264–266} *n*-butyl bromide and *n*-butyl iodide,²⁶⁷ biphenyl,²⁶⁷ naphthalene,²⁶⁷ retinal, and several retinal homologues.²⁴⁷

ET reactions from radical anions of biphenyl ($\text{Bph}^{\cdot-}$) and naphthalene ($\text{Nph}^{\cdot-}$) radical anions to *n*-butyl bromide (*n*-BuBr) and *n*-butyl iodide (*n*-BuI),²⁶⁸ and of biphenyl ($\text{Bph}^{\cdot-}$), anthracene ($\text{Anh}^{\cdot-}$), and pyrene ($\text{Py}^{\cdot-}$) to styrene (St) and *para*-substituted styrenes (*p*-X-St; X = OCH_3 , CH_3 , and Cl),²⁶³ have also been induced in THF. The respective radical anions formed via reaction (166) subsequently react with *n*-butyl bromide and iodide (167) and styrene and substituted styrenes (St) (162):



Recently, several interesting studies have been performed using radiolysis of THF for inducing radical reactions in large organic molecules. The formation of radical anions in parent and terthiophene end-capped poly(arylene-ethynylene) polymers **26** (Scheme 12) have been accomplished in an effort to characterize the spectra and dynamics of the radical anions of the polymers.²⁶⁹

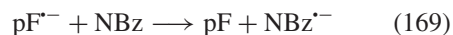
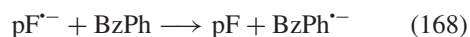
One electron reduction of an “extended viologen” *p*-phenylene-bis-4,4'-(1-aryl-2,6-diphenylpyridinium) dication (EV^{2+}) **27** (Scheme 12)



Scheme 12 Structural formulas of terthiophene end-capped poly(arylene-ethynylene) polymers and extended viologen *p*-phenylene-bis-4,4'-(1-aryl-2,6-diphenyl-pyridinium) dication.

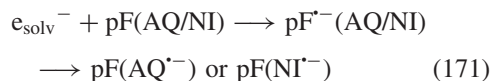
has been induced in THF, showing that e_{solv}^- reacts very rapidly with EV^{2+} ($k = (4.2 \pm 1.5) \times 10^{11} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) and the monomeric radical cation produced has a fully delocalized electronic structure.²⁷⁰

ET reactions from the radical anion of poly-2,7-(9,9-dihexyfluorene) ($\text{pF}^{\bullet-}$) to benzophenone (BzPh), nitrobenzene (NBz), and pyrene (Py) have also been induced in THF.²⁷¹ The radical anion ($\text{pF}^{\bullet-}$) formed via reaction (166) subsequently reacts with BzPh, NBz, and Py (168–170). Reaction with pyrene does not lead to completion but to an equilibrium (170):



The formation of radical anions in polyfluorenes having anthraquinone (AQ) or naphthylimide (NI) end caps that trap electrons have enabled studies on ET along the chains of conjugated polymers.²⁷² An electron attachment to a polyfluorene chain is followed by a fast ET to and trapping by end cap

(AQ/NI):

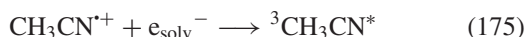
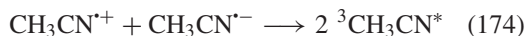
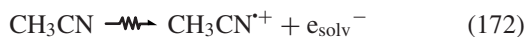


The attachment rate constants to fluorene oligomers (oF) and fluorene polymers (pF) have been determined. It was found that in going from oF₁ to pF₁₃₃, k increases by a factor of 16, which is much smaller than the 133-fold increase in length.²⁷³

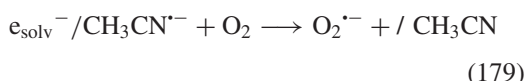
3.2.3 Radiolysis of Acetonitrile

Acetonitrile is known for pulse radiolytic generation of radical cation as well as radical anion precursors.^{274–277} Pulse irradiation of a neat acetonitrile leads to the formation of the acetonitrile positive ions and electrons/negative ions (172 and 173) and triplet states formed by solvent radical ion recombination (174 and 175). Low yields of G for the oxidizing species (~ 0.2)²⁷⁷ and for the triplets (~ 0.3) were measured.²⁷⁵ On the other hand, the

yield of reducing species was found in the range of $G = 1.03\text{--}1.55$ ²⁷⁶:



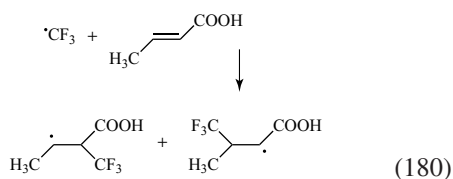
In this solvent saturated with Ar, both radical ions can be formed (176–178), while in O₂-saturated solution only radical cations of a solute are formed (178) (ionization potential of CH₃CN is ≈ 12 eV). Solute radical anions are not formed since their precursors, solvated electrons, and/or solvent radical anions are scavenged by O₂ (179):



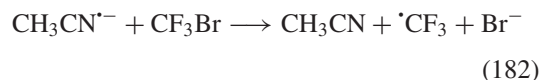
Oxygen also serves as a strong quencher for triplets of solutes and solvents.

Radical ions derived from phenol,²⁷⁷ benzhydrol,²⁷⁷ phenothiazine,²⁷⁷ BzPh,^{276,277} biphenyl,^{276,277} naphthalene,²⁷⁵ anthracene,²⁷⁵ pyrene, 4-nitro-benzyl compounds,²⁷⁸ *N*-methylacetamide,²⁷⁹ tri-*p*-tolylamine,²⁷⁷ triphenylamine,²⁷⁷ retinal,²⁴⁸ 7-aminocoumarin dyes,²⁸⁰ and oxoisoaporphines derivatives^{281,282} have been generated according to reactions depicted in (176)–(177) and (178), respectively, and characterized spectrally.

Reactions of $\cdot\text{CF}_3$ radicals with pyrene, phenanthrene, and crotonic acid (CA) (180) have been induced in CF₃Br-saturated acetonitrile.²⁸³ These reactions undergo $\cdot\text{CF}_3$ addition to form pyrene/phenanthrene rings and a double bond in CA:

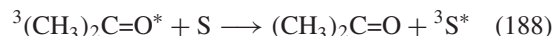
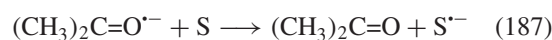
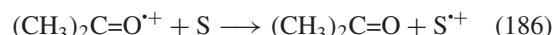
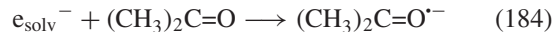
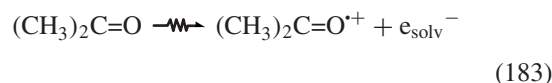


$\cdot\text{CF}_3$ radicals are formed in the following reactions:



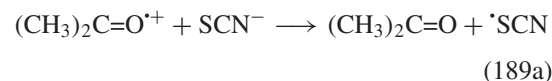
3.2.4 Radiolysis of Acetone

Radiolysis of acetone leads to the relatively long-lived radical ions (183 and 184) and triplet states (formed via geminate recombination (185)).^{284,285} The free ions and triplet yields were measured to be 0.75 and 1.0, respectively.²⁸⁶ Radical cations and anions of acetone are involved in charge transfer to a solute, which leads to the radical cations and radical anions of a solute, respectively (186 and 187). On the other hand, triplets of acetone are involved in energy transfer to a solute that leads to a triplet of a solute (188):

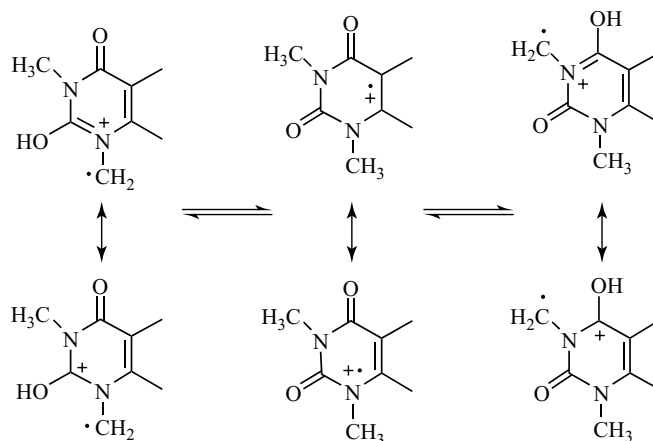


In this solvent saturated with Ar, both radical ions and triplets can be formed according to (186–188), while in O₂ saturated solution, only radical cations of a solute are formed. The total yields of excited states ($G = 1.3 \pm 0.1$) and of free ions ($G = 1.2\text{--}1.7$) were found.

The formation of $(\text{SCN})_2^{*-}$ has been observed via the following reactions²⁸⁷:

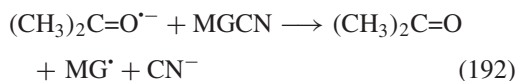
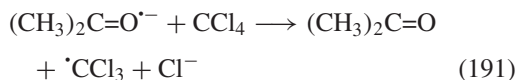
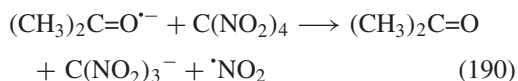


Some selected illustrative examples of dissociative ET reactions involving tetranitromethane,²⁸⁸



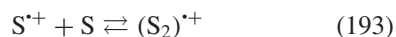
Scheme 13 Tautomerism of radical cations derived from methylated uracils and thymines.

carbon tetrachloride and leucocyanide of malachite green dye (MGCN)²⁴¹ induced in irradiated acetone are depicted in the following equations (190–192):



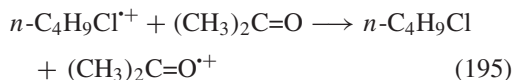
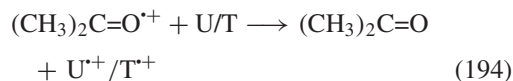
Radical cations and anions and triplet excited states of naphthalene,^{284,287} anthracene,^{287,289} pyrene,²⁸⁴ biphenyl,²⁸⁷ *trans*-stilbene,²⁸⁷ nitromethane,²⁹⁰ retinyl polyenes derivatives (retinal, retinol, retinol acetate retinoic acid, methyl retinoate, and *n*-butylamine Schiff base of retinal),²⁹¹ and retinal homologues (β -cyclocitral, β -ionone, C₁₇, C₂₂, C₂₄, and C₃₀ aldehydes)²⁴⁷ have been generated (186–188) and studied in acetone.

Radical cations ($\text{S}^{\bullet+}$) derived from pyrene,^{284,292} naphthalene,²⁸⁴ 2,6-dimethyl-naphthalene,²⁸⁴ retinal,²⁹³ retinoic acid,²⁹³ and methyl retinoate²⁹³ were found to interact with neutral, ground-state solute molecules (S) forming dimeric radical cations (193):



The dependence of the kinetics of the decay/formation processes on solute concentration can be rationalized in terms of dimer/monomer radical cation equilibria.

Radical cations of multiple methylated uracils (U) and thymines (T) were generated in acetone (194) and acetone/*n*-butyl chloride mixtures (195) (for formation of *n*-C₄H₉Cl⁺, Section 3.2.5)²⁹⁰:

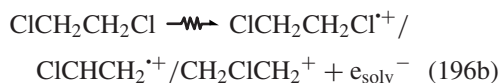
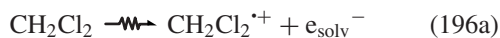


These radical cations show a transient tautomerism and exist in acetone in a lactim- and in *n*-butyl chloride in a lactam-like form (Scheme 13).²⁹⁰

3.2.5 Radiolysis of Halogenated Hydrocarbons

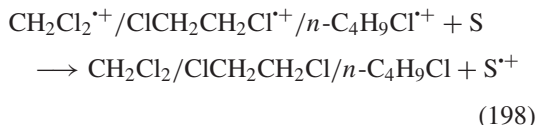
Radiolysis of halogenated solvents such as dichloromethane (CH₂Cl₂), 1,2-dichloroethane (ClCH₂CH₂Cl), and *n*-butyl chloride (*n*-C₄H₉Cl) generates radical cations or radicals that are very strong oxidants.^{294,295} In irradiated halogenated hydrocarbon liquids, after initial ionization process (196a–196c), the secondary electrons undergo a very fast dissociative attachment to the solvent, forming relatively unreactive free radicals and

chloride ions which do not react with the solute (197):



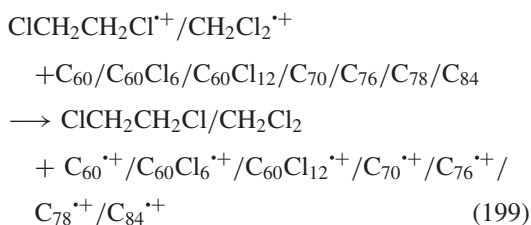
Thus, direct reactions of electrons with the solutes of interest are eliminated, and these halogenated hydrocarbon solvents are convenient for the selective generation of solute radical cations.

In the presence of additives (S) of lower ionization potential as the above solvents, a rapid ET takes place:

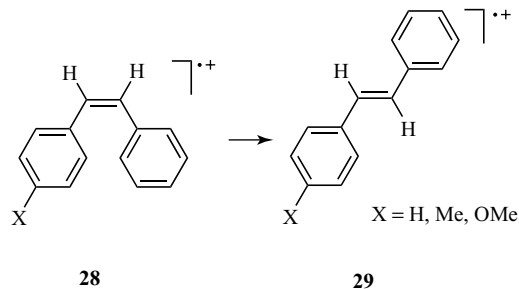


Radical cations derived from retinal and retinoic acid have been generated,²⁹¹ and their subsequent reactions with respective solutes forming dimeric radical cations have been observed in 1,2-dichloroethane.²⁹³

Radical cations derived from fullerenes (C_{60} , C_{70} , C_{76} , C_{78} , and C_{84}),^{257–262} and chlorinated fullerenes (C_{60}Cl_6 and $\text{C}_{60}\text{Cl}_{12}$),²⁹⁶ have been generated (199) and their spectral and kinetic properties have been characterized in 1,2-dichloroethane and dichloromethane (see **Radical Chemistry on Fullerenes**):

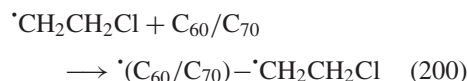


Rate constants of $\text{CH}_2\text{CH}_2\text{Cl}^{\bullet+}$ radicals additions to C_{60} and C_{70} (200) have been measured in 1,2-dichloroethane ($k_{200} = 2.2 \pm 0.5 \times 10^9 \text{ dm}^3$

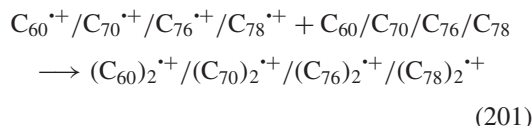


Scheme 14 Cis/trans-Isomerization of radical cations derived from stilbene derivatives.

$\text{mol}^{-1} \text{ s}^{-1}$ for C_{60} ²⁵⁹ and $1.9 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for C_{70})²⁶⁰:

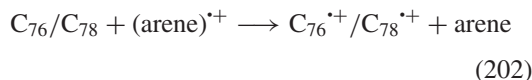


Formation of dimer radical cations of $\text{C}_{60} / \text{C}_{70} / \text{C}_{76} / \text{C}_{78}$ fullerenes according to reaction depicted in (201) have been studied in 1,2-dichloroethane and dichloromethane:

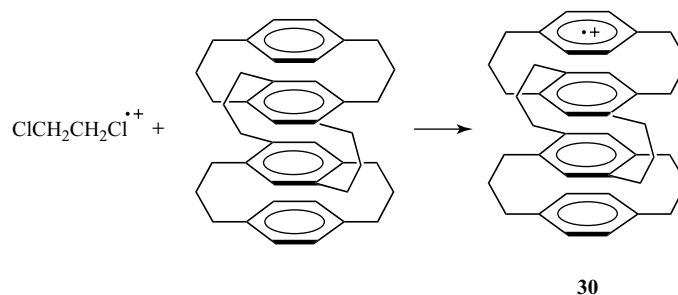


The bimolecular rate constants k_{201} were 6.0×10^9 , 6.0×10^9 , 7.9×10^8 , and $9.8 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ for C_{60} , C_{70} , C_{76} , and C_{78} , respectively.^{259,260,262}

The ET reactions from the ground state of C_{76} and C_{78} to radical cations of various arenes (202) have evidenced the Marcus inverted region.^{297–299} The formation of the arene radical cations has been achieved by reaction of $\text{CH}_2\text{Cl}_2^{\bullet+}$ with the respective arenes, analogous to reaction depicted in (199):



Generation of radical cations of stilbene derivatives **28** and **29** and their further reactions, cis to trans isomerization (Scheme 14), oxidation, and dimerization, have been induced and studied in dichloroethane and *n*-butyl chloride.³⁰⁰ Remarkable enhancement of isomerization and oxidation



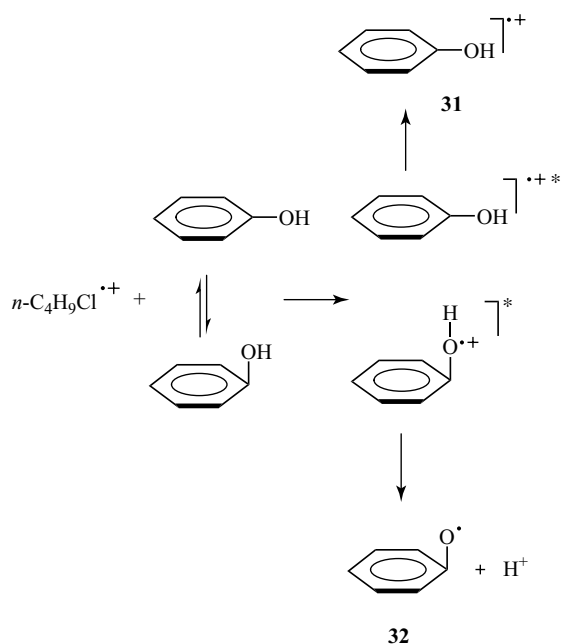
Scheme 15 Generation of intramolecular dimer radical cations of cyclophanes.

of stilbene radical cations was observed resulting from charge-spin separation induced by $-\text{OCH}_3$ groups.³⁰¹

The radical cations of oligothiophenes (nT), with number of rings $n = 1-6$, have been generated in dichloromethane.³⁰² The electronic transitions for radical cations move to lower energy as the number of thiophene rings increases. This is interpreted as a result of an extended delocalization of π -system along the chain.³⁰²

Recently, generation of highly stabilized intramolecular dimer radical cations of cyclophanes **30**, containing π -stacked multi-benzene rings connected by propyl chains, has been achieved in 1,2 dichloroethane (Scheme 15). It was revealed that efficient charge delocalization over the cyclophanes occurs and the stabilization energy depends on the distance between the two benzene rings and the number of benzene rings.³⁰³⁻³⁰⁵

Using $n\text{-C}_4\text{H}_9\text{Cl}^{\bullet+}$ as a very efficient electron acceptor toward a large variety of organic donor molecules (198), a phenomenon called *free electron transfer* (FET) has been thoroughly studied in some substituted aromatic compounds: phenol³⁰⁶⁻³⁰⁸ and substituted phenols,³⁰⁶⁻³¹¹ thiophenol^{306,308,312} and substituted thiophenols,^{308,310,312} seleno-phenol,^{308,313} aromatic amines,^{314,315} sulfides³¹⁶ and silanes,^{317,318} naphthols,^{312,319} hydroxybiphenyls,³¹⁹ trityl-containing compounds,³²⁰ and amino-, thio-, and hydroxynaphthalenes.³²¹ All these compounds constitute a group of molecules that fulfils the structural conditions necessary for FET, that is, they exhibit a low-energy barrier to rotation about the $\text{C}_{\text{sp}^2}\text{-X}$ bond. A parallel formation of two different and distinguishable FET products was observed, the expected metastable solute radical cations ($\text{X}^{\bullet+}$)



Scheme 16 Reaction sequence in free electron transfer involving phenols.

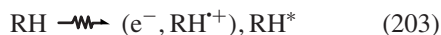
31 and the corresponding solute-derived radicals ($\text{X}^{\bullet}$) **32** (Scheme 16).

Two excellent and comprehensive reviews that present and discuss these problems in a more detailed manner have been published recently.^{322,323}

3.2.6 Radiolysis of Hydrocarbons

Liquid hydrocarbons such as alkanes, alkenes, and cycloalkanes have been used for generation of radiation in radical ions. *n*-Hexane and cyclohexane

were the most commonly used solvents.^{36, 324–329} Radiolysis of these hydrocarbons (RH) produces excited states (RH*) and electron-hole pairs (e[−], RH^{•+}):



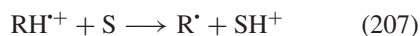
Because of the low dielectric constant ($\epsilon \sim 2$), the bulk of the ion recombination is geminate yielding energetic, excited solvent molecules:



Few of these electrons, however, can escape ion recombination and in the presence of solute, they can react forming solute radical anions (S^{•−}):



The solvent “hole” produced is characterized by a high mobility and they can undergo several ion-molecule reactions including charge (206) and proton (207) transfer reactions with solutes:



The rate constants of charge transfer processes are very high, that is, $(1-5) \times 10^{12}$ and $(10^{10}-10^{11}) \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ for reactions depicted in (206 and 207), respectively. These rates are higher in cyclohexane than in other *n*-alkanes.^{327–329}

These reactions and their radical-ion products were studied using nano- and picosecond pulse radiolysis.^{330–333}

Radical cations derived from tetraphenylethylene³³⁴ have been generated in cyclohexane solutions. The formation of intra- and intermolecular radical cation complexes during oxidation of organic di-, tri-, and tetrathia compounds (1,4- and 1,3-dithiacyclohexane, 1,3,5-trithiacyclohexane, 1,4,7,10-tetrathiacyclododecane, 1,5,8,12-tetrathiacyclotetradecane, 4-methyl-3,5-dithiaheptane in neohexane and 3-methylpentane,³³⁵ and radicals with the intermolecular 2c–3e bond between sulfur and iodide in 1-halo-2-(methylthio)ethanes³³⁶ has been observed.

Radical cations derived from (i) retinal homologues (β -ionone²⁴⁵ and β -ionylidene acetaldehyde),²⁴⁵ (ii) retinyl derivatives (retinal^{245,291} and

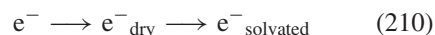
retinoic acid²⁹¹), and (iii) carotenes (β -apo-8'-carotenal,²⁴⁵ all-*trans*- β -carotene,²⁴⁹ 15,15'-*cis*- β -carotene,²⁴⁹ and all-*trans*-lycopene),²⁴⁹ 7,7'-dihydro- β -carotene,²⁵⁰ septapreno- β -carotene,²⁵⁰ decapreno- β -carotene,²⁵⁰ dodecapreno- β -carotene,²⁵⁰ and canthaxanthin²⁵⁰ have been generated in *n*-hexane and cyclohexane in a charge transfer process.

3.3 Radiolysis of Ionic Liquids

Ionic liquids (ILs) are defined as *molten salts* with melting points below 100°C. These salts are a combination of organic and inorganic ions. Owing to their unique properties, ILs are attractive media for generation of radicals (see **Free Radical Chemistry in Room-Temperature Ionic Liquids**).^{337,338}

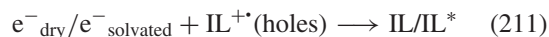
For water and organic solvents, the knowledge about the nature of primary reactive species and the approaches to convert them into specific radical intermediates is rather broad (*vide supra*). A similar knowledge has to be assembled for IL. Therefore, understanding the chemistry of IL under high-energy radiation is crucial for designing IL composition to induce specific radical reactions.

The two major processes that occur in irradiated ILs are excitation (208) and ionization (209) of IL molecules^{339–343}:

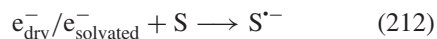


The ejected electrons start to lose their excess kinetic energy and become “thermalized” (210). These electrons are not equilibrated with the surrounding molecules and therefore they are called dry or presolvated. As the solvation process proceeds, the electrons become more and more localized and solvated, eventually.

They can also undergo recombination with the “holes” to produce a ground or excited states of the IL anions or cations:

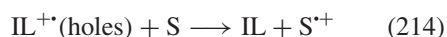
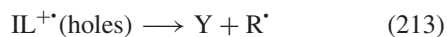


In the presence of electron scavengers, both types of electrons can form radical anions:



where S designates different types of electron scavengers: those reacting either with presolvated or solvated electrons and those reacting with both of them.

“Holes” resulting from ionization (209) can undergo recombination with electrons (211), fragmentation into fragments of any type, including radicals (213) or in the presence of “hole” scavengers form radical cations (214):



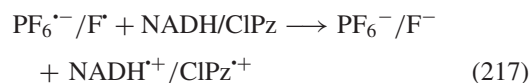
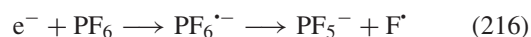
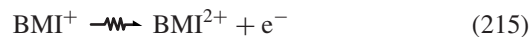
Different classes of IL on irradiation can produce different reactive intermediates, which is often advantageous. Therefore, IL can provide a new environment to induce by radiation and to test radical reactions including charge transfer processes.

Most of the radiation-induced radical intermediates have been studied in IL composed of imidazolium (BMIM⁺),^{341,344–350} quaternary ammonium (R₄N⁺),^{283,341,347,351–360} pyrrolidinium,^{341,347,348,354} pyridinium (Py),^{347,348,351,354} phosphonium cations,^{341,348} and bis(trifluoromethylsulfonyl)imide,^{283,341,347,351–360} dicyanamide,³⁴¹ bis(oxalato)-borate,^{341,348} tetrafluoroborate (BF₄[−]),^{351,354,359} hexafluorophosphate (PF₆[−]),^{346,349,351} chloride (Cl[−]),³⁵⁰ bromide (Br[−]),³⁵⁰ thiocyanate (SCN[−]),³⁵⁰ and azide (N₃[−]) anions.³⁵⁰

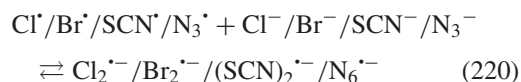
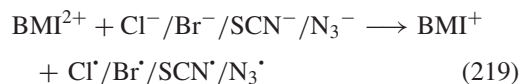
Since the issue of free radical chemistry in ILs has already been addressed (see **Free Radical Chemistry in Room-Temperature Ionic Liquids**), here only a few typical examples of radiation-induced radical reactions in various ILs are presented.

The radical cations from 1-methyl-1,4-dihydronicotinamide,³⁴⁴ chlorpromazine (215–217)), and *N,N,N,N'*-tetramethyl-*p*-phenylenediamine (TMPD) (215 and 218),³⁴⁵ and the radical cations and anions from benzoquinone, duroquinone (DQ), methyl viologen, chlorpromazine (CIPz), 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), and thiophene and its substituted derivatives were generated in the IL 1-butyl-3-methyl-imidazolium (BMI⁺) with

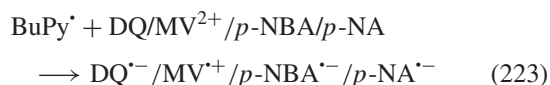
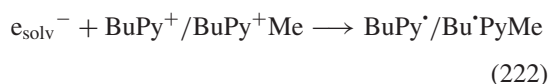
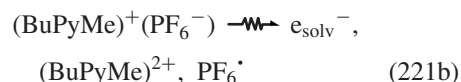
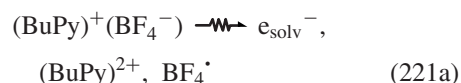
hexafluorophosphate (PF₆[−]) and tetrafluoroborate anions (BF₄[−])^{345,349}:



Dihalide (Cl₂^{•−} and Br₂^{•−}) and pseudo-halides ((SCN)₂^{•−} and N₆^{•−}) radical anions have been selectively generated in IL containing 1-butyl-3-methyl-imidazolium (BMI⁺) cation with Cl[−], Br[−], SCN[−], and N₃[−] anions (215, 219, and 220)³⁵⁰:

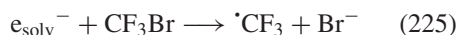
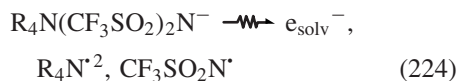


The reactions of the reductive butylpyridinyl radicals (BuPy[•]) with DQ, methyl viologen (MV²⁺), *p*-nitrobenzoic acid, and *p*-nitroacetophenone (221–223) were induced and studied in the ILs *N*-butylpyridinium tetrafluoroborate (BuPyBF₄) and *N*-butyl-4-methylpyridinium hexafluorophosphate (BuPyMePF₆). Solvated electrons cannot reduce solutes in these ILs since they are rapidly scavenged by the pyridinium cations (222)^{351,354}:

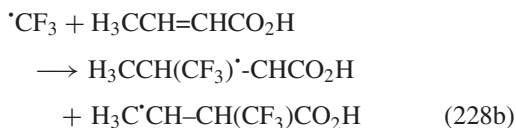
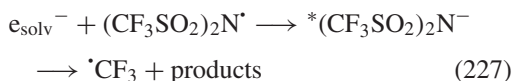


(BuPy)²⁺/BuPyMe²⁺ and BF₄[•]/PF₆[•] act as oxidants or undergo fragmentation.

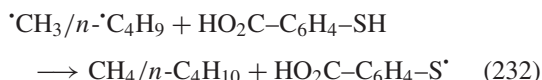
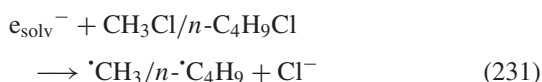
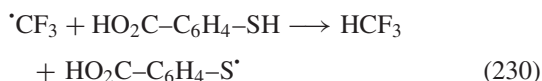
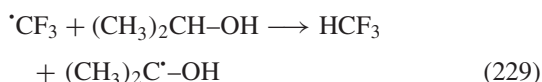
The addition reactions of trifluoromethyl radicals ($\text{CF}_3^\bullet$) to pyrene (Pyr), phenanthrene (Phen), and CA (224–228) were induced and studied in IL methyltributylammonium bis(trifluoromethylsulfonyl)imide (R_4NNTf_2) saturated with or in acidic medium without CF_3Br .²⁸³ The solvated electrons do not react with the solvent ions (R_4N) and $(\text{CF}_3\text{SO}_2)_2\text{N}^-$ and are scavenged by CF_3Br (225):



Trifluoromethyl radicals can be also formed via fragmentation of $\text{CF}_3\text{SO}_2\text{N}^\bullet$ radicals (241) and/or from excited states formed by geminate recombination (242):

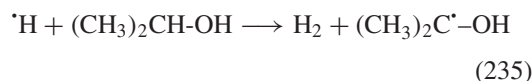
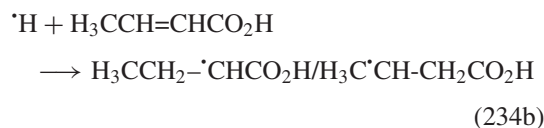
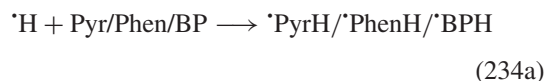
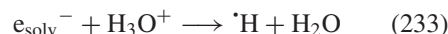


The same IL was used to induce and study (i) hydrogen abstraction reactions of $\text{CF}_3^\bullet$ radicals (229–230) and alkyl radicals (231–232) from 2-propanol and 4-mercaptobenzoic acid (229, 230, and 232)^{283,352}:

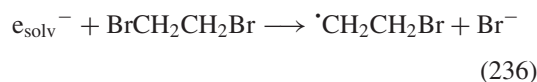


(ii) reduction of several solutes, including CCl_4 , BzPh, pyrene, quinones, and chlorophenols

by dry and/or solvated electrons,^{351,356,358–360} (iii) hydrogen atom addition reactions in acidic medium to pyrene (Pyr), phenanthrene (Phen), BzPh (233–234a), CA (233–234b), and hydrogen abstraction from 2-propanol (233 and 235),³⁵⁵



(iv) generation and reactions of dihalide radical anions (236–238) and their subsequent oxidation reactions on saturation with 1,2-dibromoethane,^{353,357}



where $\text{X} = \text{Br}$ and SCN .

4 RADIATION-INDUCED RADICAL REACTIONS IN SOLIDS

4.1 Basic Considerations

Radiolysis of solids differs from radiolysis of gases and liquids because of the higher electron density of the absorbing medium and decrease in freedom of the ionized and excited species. Since the distance traveled by energetic electrons in depositing their energy is inversely proportional to the density of the medium, the tracks are shorter and the spur radii are smaller in the solid than in the liquid. Therefore, in the solid state, the ionized and excited species will be much more closely confined and the deposited

energy will be limited to very small regions. Thus, the distribution of the species is dependent on LET. As the solids are irradiated, the primary processes of excitation and ionization take place and electronically excited molecules and atoms, radical ions, radicals, and stabilized electrons are formed. However, the close proximity of neighboring molecules in the solid favors deactivation over decomposition and thus favors prompt recombination in the parent cage. Radiation-induced radical reactions in solids have not been studied so thoroughly as in gases or liquids. This is partly justified since the dynamic, structural, and relaxation properties of a solid may play a decisive role in energy and charge transfer processes.

There are several comprehensive reviews and books, which discuss the topic of radiation generation of radical ions in solids in a detailed manner.^{2,36,361–365} Radiation-induced reactions in aqueous glasses,^{366,367} organic glasses,^{361,368} low-temperature rare gas matrices,^{364,365} involving radicals and radical ions derived from a large variety of compounds have been reviewed, previously. A special attention has been paid to radiation-induced radical reactions in amino acids, peptides, proteins, nucleobases, and DNA present in aqueous glasses and in crystalline states. The reader is referred to several excellent reviews for details,^{88,108,169,171,369–372} which cannot be covered in depth here.

This section highlights only the recently obtained examples of radiation-induced radical reactions in zeolites, a new matrix used for radiation generation of radicals and radical ions in the solid state.

4.2 Radiolysis of Zeolites

Zeolites are crystalline aluminosilicates. Their lattice consists of a network of SiO_4^- and AlO_4^- tetrahedra with Si and Al atoms at the centers and oxygen atoms in each corner.³⁷³ These rigid microporous solids can serve as excellent matrices for generating and stabilizing otherwise reactive and unstable radical cations. Radical cations in zeolites have increased lifetimes since the restricted mobility within zeolite pores limits the tendency of free radicals and radical cations to react with other reagents.^{374–376}

Energy deposited in zeolites by high-energy radiation generates “holes” (Z^+) and trapped electrons in zeolite matrix:



In the presence of adsorbate (A), “holes” (Z^+) migrate to adsorbate molecule “guests” by charge transfer:



Since the redox and the acid–base properties depend on the zeolite, one has to be aware that it is not always obvious whether the original substrate or a rearranged product is oxidized by interaction with the zeolite “hole” Z^+ .

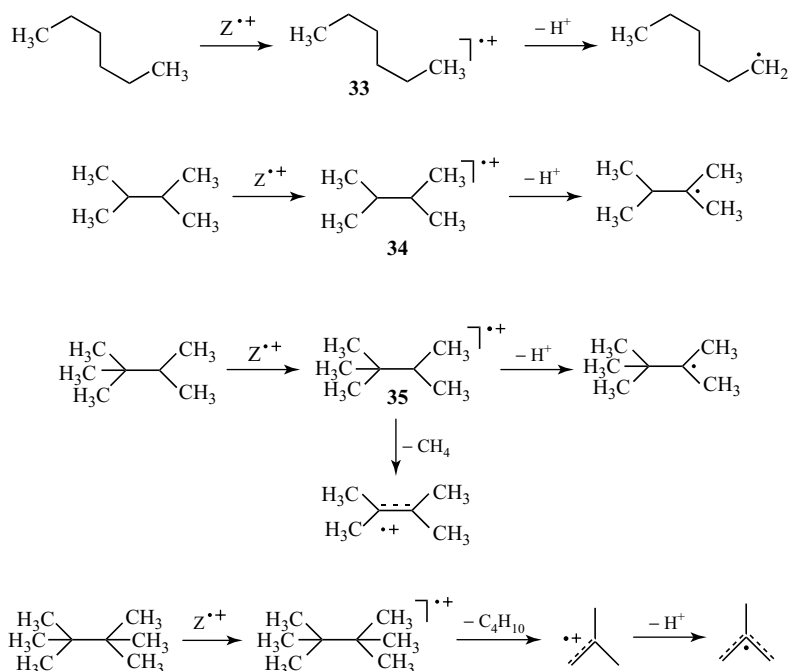
A large variety of radical cations and radicals have been generated in zeolites.³⁷⁶ This section is restricted to the most relevant examples of generation of radical cations and radicals generated in linear and branched alkanes,^{377–380} cycloalkanes,^{380,381} strained-ring compounds,³⁸² alkenes,^{378,382–385} C_7H_8 hydrocarbons,^{380,386,387} ethynes,³⁸⁵ and polynuclear aromatics^{388–390} on radiolysis.

Generation and subsequent proton transfer, fragmentation, and deprotonation reactions of radical cations derived from linear *n*-hexane **33** and branched 2,3-dimethylbutane **34**, 2,2,3-trimethylbutane **35**, and 2,2,3,3-tetramethylbutane **36** (Scheme 17) have been observed in ZSM zeolites.^{377,379,380}

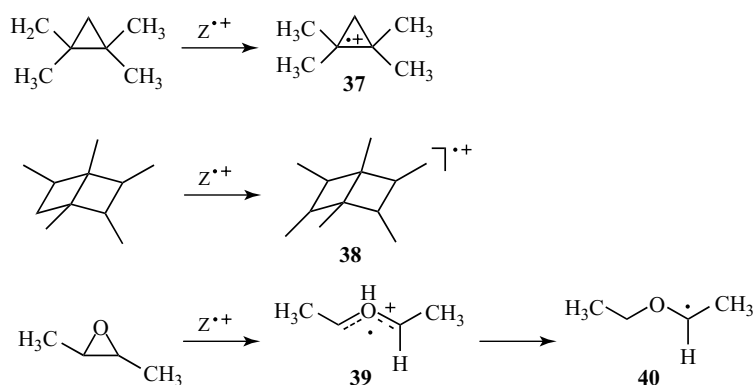
Cyclohexane³⁸⁰ and cis/trans-decaline³⁸¹ radical cations have been generated and characterized in ZSM-5 and in a number of synthetic zeolites, respectively. In the latter case, it was found that both cis/trans-decaline radical cations exist in two different electronic states.

Radical cations of 1,1,2,2-tetramethylcyclopropane (TMCP^+) **37** and hexamethylbicyclo-hexa-2,5-diene (Dewar benzene) (HMCH^+) **38** have been generated in Na–Y zeolite and characterized by ESR spectroscopy.³⁸² On the other hand, radiolysis of *trans*-2,3-dimethyl-1-oxacyclopropane resulted in the formation of a ring-opened radical species (DMOCP^+) **40** (Scheme 18) without preceding formation of a delocalized, ring-opened radical cation **39**.³⁸²

Extensive studies on radiolytically generated radical cations derived from alkenes in a number of synthetic zeolites (Na–Y, Na–X, and ZSM-5) have been performed.^{383–385,391} Radiolysis of 2,3-dimethyl-1-butene (2,3-DMB) **41**



Scheme 17 Generation of radical cations in *n*-hexane and branched methylbutanes and their subsequent reactions.



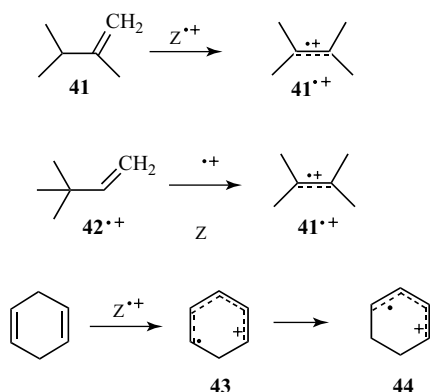
Scheme 18 Generation of radical cations in cyclic alkanes.

in various zeolites resulted in the formation of monomer radical cation (2,3-DMB^{•+}) **41**^{•+}, 2,3-DMB radical (2,3-DMB[•]), and π -dimer radical cation (2,3-DMB)₂^{•+}.³⁹¹ Interestingly, radiolysis of 3,3-dimethyl-1-butene (3,3-DMB) **42** resulted in the formation of the same radical cation (2,3-DMB^{•+}) **41**^{•+}, without preceding respective radical cation (3,3-DMB^{•+}) (Scheme 19).³⁸⁴

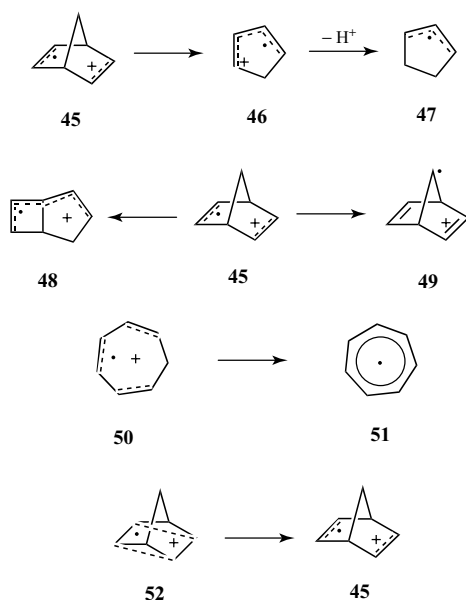
Isomerization of 1,4-cyclohexadiene radical cation (1,4-CHD^{•+}) **43** generated radiolytically in

ZSM-5 zeolites into the 1,3-cyclohexadiene radical cation (1,3-CHD^{•+}) **44** has been observed for cyclohexadienes (Scheme 19).

Radiolytically generated radical cations and radicals derived from several C₇H₈ hydrocarbons (norbornadiene (NB), quadricyclane (QC), bicyclohepta-2,5-diene (BCHD), and cycloheptatriene (CHT)) have been investigated in Na-ZSM-5 zeolite.³⁸⁶ Interesting transformations involving radical cations have been observed. Depending on



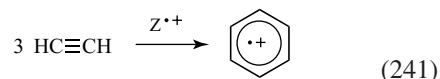
Scheme 19 Generation of radical cations in alkenes.



Scheme 20 Generation of radical cations in C_7H_8 hydrocarbons and their subsequent reactions.

the temperature, the NB radical cation ($NB^{\bullet+}$) **45** was found to rearrange into cyclopentadiene radical cation ($CP^{\bullet+}$) **46**, which further deprotonates giving cyclopentyl radical ($CP^{\bullet}$) **47** or converts either into BCHD radical cation ($BCHD^{\bullet+}$) **48** or the norbornadien-7-yl radical ($NB^{\bullet}$) **49** (Scheme 20). CHT radical cation ($CHT^{\bullet+}$) **50** deprotonates to heptatrienyl radical ($CHT^{\bullet}$) **51** (Scheme 20).³⁸⁰ The QC radical cation ($QC^{\bullet+}$) **52** undergoes a very fast valence isomerization leading to $NB^{\bullet+}$ **45**.^{386,387}

Radiolysis of ethyne (acetylene), adsorbed on Na-ZSM-5, resulted in formation of benzene radical cation³⁹²:



Naphthalene, anthracene, and pyrene radical cations have been generated on radiolysis of naphthalene in ZSM-5,³⁹⁰ anthracene in Y zeolites,³⁸⁸ and pyrene in silica/alumina,³⁸⁹ respectively. Methyl radicals ($\cdot\text{CH}_3$) and their complexes ($\cdot\text{CH}_3 \cdots \text{Na}^+$) with Na^+ have been generated in Na-A zeolites.³⁹³ Organosilver radicals ($\text{Ag}^{\bullet}\text{CH}_2\text{OH}$) have been generated in Ag-A/ CH_3OH zeolite.^{394,395}

5 CONCLUSIONS

Over 100 years have passed since the discovery of X-rays by Roentgen and radioactivity by Henry Becquerel, Maria Skłodowska-Curie, and Pierre Curie. These very important events were crucial for the development of radiation chemistry, which is concerned with the interaction of various types of high-energy radiation (γ - and X-radiation, charged particles) with matter. In the twentieth century and also the first decade of the twenty-first century, radiolysis has played a substantial and important role in providing the experimental approach for generation of radicals and radical ions, induction of radical reactions, and understanding their reaction mechanisms. In many cases, high-energy radiation offers a convenient and relatively easy way of induction of radical reactions in all phases (gases, liquids, and solids) that cannot be or can be performed with some limitations by chemical, electrochemical, and photolytic methods. With the recent progress in the time-resolution of pulse radiolysis and increased capabilities of analytical techniques available, high-energy radiation approach for inducing radical reactions is highly promising to complement these methods.

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Thermochemistry and Hydrogen Transfer Kinetics

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1 INTRODUCTION

Chemical transformations appear conceptually simple. Some bonds are broken and others are made. Knowledge of the energy required to break bonds and energy released on making bonds are basic to our understanding of chemical reactivity. Sometimes, surprisingly, reactivity is controlled by the strength of a chimera bond, one that is never broken or made. In seeking an understanding of the factors that influence reactivity, one of the first issues to be addressed is the effect of molecular structure. Many of the synthetic reactions in a chemist's arsenal are ion–molecule reactions. However, examining available data of the rates of such reactions presents a major difficulty. For example, S_N2 reaction rates can be accelerated by tens of thousands of times by simply changing the solvent from ethanol to dimethyl sulfoxide and generally do not occur at all in the gas phase near ambient temperatures. Such reaction rates are not simply a function of the molecular structure of the reactants and products but are greatly affected by interactions of reactants, transition state (TS), and products with the particular solvent. In the quest of understanding chemical reactivity in terms of properties of reactants and products, a study of radical reactions is advantageous. Reactions of neutral radicals often proceed at comparable rates in the gas phase and in various nonpolar solvents, that is, with very similar pre-exponential terms and activation energies of the Arrhenius expression of the

rate constant $k = A \times \exp(-E_a/RT)$, and we have an easier task at discerning structure–reactivity relationships and patterns.¹ Significant solvent effects have been reported to occur in some special cases of radical reactions, generally reactions of radicals that form strong hydrogen bonds with the substrate and/or with H-bonding solvents or reactions of radicals with substrates that form strong hydrogen bonds with the solvent or with themselves. Typical examples are hydrogen abstractions by oxyl radicals from RO–H and by $R_2NO\cdot$ from R_2NO-H (see **Supramolecular Radical Chemistry**).^{2,3}

Understanding the factors affecting radical reactivity has led to current widespread use of radical reactions in organic synthesis. Complex natural product synthesis and a better understanding of radical reactions in biological systems have been accomplished. Excellent reviews of these aspects have appeared.^{4,5} Other articles of this encyclopedia also address synthetic applications. There is interest in radical–molecule reactions because they are also involved in the aging process, combustion, DNA repair, ozone depletion, and so on.

Knowledge of bond dissociation enthalpies (BDEs) of the bonds that are being broken and made allows an easy calculation of the thermochemistry of the reaction. The enthalpy of reaction is given by comparing the strength of the bonds being made to those being broken via an application of Hess's Law, (1), to the reaction $A-B + C-D \rightarrow A-C + B-D$. If the sum of the

strengths of the bonds made is greater than that of the bonds broken, the reaction is exothermic.

$$\Delta H_{\text{rxn}} = -\text{BDE}[\text{A}-\text{C}] - \text{BDE}[\text{B}-\text{D}] + \text{BDE}[\text{A}-\text{B}] + \text{BDE}[\text{C}-\text{D}] \quad (1)$$

For example, in halogenations of methane, $\text{H}_3\text{C}-\text{H} + \text{X}-\text{X} \rightarrow \text{H}_3\text{C}-\text{X} + \text{H}-\text{X}$, and the enthalpy of reaction is given by $\Delta H_{\text{rxn}} = -\text{BDE}[\text{H}_3\text{C}-\text{X}] - \text{BDE}[\text{H}-\text{X}] + \text{BDE}[\text{H}_3\text{C}-\text{H}] + \text{BDE}[\text{X}-\text{X}]$.

Enthalpies of reaction are easily obtained from the known gas-phase BDE at 298.15 K of each bond involved. In kilojoules per mole at 298.15 K, the enthalpy of the reaction calculated by (1) and the known BDEs for $\text{X} = \text{F}$ is -432.6 ; for $\text{X} = \text{Cl}$ it is -101.3 ; for $\text{X} = \text{Br}$ it is -26.8 ; and for $\text{X} = \text{I}$, it is 53.1 . From this simple calculation, the indication is that, if fluorination occurs, the great exothermicity might lead to a runaway reaction or explosion. Safety considerations would suggest the need for great care and high dilutions in carrying out free-radical fluorinations of hydrocarbons. Iodination is endothermic and unlikely to proceed at a reasonable rate at room temperature, but proceeds at higher temperatures. Chlorination and bromination of hydrocarbons are exothermic overall and could proceed with radical chain initiators at or near room temperature in systems purged of radical traps or O_2 , especially when weaker $\text{C}-\text{H}$ bonds are involved. Experimental studies of these reactions confirm the indications obtained from the calculated reaction enthalpies.

Another formulation of Hess's Law uses enthalpies of formation $\Delta_f H^\circ$ of reactants and products to obtain the thermochemistry of the reaction $\text{A}-\text{B} + \text{C}-\text{D} \rightarrow \text{A}-\text{C} + \text{B}-\text{D}$ by (2).

$$\Delta H_{\text{rxn}} = \Delta_f H^\circ[\text{A}-\text{C}] + \Delta_f H^\circ[\text{B}-\text{D}] - \Delta_f H^\circ[\text{A}-\text{B}] - \Delta_f H^\circ[\text{C}-\text{D}] \quad (2)$$

$\Delta_f H^\circ$ is the change in enthalpy caused by the formation of 1 mol of a substance in the standard state from the constituent elements in their most stable form in the standard state. The standard state is 1 atm of pressure at 298.15 K. The enthalpy of the most stable form of every element in its standard state is zero by definition. For example, if the reaction of 1 mol of graphite (the most stable form of solid carbon at 298.15 K and 1 atm) with oxygen at 298.15 K and 1 atm releases $-393.51 \text{ kJ mol}^{-1}$ to

form 1 mol of carbon dioxide at 298.15 K and 1 atm, then $\Delta_f H^\circ[\text{CO}_2] = -393.51 \text{ kJ mol}^{-1}$.

An example of an application of (2) is the polymerization of ethylene, modeled by $\text{CH}_3\text{C}^\bullet\text{H}_2 + \text{CH}_2 = \text{CH}_2 \rightarrow \text{CH}_3\text{CH}_2-\text{CH}_2-\text{C}^\bullet\text{H}_2$. The needed enthalpies of formation are known:

$$\Delta_f H^\circ[\text{CH}_3\text{C}^\bullet\text{H}_2] = 120.9 \text{ kJ mol}^{-1},$$

$$\Delta_f H^\circ[\text{CH}_2=\text{CH}_2] = 52.5, \text{ and}$$

$$\Delta_f H^\circ[\text{CH}_3\text{CH}_2\text{CH}_2\text{C}^\bullet\text{H}_2] = 79.1.$$

Hence, $\Delta H_{\text{rxn}} = -94.3 \text{ kJ mol}^{-1}$. The polymerization is exothermic and measures must be taken to have sufficient cooling capacity to remove this heat from the polymerization vessel. (Note: Throughout this article, the radical sign “ $\bullet$ ” immediately follows the atom bearing the odd electron. Energy units are in kilojoules per mole throughout, $4.184 \text{ kJ} = 1.000 \text{ kcal}$.)

BDEs may be obtained directly by measuring the amount of energy required to break a particular bond homolytically, generating free radicals in their ground states. One way is via spectroscopic measurements of the observed quantized energy levels of a diatomic gas such as HF up to its dissociation limit.⁶ Alternatively, one may establish the minimum light frequency ν required to bring about the dissociation of Cl_2 into two chlorine radicals, by calculating the energy by $\text{BDE}[\text{Cl}-\text{Cl}] = h\nu$, where h is the Planck constant and ν is the frequency required for bond cleavage. Kinetic measurements are also made by measuring the reaction rate constant for breaking a particular bond as a function of temperature in pyrolysis studies, usually under very low pressure conditions to avoid possible chain decompositions. The energy of activation for such homolytic bond cleavage is a good estimate of its BDE in the temperature interval measured.

In addition to kinetic measurements of pyrolysis, measurements of the Arrhenius activation energies E_a for a reaction and its reverse are used to obtain one BDE value if the other is known.⁷ For example, in the reaction $\text{CH}_3\text{CH}_2-\text{H} + \text{H}_3\text{C}^\bullet \rightarrow \text{CH}_3\text{C}^\bullet\text{H}_2 + \text{H}-\text{CH}_3$, if $E_a(\text{forward}) = 32.7 \text{ kJ mol}^{-1}$ and $E_a(\text{reverse}) = 15.5$, then $\text{BDE}[\text{CH}_3\text{CH}_2-\text{H}] = \text{BDE}[\text{H}-\text{CH}_3] - (32.7 - 15.5)$.⁸ If $\text{BDE}[\text{CH}_3-\text{H}] = 439.3$ is known, then $\text{BDE}[\text{CH}_3\text{CH}_2-\text{H}] = 439.3 - 17.2 = 422.1 \text{ kJ mol}^{-1}$ is obtained in the temperature domain of the measurements. Measurements of the

forward and reverse rates of hydrogen abstractions by bromine atoms, that is, $\text{RH} + \text{Br}^* \rightleftharpoons \text{R}^* + \text{HBr}$, have been used to establish many $\text{BDE}[\text{R}-\text{H}]$ values. Hydrogen abstractions by iodine atoms have also been used. It must be kept in mind that bond dissociation enthalpies vary somewhat with temperature. For example, $\text{BDE}[\text{H}-\text{H}] = 436 \text{ kJ mol}^{-1}$ at 298 K but increases to 454 at 2000 K. This has important implications in understanding curvatures in the Arrhenius plots.⁹

Other experimental methods commonly used to establish values of BDE include calorimetry (enthalpy of combustion or hydrogenation), photoacoustic calorimetry (PAC) in solution, equilibrium studies and their temperature dependence, and enthalpies of isomerization.

Typical examples of calorimetry are the following: The enthalpy of formation of ethane is known to be $-84.0 \text{ kJ mol}^{-1}$ and the measured enthalpy of hydrogenation of ethylene to yield ethane is $\Delta H_{\text{rxn}} = -136.3$ at 298.15 K¹⁰; then the enthalpy of formation of ethylene is calculated from Hess's Law with $\Delta_f H^\circ[\text{H}_2] = 0.0$. The reaction is $\text{CH}_2 = \text{CH}_2 + \text{H}_2 \rightarrow \text{CH}_3\text{CH}_3$ and, by (2), $\Delta H_{\text{rxn}} = \Delta_f H^\circ[\text{CH}_3\text{CH}_3] - \Delta_f H^\circ[\text{CH}_2 = \text{CH}_2] - \Delta_f H^\circ[\text{H}_2]$. Substituting the known values leads to $-136.3 = -84.0 - \Delta_f H^\circ[\text{CH}_2 = \text{CH}_2] - (0.0)$. Solving yields $\Delta_f H^\circ[\text{CH}_2 = \text{CH}_2] = +52.3 \text{ kJ mol}^{-1}$. Similarly, for the hydrogenation of acetone with H_2 to yield 2-propanol, $\Delta H_{\text{rxn}} = -56.1 \pm 0.4 \text{ kJ mol}^{-1}$ by hydrogenation calorimetry.¹¹ If $\Delta_f H^\circ[\text{CH}_3\text{CH}(\text{OH})\text{CH}_3] = -272.8 \pm 0.8$ is known, substitution of these values into (2) yields $\Delta_f H^\circ[\text{CH}_3\text{C}(\text{O})\text{CH}_3] = -218.4 \pm 0.9 \text{ kJ mol}^{-1}$. An extensive compilation of enthalpies of hydrogenation is available.¹²

Equilibrium measurements as a function of temperature for $\text{A} \rightleftharpoons \text{B}$ yield ΔH_{rxn} and ΔS_{rxn} from a van't Hoff plot of $\ln K_e$ versus $1/T$. The slope is $-\Delta H_{\text{rxn}}/RT$ and the intercept is $\Delta S_{\text{rxn}}/R$ at the average temperature of the measurements. If $\Delta_f H^\circ[\text{A}]$ is known, $\Delta_f H^\circ[\text{B}]$ is thus calculated.

Studies of isomerizations can also lead to conclusions about relative stabilities of isomers or of bond energies. A classic example is the study of the cis-trans isomerization of 1,2-dideuterioethylene. Thermal isomerization between 460 and 540 °C indicated a requirement of $272 \pm 6 \text{ kJ mol}^{-1}$ for isomerization, presumably by allowing the p orbitals to become orthogonal thus breaking the π bond.¹³ There have been other theoretical estimates of the π -bond strength in ethylene and other

interpretations,^{14,15} but we favor of the 272 value for the π -bond strength (see below).

PAC measures BDEs in solution. Rapid heat release from a photoinitiated process produces a pressure wave, which is detected and quantified to yield the enthalpy of the process. The enthalpy is related to the strengths of bonds broken and made after appropriate corrections for solvent and volume effects. Many BDEs of bonds to H have been measured by PAC and they generally agree with those of gas-phase measurements when nonpolar solvents are used, even though early PAC values were somewhat low because corrections for effects of solvent were not adequate. A good account of the current PAC technique is available.¹⁶

Photoionization mass spectrometry (PIMS) is also used. A tunable light source establishes the threshold energy required to dissociatively ionize a target species, such as $\text{CH}_4 + h\nu_1 \rightarrow \text{H}_3\text{C}^+ + \text{H}^* + \text{e}^-$. Similarly, the ionization energy of the methyl radical is determined for $\text{H}_3\text{C}^* + h\nu_2 \rightarrow \text{H}_3\text{C}^+ + \text{e}^-$. Proper addition of the two measurements yields $\text{CH}_4 + h\nu_1 \rightarrow \text{H}_3\text{C}^* + \text{H}^* + h\nu_2$ and $\text{BDE}[\text{H}_3\text{C}-\text{H}] = h\nu_1 - h\nu_2$.¹⁷

Heterolytic bond cleavages are also used to obtain thermochemistry. These are basically measurements of acidity and redox potentials. In the case of a bond to hydrogen in molecule G-H, the heterolytic bond enthalpy is the enthalpy of deprotonation Δ_{acid} . The electron affinity of G, $EA[\text{G}]$, is obtained from $\text{G}^- + h\nu_1 \rightarrow \text{G}^* + \text{e}^-$, and the ionization energy of hydrogen $IE[\text{H}]$ from $\text{H}^* + h\nu_2 \rightarrow \text{H}^+ + \text{e}^-$. Then, $\text{BDE}[\text{G}-\text{H}] = \Delta_{\text{acid}} + EA[\text{G}] - IE[\text{H}]$.¹⁷ Bordwell and his group have obtained $\text{BDE}[\text{A}-\text{H}]$ values of weak acids AH in dimethylsulfoxide (DMSO) solvent by measuring the $\text{p}K_{\text{AH}}$ by the overlapping indicator method and the oxidation potential of A^- by cyclic voltammetry. Values of $\text{BDE}[\text{A}-\text{H}] = 5.73 \times \text{p}K_{\text{AH}} + 96.7 \times E_{\text{ox}}[\text{A}^-] + 306.7 \text{ kJ mol}^{-1}$ were reported to be in reasonable agreement with gas-phase BDE values at 298.15 K, especially when a correction for solvent effects was made.^{18,19}

Bond dissociation enthalpies are commonly calculated from known enthalpies of formation. For homolytic bond cleavage $\text{A}-\text{B} \rightarrow \text{A}^* + \text{B}^*$, the bond dissociation enthalpy is calculated by (3).

$$\text{BDE}[\text{A}-\text{B}] = \Delta_f H^\circ[\text{A}^*] + \Delta_f H^\circ[\text{B}^*] - \Delta_f H^\circ[\text{AB}] \quad (3)$$

For example, $\text{BDE}[\text{CH}_3\text{CH}_2\text{-OH}]$, which is ΔH_{rxn} for the reaction $\text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2^\bullet + \text{HO}^\bullet$, can be calculated if the enthalpies of formation of ethanol, ethyl radical, and hydroxyl radical are known: $\Delta H_{\text{rxn}} = \text{BDE}[\text{CH}_3\text{CH}_2\text{-OH}] = \Delta_f H^\circ[\text{CH}_3\text{C}^\bullet\text{H}_2] + \Delta_f H^\circ[\text{HO}^\bullet] - \Delta_f H^\circ[\text{CH}_3\text{CH}_2\text{OH}]$. Thousands of $\Delta_f H^\circ$ values of closed-shell species have been reported. An extensive compilation is available from the National Institute of Standards and Technology (NIST) for free on the Web.²⁰ Another readily available source of BDE and $\Delta_f H^\circ[\text{R}^\bullet]$ is the “Rubber Handbook.”²¹ Two monographs by Luo are also valuable.^{22,23} An older version of the NIST database contains some values not included subsequently.²⁴ Pedley’s monograph is still a good source of reliable values.²⁵ Experimental enthalpies of formation of radical species and theoretically calculated values are fewer and generally less accurate than those of closed-shell species.

2 EXPERIMENTAL AND *AB INITIO* VALUES

Experimental measurements of $\Delta_f H^\circ$ and of BDE values are difficult to perform and there have been some significant revisions of the values of common compounds in the last 40 years. For aldehydes, $\text{BDE}[\text{RC}(\text{O})\text{-H}] = 322 \text{ kJ mol}^{-1}$ was being quoted in 1971.²⁶ A higher value of 367 was suggested in 1975²⁷; the currently quoted value is 376.²⁰ Similarly, in 1972 it was suggested that the value of $\text{BDE}[\text{H}_2\text{N-H}] = 431 \text{ kJ mol}^{-1}$ used at the time was too low to account for rates of hydrogen abstractions from ammonia and a minimum of 439 was recommended²⁸; the currently quoted value is 454.²⁰ Values in current use are probably more reliable mostly because of two reasons: better instrumentation and the ability to perform *ab initio* calculations of sufficient accuracy to warn of possible large errors in experimental determinations (see **Radical Stability—Thermochemical Aspects**).

Ab initio methods have improved to the point of where G3 model calculations obtain values for $\Delta_f H^\circ$ of closed-shell species with accuracies usually better than $\pm 6\text{--}8 \text{ kJ mol}^{-1}$, which is of the same order of magnitude as in many thermochemical measurements.²⁹ A modification

denoted G3(MP2)-RAD is successful in producing $\Delta_f H^\circ$ values for many radicals with similar accuracies.^{30,31} These are high-level composite methods that include some empirical correction terms (high-level corrections, HLC). These types of calculations are quite demanding of computer resources and this places practical limits on the size of the molecules that can be treated.

Table 1 provides a listing of many of the available enthalpies of formation of radical species $\text{R}^\bullet$, along with $\text{BDE}[\text{R-H}]$, $\text{BDE}[\text{R-CH}_3]$, and $\text{BDE}[\text{R-Cl}]$, if the BDE values are available. Throughout this article, all BDE and $\Delta_f H^\circ$ values appearing without specific attribution are from Refs 20–24. More than one value for a particular entry is often available in the literature, and a subjective judgment of reliability had to be made by the author for selecting one. An empty cell in the table indicates that a value was not located in the literature.

3 REGULARITIES IN ENTHALPIES OF FORMATION

There are remarkable regularities in enthalpies of formation and in bond dissociation enthalpies of organic molecules. As a result, empirical schemes exist for estimating gas-phase enthalpies of formation with empirical parameters of group additivity (GA) found by global fittings to a large number of molecules. Many such approaches generally succeed. The GA scheme of Benson is one of the better known.^{55,56} Each group, depending on its neighbors, contributes to the stability of a molecule a specific amount, irrespective of the overall molecular structure. The original scheme was subsequently updated.⁵⁷ This widely known and used GA scheme has been implemented in the NIST database 69.^{20,58} At the site’s homepage on the Web, under Models and Tools, one of the bullets is “Group Additivity Based Estimates.” Clicking on this produces a new menu. Clicking on “Use applet to draw a structure” produces a pallet on which one can draw a desired molecule by selecting the appropriate atoms from a menu and pressing “Done” when finished. The program generates a GA-based value of $\Delta_f H^\circ$ of the molecule and is generally quite accurate, generally to within $\pm 6 \text{ kJ mol}^{-1}$ or better. The procedure is quite easy and avoids the drudgery of looking up extensive tables of group increments,

Table 1 Literature values of standard enthalpies of formation (kJ mol^{-1}) of radicals $\text{R}^\bullet$ and BDE of R-H , R-CH_3 , and R-Cl , when available.

Open shell (radical, $\text{R}^\bullet$)	$\Delta_f H^\circ[\text{R}^\bullet]$	BDE[R-H]	BDE[R-Me]	BDE[R-Cl]
$\text{H}^\bullet$	218.0	436.0	439.1	431.6
$\text{C}^\bullet$	716.7	340.6	—	335.9
$\text{F}^\bullet$	79.4	570.7	459.9	219.8
$\text{Cl}^\bullet$	121.3	431.6	351.2	242.6
$\text{Br}^\bullet$	111.9	366.2	292.4	235.2
$\text{I}^\bullet$	106.8	298.3	238.7	210.6
$\text{HO}^\bullet$	38.9	498.7	390.1	234.7
$\text{}^\bullet\text{OO}^\bullet$	0.0	204.6 ^a	137.0 $\pm$ 4	23.3 $\pm$ 4
$\text{HOO}^\bullet$	12.3 ^b	366.1 ^b	289.7	—
$\text{H}_2\text{N}^\bullet$	190.4	454.3	360.1	257.3
$\text{NO}^\bullet$	90.3	208.7	165.4	159.9
$\text{NO}_2^\bullet$	33.1	327.8	260.3	142.1
$\text{H}_2\text{P}^\bullet$	138.5 ^c	351.0	304.2	—
$\text{H}_3\text{Si}^\bullet$	200.5 $\pm$ 2.5 ^d	384.2	376.0	463.3
$\text{Cl}_3\text{Si}^\bullet$	−321.0 $\pm$ 8.0 ^e	391.0 $\pm$ 8 ^e	399.0 $\pm$ 8 ^e	461.0 $\pm$ 8 ^e
$\text{F}_3\text{C}^\bullet$	−465.7 $\pm$ 2.1	445.2 $\pm$ 3	429.3 $\pm$ 5	365.3 $\pm$ 4
$\text{Cl}_3\text{C}^\bullet$	−71.1 $\pm$ 2.5	392.5 $\pm$ 3	362.5 $\pm$ 3	296.6
$\text{HC}^\bullet$	594.1	425.7	384.4 ^f	380.7
$\text{H}_2\text{C}^\bullet$	386.4 ^b	458.2	411.7	394.4
$\text{H}_3\text{C}^\bullet$	146.2 ^a	439.1	376.2	351.4
$\text{CH}_3\text{C}^\bullet\text{H}_2$	119.0 $\pm$ 2.0	421.5	370.7	350.2 $\pm$ 8
$\text{CH}_3\text{CH}_2\text{C}^\bullet\text{H}_2$	100.0 $\pm$ 2.0	422.6 $\pm$ 2	371.7 $\pm$ 2	353.8 $\pm$ 2
$\text{CH}_3\text{C}^\bullet\text{HCH}_3$	90.0 $\pm$ 2.0	412.6 $\pm$ 2	368.4 $\pm$ 2	355.3 $\pm$ 8
Cyclopropyl radical	279.9 $\pm$ 1.3	458.6	403.1	406.6 $\pm$ 11
$\text{CH}_3(\text{CH}_2)_2\text{C}^\bullet\text{H}_2$	77.8 $\pm$ 2.1	421.3 $\pm$ 2	370.4 $\pm$ 2	353.7 $\pm$ 2
$\text{CH}_3\text{C}^\bullet\text{HCH}_2\text{CH}_3$	69.0 $\pm$ 2.1	412.5	368.7	357.0
$(\text{CH}_3)_2\text{CHC}^\bullet\text{H}_2$	70.0 $\pm$ 2.0	420.6 $\pm$ 2	369.6 $\pm$ 2	352.8 $\pm$ 2
$(\text{CH}_3)_3\text{C}^\bullet$	51.4 $\pm$ 1.7 ^a	403.6	365.3	352.6
Cyclobutyl radical	215.1 $\pm$ 4.2	404.7 $\pm$ 6	406.1	—
<i>cyclo</i> - $\text{C}_3\text{H}_5\text{-C}^\bullet\text{H}_2$	213.8 $\pm$ 6.7	408.8 $\pm$ 7	356.6	—
$\text{CH}_3(\text{CH}_2)_3\text{C}^\bullet\text{H}_2$	54.4	418.9	—	351.4
$(\text{CH}_3)_3\text{CC}^\bullet\text{H}_2$	36.4 $\pm$ 8.4	422.4	368.1	354.5
$\text{CH}_3\text{C}^\bullet\text{H}(\text{CH}_2)_2\text{CH}_3$	50.2	414.7	370.7	—
$\text{CH}_3\text{CH}_2\text{C}^\bullet\text{HCH}_2\text{CH}_3$	46.9	411.4	367.2	—
$(\text{CH}_3)_2\text{CHC}^\bullet\text{HCH}_3$	41.1	412.5	368.6	—
$(\text{CH}_3)_2\text{C}^\bullet\text{CH}_2\text{CH}_3$	31.1 ^g	—	—	353.9
Cyclopentyl radical	105.9 $\pm$ 4.2	400.3 $\pm$ 5	358.1 $\pm$ 4	346.9 $\pm$ 5 ^h
<i>Cyclo</i> - $\text{C}_5\text{H}_9\text{-C}^\bullet\text{H}_2$	99.2 ⁱ	423.2	372.5	—
Cyclohexyl radical	75.3 $\pm$ 6.3	417.9 $\pm$ 7	374.3 $\pm$ 7	363.1 $\pm$ 7
$\text{CH}_3(\text{CH}_2)_5\text{C}^\bullet\text{H}_2$	16.7	423.0	371.8	—
$\text{CH}_3\text{C}^\bullet\text{H}(\text{CH}_2)_4\text{CH}_3$	8.4 ^c	414.3	370.1	—
$\text{C}_6\text{H}_5^\bullet$ (phenyl radical)	339.0 $\pm$ 8.0 ^b	474.1 $\pm$ 8	435.1	405.9 $\pm$ 8
$\text{C}_6\text{H}_5\text{C}^\bullet\text{H}_2$	207.0 $\pm$ 4.0 ^b	374.9 $\pm$ 5	323.4	309.3 $\pm$ 5
$\text{C}_6\text{H}_5\text{C}^\bullet\text{HCH}_3$	171.5 ^j	359.8 ^j	313.8	—
$(\text{C}_6\text{H}_5)_2\text{C}^\bullet\text{H}$	302.1 $\pm$ 4.2	355.1 $\pm$ 5	291.3	—
$\text{C}_6\text{H}_5\text{C}^\bullet(\text{CH}_3)_2$	133.9 $\pm$ 4.2	347.1 $\pm$ 5	302.8	—
$(\text{C}_6\text{H}_5)_3\text{C}^\bullet$	392.0 $\pm$ 8.4	360.4 $\pm$ 9	322.3 ^q	—
Indan-1-yl radical	204.2 $\pm$ 8.4	361.3 $\pm$ 9	74.7 ^d	—
Tetrahydronaphthalen-1-yl	154.8 $\pm$ 5.0	342.8 $\pm$ 6	—	—
$\text{O}=\text{C}^\bullet\text{H}$	43.5	377.4	360.4	—
$\text{O}=\text{C}^\bullet\text{CH}_3$	−12.0 $\pm$ 3.0	376.7	352.9	360.6
$\text{O}=\text{C}^\bullet\text{C}_6\text{H}_5$	100.8 ^k	355.6	333.9	331.1
$\text{O}=\text{C}^\bullet\text{OH}$	−179.9 $\pm$ 2.0 ^l	416.7	400.1	—
$\text{O}=\text{CHC}^\bullet\text{H}_2$	10.0 $\pm$ 6.0 ^m	398.7 $\pm$ 6	344.5 $\pm$ 6	309.0 $\pm$ 6 ^m

(continued overleaf)

Table 1 (continued)

Open shell (radical, R [•])	$\Delta_f H^\circ [R^\bullet]$	BDE[R-H]	BDE[R-Me]	BDE[R-Cl]
HOC [•] H ₂	-17.1 ± 0.8 ^a	405.9 ± 10	363.4	—
HOCH ₂ C [•] H ₂	-26.7 ± 6.0 ^m	419.6	368.7	345.9 ⁿ
HOC [•] HCH ₃	-56.5 ± 4.0	395.4	362.5 ± 4	—
HOC [•] (CH ₃) ₂	-96.7 ± 6.0 ^m	394.1 ± 6	362.0 ± 6	—
HOC [•] H(CH ₂) ₇ CH ₃	-202.7	395.8	361.4	—
HOC [•] H(CH ₂) ₈ CH ₃	-222.5	395.5	362.2	—
Cyclohexanol-1-yl radical	-119.6 ± 8.4	388.4 ± 9	348.4 ^o	—
C ₆ H ₅ C [•] HOH	29.3 ± 8.4	341.9 ± 9	318.6 ^p	—
H ₂ NC [•] H ₂	148.9 ± 6.0 ^m	390.4 ± 6 ^m	342.4 ± 6	342.9 ± 6 ^m
H ₂ NC [•] HCH ₃	109.9 ± 6.0 ^m	385.4 ± 6 ^m	339.8 ± 6	348.7 ± 6 ^m
H ₂ NC [•] (CH ₃) ₂	82.0 ± 6.0 ^m	383.7 ± 6 ^m	348.4 ± 6	351.1 ± 6 ^m
CH ₃ NHC [•] H ₂	151.6 ± 6.0 ^m	388.6 ± 6 ^m	346.3 ± 6	320.6 ± 6 ^m
(CH ₃) ₂ NC [•] H ₂	147.5 ± 6.0 ^m	389.8 ± 6	344.7 ± 6	—
H ₂ NC(O)C [•] H ₂	-44.5 ± 6.0 ^m	411.8 ± 6 ^m	360.6 ± 6	335.7 ± 6 ^m
HC(O)NHC [•] H ₂	-13.5 ± 6.0 ^m	392.3 ± 6 ^m	345.2 ± 6	325.3 ± 6 ^m
CH ₃ C(O)NHC [•] H ₂	-73.7 ± 6.0 ^m	392.3 ± 6 ^m	341.5 ± 6	328.7 ± 6 ^m
CH ₃ OC [•] H ₂	1.6 ± 6.0 ^m	403.7 ± 6	364.4 ± 6	336.3 ± 6
CH ₃ CH ₂ OC [•] H ₂	-30.7 ± 6.0 ^m	403.7 ± 6	368.4 ± 6	334.9 ± 6 ^m
CH ₃ CH ₂ OC [•] HCH ₃	-81.2 ± 4.2	389.5 ± 5 ^m	348.6 ± 5	347.9 ± 6 ^m
HCO ₂ C [•] H ₂	-136.9 ± 6.0 ^m	418.0 ± 6 ^m	371.2 ± 6	338.5 ± 6 ^m
CH ₃ CO ₂ C [•] H ₂	-211.2 ± 6.0 ^m	416.8 ± 6 ^m	380.4 ± 6	340.4 ± 6 ^m
CH ₃ OC(O)C [•] H ₂	-216.0 ± 6.0 ^m	412.0 ± 6 ^m	361.4 ± 6	320 ± 12
HOC(O)C [•] H ₂	-238.4 ± 6.0 ^m	412.6 ± 6 ^m	363.8 ± 6	318.0 ± 7
CH ₃ C(O)C [•] H ₂	-34.9 ± 2.0 ^q	401.5	350.8	314.8 ± 6 ^m
CH ₃ C(O)C [•] HCH ₃	-76.0 ± 6.0 ^m	381.3 ± 6 ^m	333.0 ± 6	312.3 ± 6 ^m
C ₆ H ₅ C(O)C [•] H ₂	98.1 ± 3.8	402.8 ± 4	349.7 ± 4	306.0 ± 4
H ₃ SiC [•] H ₂	176.0 ± 6.0 ^m	423.4 ± 6 ^m	368.5 ± 6	334.7 ± 6 ^m
(CH ₃) ₃ SiC [•] H ₂	-81.5 ± 6.0 ^m	423.1 ± 6 ^m	384.1 ± 6	343.3 ± 6 ^m
(CH ₃) ₃ PC [•] H ₂	92.0 ± 6.0 ^m	410.4 ± 6 ^m	356.8 ± 6 ^m	331.8 ± 6 ^m
CH ₃ SO ₂ C [•] H ₂	-153.3 ± 6.0 ^m	437.7 ± 6 ^m	389.3 ± 6 ^m	335.6 ± 6 ^m
CH ₃ SOC [•] H ₂	58.3 ± 8.6 ^m	426.8 ± 6 ^m	354.8 ± 6 ^m	325.4 ± 6 ^m
CF ₃ C [•] H ₂	146.5 ± 6.0 ^m	443.2 ± 6 ^m	390.7 ± 6 ^m	346.4 ± 6 ^m
CCl ₃ C [•] H ₂	71.9 ± 6.0 ^m	434.9 ± 6 ^m	385.8 ± 6 ^m	348.9 ± 6 ^m
O ₂ NC [•] H ₂	123.8 ± 6.0 ^m	422.8 ± 6 ^m	372.4 ± 6	327.3 ± 6 ^m
HSC [•] H ₂	158.2 ± 6.0 ^m	399.0 ± 6 ^m	347.9 ± 6	313.2 ± 6 ^m
CH ₃ SC [•] H ₂	138.7 ± 6.0 ^m	394.2 ± 6 ^m	345.2 ± 6	310.5 ± 6 ^m
FC [•] H ₂	-29.8 ± 6.0 ^m	422.5 ± 6 ^m	388.8 ± 6	353.4 ± 6
ClC [•] H ₂	113.3 ± 6.0 ^m	415.0 ± 6 ^m	371.8 ± 6	330.1 ± 6
BrC [•] H ₂	167.9 ± 6.0 ^m	419.9 ± 6 ^m	377.7 ± 6	309.0 ± 10
HOOC [•] H ₂	66.1	415.1	372.5	—
HOOC [•] HCH ₃	26.9	406.1	371.0	—
CH ₂ =C [•] H	299.0 ± 5.0	464.5 ± 5	424.8 ± 5	398.3 ± 6
CH ₂ =CHC [•] H ₂	171.0 ± 3.0	368.6 ± 3	317.8	297.9
(E)-CH ₃ CH=C [•] H	266.9 ± 6.0	464.5 ± 6	423.9 ± 6	400.2 ± 6
CH ₂ =C [•] CH ₃	249.4 ^g	447.0	413.5	395.4
CH ₂ =CHC [•] HCH ₃	130.4 ± 8.4	349.0 ± 9	302.1 ± 9	297.3 ± 9
CH ₂ =CHC [•] (CH ₃) ₂	100.8 ± 6.0 ^m	346.6 ± 6 ^m	305.0 ± 6 ^m	294.6 ± 6 ^m
CH ₂ =CHCH(CH ₃)C [•] H ₂	177.4 ^g	423.2	372.3	—
CH ₃ CH=CHC [•] HCH ₃	103.5 ^g	353.2	309.4	—
Cyclopent-2-en-1-yl radical	160.7 ± 4.2	342.7 ± 5	316.6 ± 5	287.9 ± 5
CH ₂ =CHC [•] HCH ₂ CH ₂ CH ₃	87.6 ^g	347.3	303.6	—
CH ₂ =CHC [•] HCH=CH ₂	207.9 ^r	316.3 ^r	281.2	—
Cyclohex-2-en-1-yl radical	119.7	342.0	301.8	286.2 ± 6
Cyclohexa-2,5-dien-1-yl	208.0 ± 3.9 ^s	321.7 ± 3 ^s	277.0 ± 8	—
N≡C [•]	435.1	518.0	507.1	418.5

Table 1 (continued)

Open shell (radical, R [•])	$\Delta_f H^\circ [R^\bullet]$	BDE[R–H]	BDE[R–Me]	BDE[R–Cl]
N≡CC [•] H ₂	258.8 ± 6.0 ^m	402.8 ± 6 ^m	352.7 ± 6	292.2 ± 6
HC≡C [•]	568.2 ⁱ	559.5	529.0	475.7
HC≡CC [•] H ₂	348.9 ⁱ	381.5	329.9	307.0
CH ₃ C≡C [•]	526.3 ⁱ	558.9	527.2	442.6 ± 17
CH ₃ C≡CC [•] H ₂	293.7 ± 8.4	366.6 ± 9	310.8 ± 9	—
HC≡CCH ₂ C [•] H ₂	373.7 ^g	426.8	375.9	—
HC≡CC [•] HCH ₃	318.5 ± 6.0 ^m	371.3 ± 8 ^m	328.3	—
HC≡CCH [•] CH ₂ CH ₃	277.0 ± 8.4	350.7 ± 9	307.0 ± 9	—
HC≡CC [•] (CH ₃) ₂	281.7 ± 6.0 ^m	363.3 ^m	326.2 ± 8	300.0 ± 6 ^m
CH ₃ O [•]	17.0 ± 4.0	440.0 ± 4	347.3	202.8 ± 8 ^{u,y}
CH ₃ CH ₂ O [•]	−15.1 ± 3.3 ^a	437.2 ± 4	347.5	198.2
(CH ₃) ₂ CHO [•]	−48.1 ± 2.9 ^a	442.7	350.1	—
(CH ₃) ₃ CO [•]	−85.8 ± 2.9 ^a	444.8	345.0	202.9
C ₆ H ₅ O [•]	49.7 ± 3.0 ^v	364.1 ^v	266.3 ^w	—
4-H ₂ N-C ₆ H ₄ O [•]	19.5	328.0 ^v	251.4 ^w	—
4-O ₂ N-C ₆ H ₄ O [•]	56.0	388.7 ^v	289.8 ^{c,w}	—
2,6-di- <i>tert</i> -Bu-C ₆ H ₄ O [•]	−133.6	346.4 ^x	—	—
2,4,6-tri- <i>tert</i> -Bu-C ₆ H ₄ O [•]	−253.6	327.2 ± 5 ^y	—	—
HC(O)O [•]	−125.5 ± 12.6	469.3 ± 13	357.6	—
CH ₃ C(O)O [•]	−179.9 ± 12.6	471.1 ± 13	376.3	—
C ₆ H ₅ C(O)O [•]	−50.2 ± 16.7	465.7 ± 17	365.3	—
CH ₃ N [•] H	184.1 ± 8.4	425.6 ± 9	349.5 ± 9	230.1 ± 9
(CH ₃) ₂ N [•]	145.2 ± 8.4	382.2 ± 9	321.7 ± 9	187.0 ± 9
C ₆ H ₅ N [•] H	244.3 ± 4.2	375.3 ± 5	306.8 ± 8	—
(C ₆ H ₅) ₂ N [•]	348.8 ± 7.0	364.8 ± 6 ^z	—	—
CH ₃ S [•]	127.7 ± 1.7	365.7 ± 2	307.9 ± 3	—
C ₆ H ₅ S [•]	229.3 ± 6.0 ^a	334.7 ± 6 ^a	227.8 ± 6 ^a	—
(CH ₃) ₃ Si [•]	15.0 ± 7	396.0 ± 7	391.2 ^a	472.0 ± 8

^a Reference 17.^b Reference 32.^c Reference 33.^d Reference 34.^e Reference 35.^f Reference 36; end note a.^g Reference 37; end note b.^h Reference 38.ⁱ Reference 39.^j Reference 40.^k Reference 41.^l Reference 31, theoretical calculations by G3(MP2)-RAD. Uncertainty of ±6 kJ mol^{−1} is assigned arbitrarily to calculated values, even though the accuracy is generally better.^m Reference 42.ⁿ Reference 43; end note c.^o Benson's group additivity implemented in Ref. 20.^p Reference 44.^q Reference 45.^r Reference 46.^s Reference 47.^t Reference 48.^u Reference 49.^v Reference 50.^w Reference 51.^x Reference 52. The slightly higher value specified therein for tri-*tert*-Bu-phenol is due to the use of BDE[PhO–H] = 371 kJ mol^{−1} rather than the recommended 364 adopted in this article.^y Reference 53.^z Reference 54.

next-neighbor effects, ring strains, resonance and conjugation effects, and so on.

Regularities in the enthalpies of combustion of linear alcohols were noted as early as 1932 by Rossini.⁵⁹ Luo and Holmes noted the constancy of the relationship between vinyl and phenyl derivatives, irrespective of the nature of X: $\Delta_f H^\circ[\text{CH}_2=\text{CHX}] = \Delta_f H^\circ[\text{C}_6\text{H}_5\text{X}] - (29.7 \pm 6.7)$.⁶⁰ Improvements were made to Benson's group additivity scheme, for example, to include parameters for multichloro-substituted alkanes and alkenes.⁶¹ The Reyniers group established Benson-type GA values for the enthalpy of formation of hydrocarbons and their radicals based on *ab initio* (CBS-QB3) standard enthalpies of formation of 233 compounds, obtaining 95 GA values.⁶² Radical enthalpies of formation were predicted on the basis of the fitted GA values for many species for which there were no experimental data. Other additivity schemes have been proposed recently for hydrocarbons and their radicals.^{63,64} It appears clear that no significance can be attached to the group values obtained from empirical fitting schemes. If they are successful, then they have been shown to map onto each other.⁶⁵ Allinger's successful molecular mechanics approach (MMX) also establishes transferable structural regularities by examining a large variety of molecules with known properties.^{66,67}

3.1 Hydrocarbons and Their Carbon-Centered Radicals

Probably the simplest GA approach for calculating enthalpies of formation of hydrocarbons is (4), which requires the counting of the number of hydrogens of each type present: n_1 of primary (1°) aliphatic hydrogens (H's bonded to sp^3 carbon), n_2 of 2° aliphatic H's, n_3 of 3° aliphatic H's, n_4 of vinyl H's, n_5 of H's missing from C=C groups, n_6 is the number of terminal alkynes including acetylene, n_7 is the number of internal alkynes, n_8 is the number of H's missing from benzene rings, and n_9 is the number of benzene rings.⁶⁸

$$\begin{aligned} \Delta_f H^\circ = & -14.00n_1 - 10.42n_2 - 6.653n_3 + 13.12n_4 \\ & + 23.43n_5 + 227.7n_6 + 231.4n_7 \\ & + 9.079n_8 + 82.93n_9 \text{ kJ mol}^{-1} \end{aligned} \quad (4)$$

Equation (4) does not take account of "special effects." Such effects are (i) steric strain, as exists in di-*tert*-butyl (2,2,3,3-tetramethylbutane); (ii) angle strain, as exists in cyclopropane; (iii) conjugation stabilization, as in 1,3-butadiene; and (iv) resonance stabilization by electron delocalization, as exists only with the groups –OH, –OR, –NH₂, and –NR₂ connected to sp^2 - and sp -hybridized atoms (e.g., carbon, nitrogen of NO₂, boron of BH₂).

When (4) is applied to systems that are subject to "special effects," the calculated result differs from the experimental value by the magnitude of the special effect. The calculated $\Delta_f H^\circ$ [di-*tert*-butyl] is -251.9 versus the experimental value of -226.2 kJ mol⁻¹. The strain energy of the compound is 25.7 kJ mol⁻¹. Similarly, when (4) is used for 1,3-butadiene, the value calculated via (4) is 125.6 versus 108.8 ± 0.8 experimental. Stabilization by conjugation amounts to 16.7 kJ mol⁻¹.

The coefficients of (4) are not based on global fittings to a large set of various known compounds, as is done by well-known approaches such as Benson's GA or by Allinger's molecular mechanics. The coefficients of each term were obtained from a typical molecule in each case: c_1 from 2,2-dimethylpropane, c_2 from butane, c_3 from 2,4-dimethylpentane, c_4 from ethylene, c_5 from *trans*-2-butene, c_6 from 1-butyne, c_7 from 2-butyne and 2-pentyne, c_8 from toluene, and c_9 from benzene. Enthalpies of formation of hundreds of hydrocarbons have been calculated very accurately. The weakness of (4) in not accounting for special effects is counterbalanced by its simplicity and remarkable accuracy. For example, the value of $c_1 = -14.00$ per primary aliphatic H obtained from the 12 hydrogens of neopentane yields $\Delta_f H^\circ$ [ethane] = $6 \times (-14.00) = -84.0$ versus the experimental value of -84.0 ± 0.4 kJ mol⁻¹. The value of $c_2 = -10.42$ obtained from the four secondary aliphatic Hs of butane yields $\Delta_f H^\circ$ [cyclohexane] = $12 \times (-10.42) = -125.0$ versus the experimental value of 124.6 ± 1.8 kJ mol⁻¹. Despite the simplicity of (4), this type of accuracy is maintained to quite large molecules and yields the correct $\Delta_f H^\circ$ values for species such as the *trans*-decalin (decahydronaphthalene), 3-methyl-1,4-pentadiene, 1,5-heptadiyne, cyclohexylbenzene, and so on. The performance with decalin is typical: there are 16 secondary hydrogens ($n_2 = 16$), 2 tertiary hydrogens ($n_3 = 2$), all other n_i are zero for (4).

$\Delta_f H^\circ[\text{decalin}] = (-10.42) \times 16 + (-6.653) \times 2 = -180.0$ versus the experimental value $\Delta_f H^\circ[\text{trans-decalin}] = -182.2 \pm 2.3 \text{ kJ mol}^{-1}$. Evidently, the *trans* isomer is strain-free. Experimental $\Delta_f H^\circ[\text{cis-decalin}] = -169.2 \pm 2.3$, indicating strain of 10.8 kJ mol^{-1} . High-level *ab initio* calculations for such large molecules would require considerable computer resources and could be no more accurate. Equation (4) requires two multiplications and one addition. Nature is frugal in its patterns. Equation (4) is easily extended to apply to species other than hydrocarbons in a simple fashion.

An extension of (4) is used for carbon-centered radicals derived from hydrocarbons. Regular patterns exist for enthalpies of formation of alkyl radicals that are not allylic, propargylic, or benzylic. For species containing a strained ring, such as the primary alkyl radical cyclopentylmethyl (*cyclo*-C₅H₉-C[•]H₂), the experimental enthalpy of formation of the parent hydrocarbon methylcyclopentane is used. Standard enthalpies of formation of primary, secondary, and tertiary alkyl radicals that are not inside a strained ring can be obtained accurately from the enthalpies of formation of their parent hydrocarbons by (5)–(7).⁶⁹ Agreement with experimental values is always within the experimental uncertainty for 13 primary alkyl radicals found in the literature.

$$\Delta_f H^\circ[\text{RC}^\bullet\text{H}_2] = \Delta_f H^\circ[\text{RCH}_3] + 204.6 \quad (5)$$

$$\Delta_f H^\circ[\text{R}_2\text{C}^\bullet\text{H}] = \Delta_f H^\circ[\text{R}_2\text{CH}_2] + 194.6 \quad (6)$$

$$\Delta_f H^\circ[\text{R}_3\text{C}^\bullet] = \Delta_f H^\circ[\text{R}_3\text{CH}] + 184.5 \quad (7)$$

Table 2 provides $\Delta_f H^\circ$ values of the hydrocarbon precursors obtained by (4), $\Delta_f H^\circ$ of their carbon radicals by (5)–(7), and corresponding literature values when found. The agreement between the calculated and the literature values in Table 2 demonstrates the reliability of the calculated $\Delta_f H^\circ[\text{R}^\bullet]$ and allows confident predictions to be made regarding other radicals of interest for which no experimental data exist. Values are also provided for some radicals for which no thermodynamic data could be found.

The instabilities caused by removal of 1° hydrogen to form 1° allyl, propargyl, or benzyl radicals are smaller than $204.6 \text{ kJ mol}^{-1}$ because of resonance stabilization of the odd electron of

such radicals. The instability of the allyl radical relative to the parent hydrocarbon propene is $\Delta_f H^\circ[\text{CH}_2=\text{CHC}^\bullet\text{H}_2] - \Delta_f H^\circ[\text{CH}_2=\text{CHCH}_3] = 150.3$. For propargyl radical, the difference is 163 and for benzyl radical 157. Hence, the vinyl group is the most effective of the three in stabilizing an odd electron on adjacent carbon, followed by phenyl, with the ethynyl group being the least effective.

Cyclization of radicals of the type of 5-hexen-1-yl to cyclohexyl or to cyclopentylmethyl is a reaction of the type used as a “radical clock” and is a useful tool for the synthesis of complex molecules.^{72,73} A review is also available.⁷⁴ Houk *et al.* have performed high level *ab initio* calculations (G3MP2B3) of the thermodynamics of cyclization of the 5-hexen-1-yl radical.⁷⁵ The total enthalpies calculated, H^{298} , are in units of hartrees (E_h) and pertain to the formation of the species from the naked nuclei and electrons ($2625.5 \text{ kJ mol}^{-1}$ per hartree). The reported values are shown in the first line of Figure 1.

Relative to 5-hexen-1-yl, the cyclohexyl radical is more stable by $-0.032485 E_h$ or 85.3 kJ mol^{-1} with a stated uncertainty of ± 4.2 (path *a*). The cyclopentylmethyl radical is more stable than 5-hexen-1-yl by $-0.022560 E_h$ or $-59.2 \pm 4.2 \text{ kJ mol}^{-1}$ (path *b*). An alternative approach to obtaining the energetics of these cyclizations is shown in Figure 1 the chemical structures and is as follows. The standard enthalpy of formation of the cyclohexyl radical is known, $\Delta_f H^\circ[\text{C}_6\text{H}_{11}^\bullet] = 75.3 \pm 6.3 \text{ kJ mol}^{-1}$. This is not

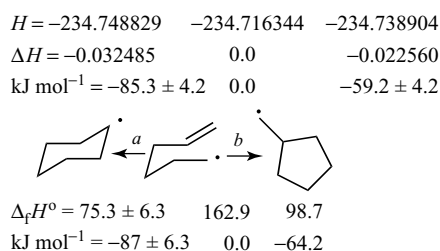


Figure 1 Energetics of cyclization of 5-hexen-1-yl radical. First line: total enthalpy of formation in hartrees by G3MP2B3. Second line: stabilizations in hartrees relative to 5-hexen-1-yl. Third line: relative stabilizations in kilojoules per mole. First line below the chemical structures: standard enthalpies of formation in kilojoules per mole. Second line: relative stabilizations in kilojoules per mole.

Table 2 Standard enthalpies of formation of hydrocarbon precursors obtained by (4), those of 1°, 2°, and 3° carbon radicals by (5)–(7), and literature values found (kJ mol^{−1}).

RH	R [•]	Calculated $\Delta_f H$ [RH]	Calculated $\Delta_f H$ [R [•]]	Literature $\Delta_f H$ [R [•]] ^a
CH ₃ CH ₃	CH ₃ C [•] H ₂	−83.7	120.9	118.8 ± 2.1
CH ₃ CH ₂ CH ₃	CH ₃ CH ₂ C [•] H ₂	−104.6	100.0	100.0 ± 2.1
CH ₃ CH ₂ CH ₃	(CH ₃) ₂ C [•] H	−104.6	90.0	92.0 ± 2.1, 87.9 ± 2.1 ^b
CH ₃ (CH ₂) ₂ CH ₃	CH ₃ (CH ₂) ₂ C [•] H ₂	−125.5	79.1	77.8 ^b
CH ₃ (CH ₂) ₂ CH ₃	CH ₃ CH ₂ C [•] HCH ₃	−125.5	69.0	66.9 ± 2.1, 67.8 ± 2.1 ^b
(CH ₃) ₂ CHCH ₃	(CH ₃) ₂ CHC [•] H ₂	−132.6	72.0	71.1 ± 2.1, 69.9 ± 4.2 ^b
(CH ₃) ₂ CHCH ₃	(CH ₃) ₃ C [•]	−132.6	51.9	46.0 ± 2.9, 48.1 ± 2.9 ^b
CH ₃ (CH ₂) ₃ CH ₃	CH ₃ (CH ₂) ₃ C [•] H ₂	−146.9	57.7	54.4
CH ₃ (CH ₂) ₃ CH ₃	CH ₃ (CH ₂) ₂ C [•] HCH ₃	−146.9	47.7	50.2
CH ₃ (CH ₂) ₃ CH ₃	CH ₃ CH ₂ C [•] HCH ₂ CH ₃	−146.9	47.7	46.9 ^b
(CH ₃) ₃ CCH ₃	(CH ₃) ₃ CC [•] H ₂	−167.8	36.8	36.4 ± 8.4, 33.5 ^c
(CH ₃) ₂ CHCH ₂ CH ₃	(CH ₃) ₂ C [•] CH ₂ CH ₃	−153.6	31.0	28.0 ± 2.9, 29.3 ^b
CH ₃ (CH ₂) ₄ CH ₃	CH ₃ (CH ₂) ₄ C [•] H ₂	−166.9	37.7	33.5 ^b
CH ₃ (CH ₂) ₄ CH ₃	CH ₃ (CH ₂) ₃ C [•] HCH ₃	−166.9	27.6	29.3 ^b
(CH ₃ CH ₂) ₂ CHCH ₃	(CH ₃ CH ₂) ₂ C [•] CH ₃	−171.5	13.0	14.2 ^b
(CH ₃) ₂ CHCH ₂ CH ₂ CH ₃	(CH ₃) ₂ C [•] CH ₂ CH ₂ CH ₃	−174.5	10.0	3.3 ± 8.4 ^b
CH ₃ CH(CH ₃)CH(CH ₃)CH ₃	CH ₃ C [•] (CH ₃)CH(CH ₃)CH ₃	−181.2	3.3	2.9 ± 10.0 ^b
CH ₃ (CH ₂) ₅ CH ₃	CH ₃ (CH ₂) ₅ C [•] H ₂	−188.3	16.3	16.7 ^c
CH ₃ (CH ₂) ₅ CH ₃	CH ₃ (CH ₂) ₄ C [•] HCH ₃	−188.3	6.7	8.4 ^c
CH ₂ =CHCH ₂ CH ₃	CH ₂ =CHCH ₂ C [•] H ₂	0.0	204.6	192.5 ^b
CH ₂ =CH(CH ₂) ₂ CH ₃	CH ₂ =CH(CH ₂) ₂ C [•] H ₂	−20.9	183.7	179.5 ^b
CH ₂ =CHCH(CH ₃) ₂	CH ₂ =CHCH(CH ₃)C [•] H ₂	−28.0	176.6	177.0 ^c
C ₆ H ₅ CH ₂ CH ₃	C ₆ H ₅ CH ₂ C [•] H ₂	29.3	233.9	232.6 ^b
C ₆ H ₅ (CH ₂) ₃ CH ₃	C ₆ H ₅ (CH ₂) ₃ C [•] H ₂	−12.6	192.0	192.0 ^b
C ₆ H ₅ (CH ₂) ₃ CH ₃	C ₆ H ₅ CH ₂ C [•] HCH ₂ CH ₃	−12.6	182.0	184.5 ^b
cyclo-C ₆ H ₁₁ -CH ₃	cyclo-C ₆ H ₁₁ C [•] H ₂	−152.8	51.8	51.3 ^d
cyclo-C ₄ H ₇ -CH ₃ ^e	cyclo-C ₄ H ₇ -C [•] H ₂	−5.4	199.2	n. f. ^f
cyclo-C ₅ H ₉ -CH ₃ ^e	cyclo-C ₅ H ₉ C [•] H ₂	−105.9	98.7	n. f. ^f
(CH ₃) ₃ CCH(CH ₃) ₂	(CH ₃) ₃ CC [•] (CH ₃) ₂	−216.6	−32.1	n. f. ^f
CH ₂ =CH(CH ₂) ₃ CH ₃	CH ₂ =CH(CH ₂) ₃ C [•] H ₂	−41.8	162.8	n. f. ^f
CH ₃ C≡C(CH ₂) ₄ CH ₃	CH ₃ C≡C(CH ₂) ₄ C [•] H ₂	64.0	268.6	n. f. ^f
C ₆ H ₅ (CH ₂) ₂ CH ₃	C ₆ H ₅ CH ₂ CH ₂ C [•] H ₂	8.4	213.0	n. f. ^f
C ₆ H ₅ C(CH ₃) ₃	C ₆ H ₅ C(CH ₃) ₂ C [•] H ₂	−34.0	170.6	n. f. ^f

^a Reference 20, unless indicated otherwise.^b Reference 22.^c Reference 24.^d Reference 70.^e Reference 71.^f $\Delta_f H$ [R[•]] not found.^g Because the cyclopentane ring is strained, the experimental value of $\Delta_f H$ [methylcyclopentane] is used.

the case for the other two 1° radicals, but they can be calculated easily. The precursor hydrocarbon of the 5-hexen-1-yl radical is 1-hexene with $\Delta_f H^\circ[\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{CH}_3] = -41.7$ kJ mol^{−1} calculated by (4) (experimental -42 ± 2). Hence, $\Delta_f H^\circ[\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{C}^\bullet\text{H}_2] = -41.7 + 204.6 = 162.9$. The precursor hydrocarbon for the cyclopentylmethyl radical is methylcyclopentane, with experimental enthalpy of formation $\Delta_f H^\circ[\text{cyclo-C}_5\text{H}_9\text{CH}_3] = -106.0$. Hence, $\Delta_f H^\circ[\text{cyclo-C}_5\text{H}_9\text{C}^\bullet\text{H}_2] = -106.0 + 204.6 = 98.7$. By the

alternative approach presented here, cyclohexyl is more stable by -87.6 kJ mol^{−1} (path *a*) relative to 5-hexen-1-yl and cyclopentylmethyl is more stable by -64.2 (path *b*). The *ab initio* approach and the above simple calculation yield essentially the same results within reasonably expected uncertainties.

With ethane as the parent hydrocarbon, the enthalpy of formation of the diradical species C[•]H₂C[•]H₂ can be calculated by (4) and (5) as $\Delta_f H^\circ[\text{CH}_3\text{CH}_3] + 2 \times 204.6 = -84 + 409.2 = 325.2$ kJ mol^{−1}. The diradical would collapse to

ethylene, $\Delta_f H^\circ[\text{CH}_2=\text{CH}_2] = 52.5$, thereby releasing $272.2 \text{ kJ mol}^{-1}$. This value is identical to the energy of the π bond of ethylene as determined from the cis–trans isomerization of dideuterioethylene, $272 \pm 6 \text{ kJ mol}^{-1}$.

3.2 Alcohols and Alkoxy Radicals

Enthalpies of formation of other common organic species can also be obtained with high accuracy by similar approaches that reflect existing regularities.

Enthalpies of formation of primary, secondary, and tertiary alcohols may be obtained accurately by (8)–(10). $\Delta_f H^\circ$ of the parent hydrocarbons may be calculated by (4) or taken from the literature.⁶⁹ In case of strained species, the experimental value of $\Delta_f H^\circ$ of the hydrocarbon precursor is used. Equations (8)–(10) are also valid for allylic, propargylic, and benzylic alcohols.

$$\Delta_f H^\circ[\text{RCH}_2\text{OH}] = \Delta_f H^\circ[\text{RCH}_3] - 150.6 \pm 2.5 \quad (8)$$

$$\Delta_f H^\circ[\text{R}_2\text{CHOH}] = \Delta_f H^\circ[\text{R}_2\text{CH}_2] - 168.2 \pm 0.8 \quad (9)$$

$$\Delta_f H^\circ[\text{R}_3\text{COH}] = \Delta_f H^\circ[\text{R}_3\text{CH}] - 179.9 \quad (10)$$

Examples of $\Delta_f H^\circ$ values of primary alcohols calculated via $\Delta_f H^\circ[\text{RCH}_3]$ of (4), are as follows with the experimental values in parentheses: 1,2-ethanediol, -384.9 (-394.6 , -387.9 , -390.4 , -387.4); neopentyl alcohol, -318.4 (-318.4); 1-decanol, -401.2 (-393.3 ± 12.6); and allyl alcohol -129.7 (-123.8 ± 1.7 , -128.4 ± 2.9^{11}). In all, 27 available values of primary alcohols were calculated satisfactorily.⁶⁹

For secondary alcohols, with $\Delta_f H^\circ[\text{RR}'\text{CH}_2]$ calculated by (4), some examples are as follows with experimental values in parentheses: cyclohexanol, -293.2 (-288.7 ± 8.4); 2,3-butanediol, -461.9 (-462.3). For 1,2,3-propanetriol, $\Delta_f H^\circ$ [propane] = -104.8 and twice 150.6 ± 2.5 is subtracted for the two 1° alcohol functions and 168.2 ± 0.8 for the 2° alcohol to yield 574.2 ± 3.5 versus experimental 577.8 ± 1.3 and 577.0 . For the strained cyclopentanol, with the experimental $\Delta_f H^\circ$ [cyclopentane] = -76.6 ± 0.8 , the calculation obtains $\Delta_f H^\circ$ [cyclopentanol] = -244.8 versus

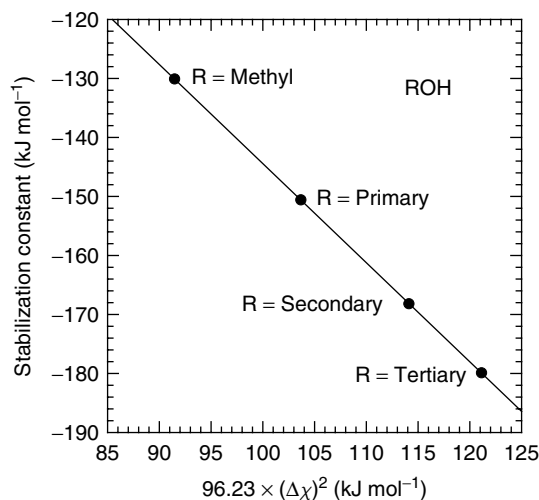


Figure 2 Plot of the stabilization constants of (8)–(10) and of methyl for converting enthalpies of formation of the parent hydrocarbons to those of methyl, primary, secondary, and tertiary alcohols versus the dipole contribution to BDE[R–OH] given by Pauling's $96.23 \times (\chi[\text{R}] - \chi[\text{OH}])^2$.

experimental -243.1 and -242.7 ± 1.6 . Secondary allylic, propargylic, and benzylic alcohols are calculated accurately. The 27 experimental values for 2° alcohols that are available in the literature are matched well.⁶⁹

For tertiary alcohols, the pattern is $\Delta_f H^\circ[\text{RR}'\text{R}''\text{OH}] = \Delta_f H^\circ[\text{RR}'\text{R}''\text{OH}] - 179.9$ and good agreements are obtained with the few available experimental values.⁶⁹

For the unique methane–methanol transformation, the stabilizing constant is $\Delta_f H^\circ[\text{CH}_3\text{OH}] - \Delta_f H^\circ[\text{CH}_4] = -205 - (-74.9) = -130.1 \text{ kJ mol}^{-1}$. Figure 2 shows a plot of the four stabilization constants for these alcohols versus the dipole contribution to BDE[R–OH] given by Pauling's $96.23 \times (\chi[\text{R}] - \chi[\text{OH}])^2$, which will be discussed below. An excellent linear dependence is seen with a correlation coefficient of 0.99999.

There are not many experimental values of the enthalpies of formation of alkoxy radicals and those that exist are not known as accurately as those of carbon radicals. There are quite disparate values in the literature of the past decade and there is no self-consistent set. For species in which the oxygen bearing the odd electron is connected to an sp^3 carbon, unpublished work from this laboratory indicates that enthalpies of formation

can be estimated by $\Delta_f H^\circ[\text{RO}^\bullet] = \Delta_f H^\circ[\text{ROH}] + (222 \pm 6) \text{ kJ mol}^{-1}$. Table 3 shows the calculated $\Delta_f H^\circ$ of the precursor alcohols, the calculated values of the alkoxy radicals, and corresponding literature values. The table also provides estimates for alkoxy radicals for which no values were found in the literature: neopentyloxy, the doubly allylic 1,4-pentadien-3-oxyl, and the cumyloxy radical that has often been used as a hydrogen abstractor.

There are some values of enthalpies of formation available for oxyl radicals having the oxygen on an sp^2 carbon. For vinyl alcohol, $\Delta_f H^\circ[\text{CH}_2=\text{CHOH}] = -128$ and $\Delta_f H^\circ[\text{CH}_2=\text{CHO}^\bullet] = 10.5$.⁸⁰ For phenol, $\Delta_f H^\circ[\text{C}_6\text{H}_5\text{OH}] = -96.4$ and $\Delta_f H^\circ[\text{C}_6\text{H}_5\text{O}^\bullet] = 49.7 \pm 1 \text{ kJ mol}^{-1}$.⁴⁹

BDE[O–H] values, but not enthalpies of formation, are available for some other important precursors of oxyl radicals. For the antioxidant α -tocopherol, BDE[O–H] = $327.3 \pm 1 \text{ kJ mol}^{-1}$.⁸¹

The persistent *N*-oxyl radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) is often used to bring about commercially important “living free-radical polymerization” (LFRP, see **Nitroxide-Mediated Polymerization and its Applications**). In 1979, Rizzardo *et al.* showed

that vinyl free-radical polymerization can be controlled by reversible capping with nitroxides, because of the weak C–O bond formed in the capping reaction⁸²; subsequent work provided valuable additional information.^{83,84} In 1993, Georges *et al.* discussed the preparation of low-polydispersity polystyrene by LFRP regulated by nitroxides, and this stimulated widespread research in this area.⁸⁵ Measurements of the strength of the O–C bond formed in the capping process ($\text{R}_2\text{NO–CR}_3$) have been made via kinetic studies. Results relevant to polymerization of styrene have been reported for TEMPO– CH_2Ph , TEMPO– $\text{CH}(\text{CH}_3)\text{Ph}$, and TEMPO– $\text{C}(\text{CH}_3)_2\text{Ph}$: BDE[O–C] = 128.9, 118.8, and $102.9 \text{ kJ mol}^{-1}$, respectively. For mimicking a growing polystyrene polymer, the secondary benzyl radical result is the best model.⁸⁶ Theoretical calculations (G3(MP2)-RAD) have yielded, after adjustment to 298 K, BDE [TEMPO–R] = 204 for $\text{R} = \text{CH}_3$, 218.1 for $\text{R} = \text{CH}_2\text{CH}_3$, 213 for $\text{R} = \text{CH}(\text{CH}_3)_2$, and 221 for $\text{R} = \text{C}(\text{CH}_3)_3$.⁸⁷ A weak O–C bond has also been reported for a structurally simpler alkoxyamine, BDE[(CH_3CH_2) $_2\text{NO–CH}(\text{CH}_3)\text{Ph}$] = 143.5 ± 6.7 .⁸⁸

Table 3 Standard enthalpies of formation of alcohol precursors, those of the corresponding alkoxy radicals by $\Delta_f H^\circ[\text{RO}^\bullet] = [\text{ROH}] + 222$, and literature values (kJ mol^{-1}).

ROH	$\Delta_f H^\circ[\text{ROH}]^a$	Calculated $\Delta_f H^\circ[\text{RO}^\bullet]$	Literature $\Delta_f H^\circ[\text{RO}^\bullet]$
CH_3OH	–205.0	17.0 ± 6	17 ± 4 , 18 ± 0.8 , ^b 17.2 ± 4.2 ^c
$\text{CH}_3\text{CH}_2\text{OH}$	–234.3	-12.3 ± 6	-13.6 ± 3.3 , -15.1 ± 3.3 , ^b -24.3 ^d
$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$	–255.2	-33.2 ± 6	-30.1 ± 8 , -37.7 , ^e -8.5 ± 1.6 , ^c -48.5 ^d
$\text{CH}_2=\text{CHCH}_2\text{OH}$	–129.7	92.3 ± 6	87.0 , 98.2 ± 1.3 ^c
$(\text{CH}_3)_2\text{CHOH}$	–272.8	-50.8 ± 6	-48.5 ± 3.3 , -48.1 ± 2.9 , ^e -56.9 ^d
$\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{OH}$	–276.1	-54.1 ± 6	-62.8 , -56.4 ± 8 , ^e -69.0 ^d
$\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$	–293.7	-71.7 ± 6	-69.5 , -69.8 ± 8 , ^e -73 ± 2 ^d
$(\text{CH}_3)_2\text{CHCH}_2\text{OH}$	–283.3	-61.3 ± 6	-65.1 ± 8 , ^a -74.1 ^d
$(\text{CH}_3)_3\text{COH}$	–312.5	-90.5 ± 6	-85.8 ± 4 , -86.9 , ^e -85.8 ± 2.9 , ^b -91.6 ^d
$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	–100.8	121.2 ± 6	136.0 ± 12.6
$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{OH}$	–297.1	-75.1 ± 6	-73.2 ^d
<i>cyclo</i> - $\text{C}_6\text{H}_{11}\text{OH}$	–293.2	-71.2 ± 6	-72.8 ^d
$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	–100.6	121.4 ± 6	125.5 ^f
$(\text{CH}_3)_3\text{CCH}_2\text{OH}$	–318.4	-96.4 ± 6	n. f. ^g
$(\text{CH}_2=\text{CH})_2\text{CHOH}$	–45.9	176.1 ± 6	n. f. ^g
$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)_2\text{OH}$	–178.6	43.4 ± 6	n. f. ^g

^a Calculated by $\Delta_f H^\circ[\text{ROH}] = \Delta_f H^\circ[\text{RH}] - c_1$, with $\Delta_f H^\circ[\text{RH}]$ by (4) and c_1 according to (8)–(10) for 1°, 2°, and 3° alcohols.

^b Reference 17.

^c Reference 76.

^d Reference 77.

^e Reference 78.

^f Reference 79.

^g No values found in the literature for neopentyloxy, the doubly allylic 1,4-pentadien-3-oxyl, and cumyloxy radicals.

There are several reports for BDE[O–H] of the TEMPO precursor *N*-hydroxy-2,2,6,6-tetramethylpiperidine. BDE[O–H] = 288.7 in benzene solvent,⁸⁹ 299.2 ± 2.1 in acetonitrile, 292.9 ± 3.8 in benzene,⁵² 291.6 in DMSO,⁹⁰ and 293.3 ± 1.6 in heptane.⁹¹ The value in heptane solvent should be quite similar to the gas-phase value. Relative to TEMPO–H, di-*tert*-butylhydroxylamine has an O–H BDE weaker by 13 kJ mol^{−1} resulting in BDE[(*tert*-Bu)₂NO–H] = 280.⁹²

Another type of *N*-oxyl radicals has been found to be an effective catalyst in the oxidation of organic compounds by molecular oxygen under mild conditions in the presence of cobalt salts (see **Nitroxides in Synthetic Radical Chemistry**).^{93,94} *N*-Hydroxyphthalimide (NIPI) is effective in this respect by giving rise to the phthalimide *N*-oxyl (PINO) radical. BDE[O–H] = 368.6 ± 2.5 kJ mol^{−1} has been obtained by using the electron paramagnetic resonance (EPR) radical equilibration technique⁹⁵; a semiempirical calculation based on a thermodynamic cycle gave 374.9 ± 10.0.⁹⁶ A considerably lower value of BDE[O–H] = 349.3 ± 4.2 for NIPI has also been reported from theoretical calculations.⁹⁷ Functionalization of organic compounds by NIPI catalysis has been reviewed.⁹⁸ *N*-Methylbenzohydroxamic acid has been used to selectively synthesize lipid hydroperoxides and alcohols. It has BDE[O–H] = 331.4 kJ mol^{−1}, which is intermediate between those of TEMPO–H and NHPI.⁹⁹

Hydroxylamine and H₂NO•, the simplest *N*-oxyl radical, have also been studied experimentally and by theoretical calculations. Experimental $\Delta_f H^\circ$ [H₂NOH] = 50 ± 10 kJ mol^{−1}.¹⁰⁰ By (Coupled-Cluster Singles and Doubles model with perturbative Triplets) CCSD(T)-type calculations, extrapolated to the CBS limit, $\Delta_f H^\circ$ [H₂NOH] = 42.3 ± 1.3, $\Delta_f H^\circ$ [H₂NO•] = 66.9 ± 3.3 and $\Delta_f H^\circ$ [HN•OH] = 96.7 ± 3.3 kJ mol^{−1}.¹⁰¹ The theoretical values lead to BDE[H₂NO–H] = 327.2 and BDE [HONH–H] = 356.9. A study of the oxidation of hydroxylamine and the kinetics of the products led to a BDE[H₂NO–H] = 318 ± 4.2 and BDE[HONH–H] = 341 ± 2.1 kJ mol^{−1}.¹⁰²

3.3 Hydroperoxides and Hydroperoxyl Radicals

Hydroperoxides and peroxy radicals are important in combustion, autoxidations of oleates and

linoleates, DNA damage, and so on. Existing experimental and theoretical values of enthalpies of formation show wide scatter. The regularities in enthalpies of formation of primary, secondary, and tertiary hydroperoxides allow their accurate calculation by (11)–(14), when the –OOH functionality is not connected to sp²- or sp-hybridized carbons.

$$\Delta_f H^\circ [\text{CH}_3\text{OOH}] = \Delta_f H^\circ [\text{CH}_4] - 55.6 \quad (11)$$

$$\Delta_f H^\circ [\text{RCH}_2\text{OOH}] = \Delta_f H^\circ [\text{RCH}_3] - 76.6 \quad (12)$$

$$\Delta_f H^\circ [\text{R}_2\text{CHOOH}] = \Delta_f H^\circ [\text{R}_2\text{CH}_2] - 93.3 \quad (13)$$

$$\Delta_f H^\circ [\text{R}_3\text{COOH}] = \Delta_f H^\circ [\text{R}_3\text{CH}] - 105.8 \quad (14)$$

$\Delta_f H^\circ$ of the parent hydrocarbons may be calculated by (4) or taken from the literature. Equations (11)–(14) are also valid for allylic, propargylic, and benzylic hydroperoxides. Table 4 shows the calculated $\Delta_f H^\circ$ [ROOH] and existing literature values. The table also provides values for some hydroperoxides for which none was found in the literature. There do not appear to be any experimental values available for enthalpies of formation of secondary allylic hydroperoxides, which are of interest in peroxidations or autoxidations of unsaturated lipids; 2-hydroperoxy-3-butene is included as a model for them. For polyunsaturated lipids, the doubly allylic 3-hydroperoxypenta-1,4-diene is also calculated.

A plot of the stabilization constants of (11)–(14) versus the dipole contribution to BDE[R–OOH] given by Pauling's $96.23 \times (\chi[\text{R}] - \chi[\text{OOH}])^2$ yields a straight line with a correlation coefficient of 0.9999.

For a hydroperoxide function connected to sp²- or sp-hybridized carbon, the following have been reported from theoretical calculations based on B3LYP/6-311G(d,p).¹⁰⁵ $\Delta_f H^\circ$ [CH₂ = CHOOH] = −40.3, $\Delta_f H^\circ$ [C₆H₅OOH] = −11.2, and $\Delta_f H^\circ$ [HC≡COOH] = 176.8 kJ mol^{−1}.

Enthalpies of formation of peroxy radicals, which are the chain-propagating species in autoxidations, have also been studied but the reported results are often inconsistent. A consistently accurate set of enthalpies of formation is obtained by $\Delta_f H^\circ$ [ROO•] = $\Delta_f H^\circ$ [ROOH] + 140 kJ mol^{−1}, where R is any sp³-hybridized carbon. Values of $\Delta_f H^\circ$ [ROO•] so obtained are given in Table 5, along with corresponding literature values. Agreement between the values calculated here and those in the literature should lend confidence

Table 4 Standard enthalpies of formation of precursors by (4), those of their hydroperoxides by (11)–(14), and literature values (kJ mole^{−1}).

ROOH	$\Delta_f H^\circ$ [RH]	Calculated $\Delta_f H^\circ$ [ROOH]	Literature $\Delta_f H^\circ$ [ROOH]
MeOOH	−74.9	−130.5	−131, ^a −139.0 ± 8.1, ^b −129.5 ± 0.9 ^c
EtOOH	−84.0	−160.2	−210, ^a −175.4 ± 12.9, ^b −163.7, ^c −164.3 ^d
<i>n</i> -PrOOH	−104.8	−181.2	−250, ^a −183.4 ± 1.1, ^c −189.1 ^d
<i>iso</i> -PrOOH	−104.8	−197.9	−197.1, ^a −213 ± 14, ^b −200.4 ± 0.9, ^c −205.5 ^d
AllylOOH	20.8	−55.8	−56.8 ^d
<i>n</i> -BuOOH	−125.6	−202.1	−202.4 ± 1.0 ^c
<i>iso</i> -BuOOH	−132.6	−209.2	−210.0 ± 0.9 ^c
<i>sec</i> -BuOOH	−125.6	−218.8	−220.3 ± 0.9 ^c
<i>tert</i> -BuOOH	−132.6	−238.5	−234.9, ^a −249.5 ± 12.2, ^b −239.5 ± 0.9 ^c
<i>neo</i> -C ₅ H ₁₁ OOH	−167.9	−244.5	−245.2 ^e
CyclohexylOOH	−167.9	−218.3	−214.9 ^a
BenzylOOH	12.0	−26.5	−20.9 ^f
CumylOOH ^g	0.3	−105.8	−78.7 ± 6.7 ^a
CH ₂ =CHCH(OOH)CH ₃	−0.1	−93.4	n. f. ^h
(CH ₂ =CH) ₂ CHOOH	104.7	11.4	n. f. ^h
(CH ₃) ₂ C(OH)CH ₂ OOH	−312.5 ⁱ	−389.1	n. f. ^h

^aReference 20.^bReference 103.^cReference 104.^dReference 105.^eReference 106.^fReference 107.^gCumene = isopropylbenzene.^hValue not found in the literature.ⁱValue of *tert*-butyl alcohol precursor from Table 3.

to the methods used. Particularly noteworthy is the agreement with the experimental value for the enthalpy of formation of the doubly allylic peroxy radical (CH₂=CH)₂CHOO•, 151.4, calculated versus 144 ± 11 experimental.¹⁰⁸ For bonds to sp² carbon, $\Delta_f H^\circ$ [CH₂=CHOO•] = 101.8 ± 1.8 and $\Delta_f H^\circ$ [C₆H₅OO•] = 130.9 ± 2.0 have been reported.¹⁰⁵ Hence, BDE[CH₂=CH–OO•] = 192.7 ± 5.3 and BDE[C₆H₅–OO•] = 208.1 ± 8.2 kJ mol^{−1}.

Also of interest are BDE values of species involved in combustion and autoxidation, and there are literature reports of some BDE[R–OOH] and BDE[R–OO•]. Their values BDEs can be calculated with $\Delta_f H^\circ$ [HOO•] = 12.3 kJ mol^{−1} and $\Delta_f H^\circ$ [R•] from Tables 1 and 2 the established $\Delta_f H^\circ$ [ROOH] and $\Delta_f H^\circ$ [ROO•] by ((15) and (16)).

$$\begin{aligned} \text{BDE}[R - \text{OOH}] &= \Delta_f H^\circ[R^\bullet] + \Delta_f H^\circ[\text{HOO}^\bullet] \\ &\quad - \Delta_f H^\circ[\text{ROOH}] \end{aligned} \quad (15)$$

$$\begin{aligned} \text{BDE}[R - \text{OO}^\bullet] &= \Delta_f H^\circ[R^\bullet] + \Delta_f H^\circ[\text{O}_2] \\ &\quad - \Delta_f H^\circ[\text{ROO}^\bullet] \end{aligned} \quad (16)$$

The results are given in Table 6. The calculated BDE[R–OO•] for R = secondary allylic radical is sufficiently strong at 95 kJ mol^{−1} for the R• and •O–O• to react near room temperature forming the peroxy radical that propagates chain reactions. However, the calculated BDE of 53.2 for R = secondary doubly allylic radical is sufficiently weak to indicate that the equilibrium R• + •O–O• ⇌ ROO• may not be particularly favorable for the forward reaction at ambient temperatures. This is consistent with the report that at 333 K (60 °C) the rate of disappearance of (CH₂=CH)₂C•H radicals becomes independent of O₂ pressure and the rate of the reverse reaction becomes so fast that little net reaction occurs between the radical and O₂.¹⁰⁸ The calculated BDE is in excellent agreement with the reported experimental value of 56 ± 5 kJ mol^{−1}. For oxygen bonded to sp²- and sp-hybridized carbons, reported values are¹⁰⁵ BDE[R–OOH] = 360.1 ± 5.1, 393.1 ± 2.1, and 360.1 ± 4.1 kJ mol^{−1} for R = vinyl, ethynyl, and phenyl, respectively; also, BDE[R–OO•] = 198.2 ± 5.0, 204.6 ± 1.7, and 209.7 ± 2.7 kJ mol^{−1} for R = vinyl, ethynyl, and phenyl, respectively.

Table 5 Enthalpies of formation of peroxy radicals calculated by $\Delta_f H^\circ[\text{ROO}^\bullet] = \Delta_f H^\circ[\text{ROOH}] + 140$ and literature values (kJ mol^{-1}).

ROOH	Calculated $\Delta_f H^\circ[\text{ROO}^\bullet]$	Literature $\Delta_f H^\circ[\text{ROO}^\bullet]$
MeOOH	9.5	20.1 ± 5^a , 9.0 ± 5.1^b , 12.2^c , 8.5 ± 5^d
EtOOH	-20.2	-28.5 ± 9.6^a , -27.4 ± 9.9^b , -23.5^c
<i>n</i> -PrOOH	-41.2	-44.1 ± 1.1^c
<i>iso</i> -PrOOH	-57.9	$-65.4 \pm 11.3^{a,b}$, -62.3^c
AllylOOH	84.2	-88.7^a , 86.2 ± 5.8^d
<i>n</i> -BuOOH	-62.1	-62.8 ± 1.0^c
<i>iso</i> -BuOOH	-69.2	-70.7 ± 1.0^c
<i>sec</i> -BuOOH	-78.8	-82.6 ± 1.1^c
<i>tert</i> -BuOOH	-98.5	$-101.5 \pm 9.2^{a,b}$, -103.3 ± 0.8^c
<i>neo</i> -C ₅ H ₁₁ OOH	-104.5	-115.5^a , -113.4^e
CyclohexylOOH	-78.3	-93.3^f
BenzylOOH	113.5	114.6 ± 4.2^a , 123.8^g , 117 ± 6^h
C ₆ H ₅ C(CH ₃) ₂ OOH	34.2	n. f. ⁱ
CH ₂ =CHCH(OOH)CH ₃	46.6	n. f. ⁱ
(CH ₂ =CH) ₂ CHOOH	151.4	144 ± 11^j
(CH ₃) ₂ C(OH)CH ₂ OOH	-249.1	-258.6^k

^a Reference 21.^b Same as footnote *b* of Table 4.^c Same as footnote *c* of Table 4.^d Reference 105.^e Same as footnote *e* of Table 4.^f Reference 109.^g Same as footnote *f* of Table 4.^h Reference 110.ⁱ Value not found in the literature.^j Reference 108.^k Reference 111.

3.4 Amines and Nitrogen-Centered Radicals

Enthalpies of formation of primary amines with the amino group connected to an sp³-hybridized carbon also follow very regular patterns.⁶⁹ For the -NH₂ group connected to an sp³-hybridized carbon, enthalpies of formation are accurately calculated by (17)–(20).

$$\Delta_f H^\circ[\text{CH}_3\text{NH}_2] - \Delta_f H^\circ[\text{CH}_4] = 51.5 \quad (17)$$

$$\Delta_f H^\circ[\text{RCH}_2\text{NH}_2] = \Delta_f H^\circ[\text{RCH}_3] + 36.4 \quad (18)$$

$$\Delta_f H^\circ[\text{RR}'\text{CHNH}_2] = \Delta_f H^\circ[\text{RR}'\text{CH}_2] + 20.9 \quad (19)$$

$$\Delta_f H^\circ[\text{RR}'\text{R}''\text{CNH}_2] = \Delta_f H^\circ[\text{RR}'\text{R}''\text{CH}] + 12.1 \quad (20)$$

For the unique methylamine, using experimental values, $\Delta_f H^\circ[\text{CH}_3\text{NH}_2] - \Delta_f H^\circ[\text{CH}_4] = -23.4 - (-74.9) = 51.5 \text{ kJ mol}^{-1}$ as the destabilization ensuing from the formation of the nitrogen-centered radical.

For the available $\Delta_f H^\circ$ of 20 amines of the type RCH₂NH₂, (18) yields results within the uncertainty of reported values. For example, $\Delta_f H^\circ[2\text{-aminoethanol}]$ is obtained from $\Delta_f H^\circ[\text{CH}_3\text{CH}_3]$ by subtracting 150.6 for the 1° alcohol function and adding 36.4 for -NH₂ group connected to 1° carbon. The calculated result of -197.9 is well within experimental uncertainty of reported measurements of -200.8 and -201.7. For benzylamine, the calculated $\Delta_f H^\circ = 86.2$ versus experimental 87.9 ± 2.9 and 83.7 ± 2.9 .

For the -NH₂ group connected to 2° carbon, $\Delta_f H^\circ[\text{RR}'\text{CHNH}_2] = \Delta_f H^\circ[\text{RR}'\text{CH}_2] + 20.9 \text{ kJ mol}^{-1}$. Available literature values for such amines are matched well by the calculation even for quite large molecules. For amphetamine (2-amino-1-phenylpropane) as an example, the hydrocarbon precursor is propylbenzene with $\Delta_f H^\circ = 8.3$ by (4) and $\Delta_f H^\circ[\text{C}_6\text{H}_5\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}_3] = 8.3 + 20.9 = 29.2$ versus experimental 29.3. The gas-phase enthalpy of formation of norephedrine (2-amino-1-phenyl-1-propanol) is not available

Table 6 Calculated BDE[R–OOH] by (15) with literature values and calculated BDE[R–OO•] by (16) with literature values (kJ mol^{−1}).

R	Calculated BDE [R–OOH]	Literature BDE [R–OOH]	Calculated BDE [R–OO•]	Literature BDE [R–OO•]
Me	289.5	300 ± 13, ^a 288 ± 1 ^b	137.0	137.0 ± 3.8, ^a 134, ^b 136.7 ^c
Et	293.7	332 ± 21, ^a 296 ± 1 ^b	141.1	143, ^b 147.7, ^c
<i>n</i> -Pr	293.8	364, ^a 297 ± 2 ^b	141.2	145.2 ± 2 ^b
<i>iso</i> -Pr	300.4	298.3, ^a 303 ± 3 ^b	157.9	152 ± 3 ^b
Allyl	239.4	234.2 ^c	86.8	79.5 ^d
<i>n</i> -Bu	293.7	297 ± 4 ^b	141.2	145 ± 4 ^b
<i>iso</i> -Bu	293.7	296 ± 4 ^b	141.2	145 ± 4 ^b
<i>sec</i> -Bu	298.3	303 ± 2 ^b	147.8	153 ± 2 ^b
<i>tert</i> -Bu	303.0	309 ± 4, ^a 307 ± 3 ^b	150.4	158 ± 3 ^b
<i>neo</i> -C ₅ H ₁₁	293.7	n. f. ^e	135.9	152.2 ^a
Cyclohexyl	306.2	n. f. ^e	153.6	n. f. ^e
Benzyl	246.1	240.5 ± 4 ^f	93.5	93 ± 6, ^a 95.7 ± 4, ^f 91 ± 4 ^g
C ₆ H ₅ C(CH ₃) ₂	252.4	n. f. ^e	99.8	n. f. ^e
CH ₂ =CHC(CH ₃)H	252.7	n. f. ^e	95.1	n. f. ^e
(CH ₂ =CH) ₂ CH	204.2	n. f. ^e	53.2 ^h	56 ± 5 ⁱ

^aReference 21.^bSame as footnote *c* of Table 4.^cReference 105.^dSame as footnote *r* of Table 1.^eValue not found in the literature.^fSame as footnote *f* of Table 4.^gSame as footnote *h* of Table 5.^hFrom BDE[(CH₂=CH)₂CH–H] = 316.3 (footnote *d* above) and $\Delta_f H^\circ[(CH_2=CH)_2CH_2] = 106.3 \pm 1.3$ (Ref. 20), $\Delta_f H^\circ[(CH_2=CH)_2C^\bullet H] = 204.6$ kJ mol^{−1}.ⁱSame as footnote *j* of Table 5.

and the calculation yields -138.9 kJ mol^{−1} by adding 20.9 to $\Delta_f H^\circ[C_6H_5CH_2CH_2CH_3]$ 8.3 for the RR'CHNH₂ function and subtracting 168.2 for the 2° alcohol RR'CHOH function.

For NH₂ connected to 3° carbon, there appear to be only two experimental values available. Both are accommodated accurately by $\Delta_f H^\circ[RR'R''CNH_2] = \Delta_f H^\circ[RR'R''CH] + 12.1$ kJ mol^{−1} and the relationship should be applicable to all such amines.

A plot of the four destabilizing constants of (17)–(20) versus the dipole contribution to BDE[R–NH₂] given by Pauling's $96.23 \times (\chi[R] - \chi[NH_2])^2$ yields a straight line with a correlation coefficient of 0.9996.

There are relatively few values of the enthalpies of formation of nitrogen-centered radicals. It appears that enthalpies of such radicals derived from primary amines can be estimated by $\Delta_f H^\circ[RNH^\bullet] = \Delta_f H^\circ[RNH_2] + 200$ kJ mol^{−1} when the nitrogen is not connected to an sp²- or sp-hybridized carbon. Three available examples are, $\Delta_f H^\circ[CH_3NH^\bullet] = \Delta_f H^\circ[CH_3NH_2] + 200 =$

$-23.4 + 200 = 176.7$ versus experimental 184.1 ± 8.2 ; $\Delta_f H^\circ[(CH_3)_3CNH^\bullet] = \Delta_f H^\circ[(CH_3)_3CNH_2] + 200 = -120.5 + 200 = 79.5$ versus experimental 95.4 ± 12.6 ; and $\Delta_f H^\circ[C_6H_5CH_2NH^\bullet] = \Delta_f H^\circ[C_6H_5CH_2NH_2] + 200 = 87.9 + 200 = 287.9$ versus experimental 288.3 ± 12.6 . Using the known $\Delta_f H^\circ$ values for ethylamine, propylamine, and isopropylamine and adding 200, we calculate for the corresponding $\Delta_f H^\circ[RNH^\bullet] = 152.7$, 131.8, and 116.3, respectively. These values lead to BDE[RNH–H] = 417.9 kJ mol^{−1} for all three, which is consistent with available experimental values of BDE[CH₃NH–H] = 425.1 ± 8.4 and BDE[C₆H₅CH₂NH–H] = 418.4. The results are also consistent with theoretical CBS-Q calculations that have obtained BDE[CH₃NH–H] = 413.4, BDE[CH₃CH₂NH–H] = 415.9 and BDE[CH₃CH₂CH₂NH–H] = 422.5 kJ mol^{−1}, with an expected uncertainty of about ±6.¹¹²

Other available values for nitrogen-centered radicals are $\Delta_f H^\circ[PhNH^\bullet] = 244.3 \pm 4.2$, leading to BDE[PhNH–H] = 375 ± 5 kJ mol^{−1}; $\Delta_f H^\circ[H_2NNH^\bullet] = 243.5$, leading to BDE[H₂NNH–H]

$= 366.1$ and $\text{BDE}[\text{H}_2\text{N}-\text{NH}_2] = 285.3 \text{ kJ mol}^{-1}$. CBS-QB3 calculations have given $\Delta_f H^\circ[\text{CH}_3\text{N}^+\text{NH}_2] = 202.9 \pm 7.5$, $\Delta_f H^\circ[\text{CH}_3\text{NHN}^+\text{H}] = 213.8 \pm 7.5$, $\text{BDE}[\text{CH}_3\text{N}(\text{NH}_2)-\text{H}] = 331$, and $\text{BDE}[\text{CH}_3\text{NHNH}-\text{H}] = 341 \text{ kJ mol}^{-1}$.¹¹³ 2,2-Diphenyl-1-picrylhydrazyl (2,4,6-tri-O₂N-C₆H₂-N⁺N(C₆H₅)₂ = DPPH) is a persistent free radical that has been used extensively, particularly for assaying total concentration of antioxidants in foods. The N-H bond dissociation enthalpy is quoted as $334.7 \text{ kJ mol}^{-1}$; density functional theory (DFT) calculations led to 341.4 ¹¹⁴ and 346 .¹¹⁵

In free-radical brominations of hydrocarbons by *N*-bromosuccinimide, the succinimidyl radical was suspected of being the hydrogen abstracting species. However, it has been established that, under the usual bromination conditions (nonpolar solvents), Br[•] is the abstracting radical.^{116,117} Compounds of the type RC(O)NH₂ have been reported to have quite strong N-H bonds: $\text{BDE}[\text{HC}(\text{O})\text{NH}-\text{H}] = 476 \text{ kJ mol}^{-1}$ and $\text{BDE}[\text{CH}_3\text{C}(\text{O})\text{NH}-\text{H}] = 469$,¹¹⁸ compared to $\text{BDE}[\text{CH}_3\text{NH}-\text{H}] = 425.6$. Evidently, in RC(O)N[•]H, the carbonyl function does not seem to stabilize the odd electron on the adjacent nitrogen.

Enthalpies of formation of compounds free of “special effects” can be obtained for many other functional groups from $\Delta_f H^\circ$ of the precursor hydrocarbon obtained by (4) plus a constant: ethers, aldehydes, ketones, carboxylic acids, esters, chlorides, nitriles, and amides.⁶⁹ The relationships can be used to calculate enthalpies of formation for compounds QH and obtain $\Delta_f H^\circ[\text{Q}^{\bullet}]$ if $\text{BDE}[\text{Q}-\text{H}]$ is known. Unpublished work from this laboratory for thiols indicates $\Delta_f H^\circ[\text{RSH}] = \Delta_f H^\circ[\text{RH}] + c_i$, where c_i depends on the nature of H: 52.3 for replacing H of methane, 38.1 for 1° H, 29.3 for 2° H, 25.5 for 3° H, and 29.7 for aromatic H.

4 RADICAL STABILIZATION ENERGIES AND SCALES

Knowledge of relative radical stabilities is fundamental to the design of radical reactions. All else being equal, more stable radicals should be easier to form than less stable ones. For example, in the well-studied unimolecular cleavage of alkoxy radicals, $\text{RR}'\text{R}''\text{CO}^{\bullet} \rightarrow \text{R}'\text{R}''\text{C}=\text{O} + \text{R}^{\bullet}$, generally the amounts of various radical products formed should reflect the relative radical stabilities

of the three R groups. The more stable radical should be the predominant radical product of cleavage.^{119,120} In radical additions to double bonds, the site of attack is generally the one that leads to the more stable radical product as in $\text{H}_3\text{C}^{\bullet} + \text{H}_2\text{C}=\text{CHPh} \rightarrow \text{CH}_3\text{CH}_2\text{C}^{\bullet}\text{HPh}$, rather than $\text{PhCH}(\text{CH}_3)\text{C}^{\bullet}\text{H}_2$, because the benzyl radical is more stable than a primary alkyl radical. In hydrogen abstraction by bromine atoms from isobutane, the hydrogen abstracted is the single one that leads to the formation of the more stable tertiary alkyl radical 98% of the time, rather than one of the other nine that lead to the formation of a primary radical. Excellent descriptions of the importance of radical stability and its role in synthesis and catalysis are available.^{121,122}

A perennial problem with the concept of relative radical stabilization energies has been the question “relative to what?” Common current practice is to use the C-H bond of methane as the reference standard. Accordingly, the radical stabilization energy of a species R[•] is defined as $\text{RSE} = \text{BDE}[\text{H}_3\text{C}-\text{H}] - \text{BDE}[\text{R}-\text{H}]$. This appears to be a logical definition: Cleavage of the C-H bond of methane to produce a methyl radical and a hydrogen atom requires $439.3 \text{ kJ mol}^{-1}$. Cleavage of the C-H bond of ethane to produce an ethyl radical and a hydrogen atom requires only 422.6. In both cases, a hydrogen atom is formed; hence it is easier to form an ethyl radical than a methyl radical by 24.9 kJ mol^{-1} , which is assumed to be a quantitative measure of the resonance stabilization energy of ethyl relative to methyl radicals. This argument has been presented in many textbooks for many years, but it has been shown to be embarrassingly illogical. The same argument can be applied to the cleavage of the C-F bonds of methyl fluoride and of ethyl fluoride. In both cases, a fluorine atom is formed, but $460.2 \text{ kJ mol}^{-1}$ is required to cleave the bond and form the methyl radical and 467.4 is required to form the ethyl radical. With the fluorides, it is easier to make methyl rather than ethyl radicals. Now the conclusion is that the ethyl radical is more stable! The fault in the argument presented is that it considers only the products and disregards the relative stabilities of the reactants. As Pauling has pointed out, dipoles strengthen bonds.¹²³ The C-F bond dipole in ethyl chloride is stronger than the C-F dipole in methyl chloride, because there is a greater electronegativity difference between ethyl and fluorine than between methyl and fluorine. The difference in dipole effect

makes the C–F bond of ethyl fluoride stronger. The C–F bond of *tert*-butyl fluoride is stronger than that of methyl fluoride by 35.6 kJ mol^{-1} . In using $\text{BDE}[\text{H}_3\text{C}-\text{H}]$ as a reference standard, one disregards potentially different effects of the C–H dipole in comparing $\text{H}_3\text{C}-\text{H}$ to various R–H.

The argument has been made that the C–H bond dipole is very weak and can be safely neglected. While it is true that various C–H bond dipole contributions to BDE constitute a relatively small percentage of the total BDE, the dipole effects are not negligibly small compared to the relative stabilization energies of carbon radicals versus methyl.¹²⁴ Pauling used $\text{BDE}[\text{H}_3\text{C}-\text{CH}_3] - \text{BDE}[\text{R}-\text{R}]$ to estimate the radical stabilization energy of the allyl and benzyl radicals relative to $\text{RSE}[\text{H}_3\text{C}^\bullet] = 0$, from $\text{BDE}[\text{CH}_2=\text{CHCH}_2-\text{CH}_2\text{CH}=\text{CH}_2]$ and $\text{BDE}[\text{PhCH}_2-\text{CH}_2\text{Ph}]$. This avoids complications from differing dipole effects of C–H bonds that would occur in comparing $\text{BDE}[\text{H}_3\text{C}-\text{H}]$ to $\text{BDE}[\text{R}-\text{H}]$.¹²⁵ Preferences for using the symmetrical option of $\text{BDE}[\text{R}-\text{R}]$ to establish relative radical stabilizations have been expressed by others in the past.¹²⁶ An extensive tabulation of radical stabilization values based on $\text{BDE}[\text{R}-\text{R}]$ is available.¹²⁷ Nevertheless, the use of $\text{RSE} = \text{BDE}[\text{H}_3\text{C}-\text{H}] - \text{BDE}[\text{R}-\text{H}]$ is still widespread.^{128,129} Estimating the extent to which a radical is stabilized in this way has the advantages of (i) simplicity, (ii) the fact that more C–H bond strengths have been measured than R–R, and (iii) the minimization of steric effects since hydrogen is the smallest substituent that can be attached to the radical.¹³⁰ In addition, the ordering of the stabilization of various radicals appears to be about the same for both options. Even though it was recognized that the use of $\text{BDE}[\text{R}-\text{R}]$ is better suited to quantifying substituent effects in radical centers, a justification that has been offered for continued use of C–H bond strengths is that they have the advantage of relating directly to the elementary process of transferring a hydrogen atom from one radical to another, the much studied hydrogen abstraction reaction.¹²¹

There are, however, two major problems with using $\text{BDE}[\text{R}-\text{H}]$ to quantify stabilization energies. The first is that anything called “radical stabilization energy” must be an inherent property of the radical.¹³⁰ It must be transferable with the radical to species other than the one from which it was derived. Such RSE values are

not transferable. For example, RSE values relative to $\text{BDE}[\text{H}_3\text{C}-\text{H}] = 376.6 \text{ kJ mol}^{-1}$ are $\text{RSE}[\text{H}_3\text{C}^\bullet] = 0.0$, $\text{RSE}[\text{CH}_3\text{C}^\bullet\text{H}_2] = 18.3 \pm 2$ and $\text{RSE}[\text{CH}_2=\text{CHC}^\bullet\text{H}_2] = 70.7 \pm 3$. Therefore, $\text{BDE}[\text{CH}_3-\text{CH}_2\text{CH}_3]$ should be equal to $\text{BDE}[\text{CH}_3-\text{CH}_3] - \text{RSE}[\text{H}_3\text{C}^\bullet] - \text{RSE}[\text{CH}_3\text{C}^\bullet\text{H}_2]$. Substituting these RSE values results in $\text{BDE}[\text{CH}_3-\text{CH}_2\text{CH}_3] = 376.6 - 0.0 - (18.3 \pm 2) = 358.3 \pm 2$; the experimental value of 370.1 ± 3 is significantly different. Also, $\text{BDE}[\text{CH}_3\text{CH}_2-\text{CH}_2\text{CH}=\text{CH}_2]$ should be equal to $\text{BDE}[\text{CH}_3-\text{CH}_3] - \text{RSE}[\text{CH}_3\text{C}^\bullet\text{H}_2] - \text{RSE}[\text{CH}_2=\text{CHC}^\bullet\text{H}_2] = 376.6 - (18.3 \pm 2) - (70.7 \pm 3) = 287.6 \pm 4$; the experimental value is 312.9 ± 10 . Clearly, such RSE values are not transferable to carbon–carbon bonds. The second problem is that, when dealing with radicals that are not carbon-centered, the reference bond is changed. For nitrogen-centered radicals, the reference bond becomes $\text{BDE}[\text{H}_2\text{N}-\text{H}]$.^{131,132} For oxygen-centered radicals, it is $\text{BDE}[\text{HO}-\text{H}]$, for sulfur-centered radicals $\text{HS}-\text{H}$, and so forth.¹²¹ It is not clear exactly how these different stability scales relate to each other. What has become clear is that, no matter what bond and species are chosen as the reference point for radical stabilization energies, arguments can and have been made in favor of some other, presumably superior choice.^{133,134}

The ideal situation is to have no particular reference compound and to have only one stability scale for all radicals. This is attainable, provided the focus is not on stability but on instability. An instability scale is established by defining the instability of any radical $\text{Q}^\bullet$ as $\text{DE}[\text{Q}^\bullet] = \frac{1}{2} \times \text{BDE}[\text{Q}-\text{Q}]$, where DE denotes destabilization energy. The zero of this scale simply corresponds to a hypothetical $\text{BDE}[\text{Q}-\text{Q}] = 0.0$.¹³⁵ Values of DE for many common groups are given in Table 7. To obtain $\text{BDE}[\text{CH}_3-\text{CH}_2\text{CH}_3]$, one simply adds $\text{DE}[\text{CH}_3]$ and $\text{DE}[\text{CH}_2\text{CH}_3]$. The result is $373.2 \text{ kJ mol}^{-1}$, which agrees with the experimental value of 370.1 ± 3 . For $\text{BDE}[\text{CH}_3\text{CH}_2-\text{CH}_2\text{CH}=\text{CH}_2]$, the result is 313.3 versus experimental 312.9 ± 10 . Simply adding the DE values in these two cases is successful because the electronegativity difference between these particular carbon radicals is very small and contributes little to the BDE. In the general case of an A–B bond, bond dissociation enthalpies are obtained from (21).

$$\text{BDE}[\text{A}-\text{B}] = \text{DE}[\text{A}] + \text{DE}[\text{B}] + 96.23(\chi_{\text{A}} - \chi_{\text{B}})^2 \quad (21)$$

Table 7 Destabilization energies of R (kJ mol⁻¹) and electronegativities for use with (21), where A and B are replaced by R' and R''.^a $BDE[R' - R''] = DE[R'] + DE[R''] + 96.23 \times (\chi[R'] - \chi[R''])^2$.

Species, R	DE[R]	χ [R]
HC≡C•	328.4 ^b	2.789
N≡C•	301.2 ^b	2.940
C ₆ H ₅ •	242.7 ^b	2.548
CH ₂ =CH•	236.4 ^b	2.548
•CH ₂	223.8	2.525
H ₂ B•	219.7	1.870
H ₃ C•	188.3	2.525
CH ₃ C•H ₂	184.9	2.462
(CH ₃) ₂ C•H	181.2 ^c	2.411
(CH ₃) ₃ C•	172.4 ^c	2.378
(CH ₃) ₃ Si•	163.2	1.838
H ₃ Si•	159.0	1.879
CH ₃ C•(O)	159.0 ^b	2.260
H ₂ N•	142.7	3.100
C ₆ H ₅ C•H ₂	139.3	2.506
CH ₃ N•H	131.4	3.018
CH ₂ =CHC•H ₂	128.4	2.489
CH ₃ S•	127.6	2.600
Cl•	121.3	3.174
H ₂ P•	115.9	2.273
HO•	107.1	3.500
C ₆ H ₅ N•H	92.0	3.051
F•	79.5	3.938
CH ₃ O•	79.5	3.439
(CH ₃) ₃ CO•	79.5	3.393
O ₂ NO•	51.5	3.543
F ₂ N•	46.0	3.226
CH ₃ OO•	35.8	3.303
HOO•	31.4	3.390
O ₂ N•	28.5	3.177
C ₆ H ₅ O•	7.5	3.376
ON•	-23.0	2.377
ONO•	-23.8	3.436
•OO•	-98.2	3.225
O≡C	-140.6	2.482

^aNot to be used when the A–B combination will result in steric hindrance or conjugation. Not to be used for groups –OR and –NR₂ connected to sp²- or sp-hybridized atoms (e.g., –C₆H₅, –CR=CR₂, –C≡CR, –NO₂, –BH₂).

^bConjugation-free value obtained from BDE[R–CH₃] and BDE[R–Cl].

^cStrain-free value obtained from BDE[R–CH₃] and BDE[R–OH].

This is Pauling's electronegativity equation,¹²⁵ where DE is the inherent bonding ability and χ is the electronegativity, which is a measure of the affinity of the atom or group for electrons. The value of χ was defined by Pauling to pertain to an atom or group in a stable molecule and in its normal oxidation state.

In the case of a group like *tert*-butyl, it is obvious that BDE[(CH₃)₃C–C(CH₃)₃] is not useful for obtaining inherent bonding ability because

of the known steric hindrance that weakens the central C–C bond. However, the inherent bonding ability of *tert*-butyl is obtainable from the known BDE[(CH₃)₃C–OH], BDE[(CH₃)₃C–Cl] or BDE[(CH₃)₃C–CH₃] and their combinations. Similarly, the central bond of 1,3-butadiene does not reflect the inherent bonding ability of vinyl because of the known strengthening of the central C–C bond by conjugation. The inherent bonding ability of vinyl is obtainable from vinyl compounds not subject to “special effects” of conjugation such as BDE[CH₂=CH–Cl], BDE[CH₂=CH–CH₃], and so on. The DE values of Table 7 are inherent properties of the species and are free from “special effects” that are present in A–A but not in A–B, or vice versa. Justification for the negative DE values of Table 7 has been provided.⁶⁹ An example of using the negative DE of O₂ in Table 7 is for the calculation of BDE[CH₂=CHCH₂–OO•] by (21) and the values for CH₂=CHC•H₂ and •OO• from Table 7: $BDE = 128.4 + (-98.2) + 96.23(2.489 - 3.225)^2 = 82.3$ versus 86.8 by a different calculation in Table 6, and 79.5 experimental. Not only does the negative DE work, but it also makes sense; there is no positive BDE[•OO–OO•] because O₄ does not exist. Two molecules of oxygen at covalent bond distances repel each other—negative BDE.

In addition to its utility in calculating BDE among many common groups, there are some important lessons lurking in Table 7. When thinking of radical reactivity, we tend to think that HO• is inherently very reactive. However, HO• is not even in the top half of Table 7. Methyl radical is more destabilized and, therefore, should be more reactive than hydroxyl. In fact, H₃C• is more reactive in abstracting halogen atoms. At 300 K, methyl radicals abstract chlorine from Cl₂ about 30 times faster than hydroxyl radicals do.¹³⁶ Our concept of reactivity is skewed by the fact that abstraction of hydrogen by hydroxyl or fluorine radicals form very strong bonds to the hydrogen. However, this has nothing to do with their inherent reactivity. Neither is very good at abstracting halogens. The high strength of the H–F and H–OH bonds has nothing to do with their inherent bonding ability. It is caused by the great difference in their respective electronegativities from that of hydrogen.

Pauling estimated the electronegativity of the elements by global fittings to the then known BDE values and noted that, unlike all other elements or

groups, the electronegativity of H is unique in its variability depending on what is bonded to it. There have been many published examples of failures of (4), but in every instance such reported failures are due to misapplication of the equation. Using (21) for species such as BDE[C–H] or BDE[Si–F] will, of course, lead to failure because the electronegativity of tetravalent carbon in a stable molecule such as methane will not be the same as its electronegativity in a species like CH. The carbon is not in its normal oxidation state and is not in a stable molecule. Similarly, the electronegativity of silicon in SiF will not be the same as that in SiF₄. Also, because bonds to hydrogen are among the most extensively and accurately known, (21) has been tested repeatedly against such bonds and has been found to give marginal results when using an average value for $\chi[\text{H}] = 2.2$, without regard to its known variability. However, in the last decade, it was demonstrated that (21) yields very accurate results with hundreds of common molecules with many different functionalities, hydrocarbons, alcohols, ethers, amines, halides, peroxides, silanes, thiols, sulfides, nitro compounds, and so on.¹²⁴ As a result, Pauling's equation is useful for estimating BDEs that are not available from experimental determinations and is as accurate as the highest level *ab initio* calculations available today. Unlike high-level *ab initio* theoretical calculations, (21) is equally as easy to apply to large complex molecules as to simple ones. Equation (21) does not take account of "special effects" (i)–(iv) as defined previously. Stabilization and destabilization constants of (8)–(20) were obtained without the use of Pauling's equation (21). Their excellent correlations with the electronegativity term of (21) are noteworthy.

5 HYDROGEN TRANSFER KINETICS

Attempts to predict reaction rates by some sort of *a priori* calculation go back to 1929, when London proposed the first quantum mechanically based equation for a reacting system.¹³⁷ For an atom transfer reaction $\text{A–B} + \text{C}^{\bullet} \rightarrow \text{A}^{\bullet} + \text{B–C}$, the energy of the reacting system was expressed in terms of the bonding and antibonding energies of three molecules: A–B, B–C, and A–C, at various combinations of bond distances on the way from reactants to the TS and to products. Resonance, then called the "overlap integral," was explicitly stated

to have been left unaccounted. This resonance stabilization energy would be due to the delocalization at the TS of the odd electron over the three-body system. There have been several attempts since that time to calculate reaction rates in terms of the components of the rate constant in the familiar Arrhenius equation $k = A \times \exp(-E_a/RT)$ or in Eyring's well-known formulation $k = (k_B T/h) \times \exp(-\Delta S^{\ddagger}/R) \times \exp(\Delta H^{\ddagger}/RT)$. For the most common type of atom abstractions, those of hydrogen transfer, the approximation can be made that $A \approx 10^{9\pm 1}$ for many reactions, and a successful calculation of the energy of activation would allow a decent estimate to be made of the rate constant and its temperature dependence. One of the early successes with a large variety of hydrogen abstractions was the BEBO method, despite a small number of failures.¹³⁸ The method calculated bonding energies at various distances using a bond energy–bond order correlation of Pauling and, significantly, a repulsive term between the terminal atoms A–C to calculate the energy hill from reactants to TS. Since that time, there have been many attempts to improve such calculations. Some are strictly empirical formulating parametric equations based on fitting to a large number of experimentally known energies of activation. One typical example is the work of Roberts and Steel.¹³⁹ A typical semiempirical approach is that of Formosinho *et al.*¹⁴⁰ With the advent of accurate quantum mechanical calculations there have been *ab initio* theoretical efforts. Examples are the study of the reaction of ethyl radical with ethylene¹⁴¹; hydrogen abstractions from alkanes by H and CH₃ via GA values based on CBS-Q calculations¹⁴²; the reactions of carbon radicals with thiols¹⁴³; CBS-QB3 calculations of hydrogen abstractions by alkyl radical from hydrocarbons¹⁴⁴; assessing various theoretical procedures for H abstraction by methyl radicals from benzene¹⁴⁵; and comparisons of various high levels of theory, testing for performance with hydrogen abstractions by variously substituted carbon radicals from methane and additions to variously substituted alkenes.¹⁴⁶ All these efforts however have not produced a basic, intuitive understanding of the factors involved, one that would allow us to guess whether a particular hydrogen abstraction would have a high or low energy of activation, without performing any calculations. One drawback of high-level *ab initio* calculations is that, even when they produce the correct result,

they do not necessarily provide an intuitive feeling or understanding of the physical process.

Typical of the current state of affairs is a recent account on “Understanding Hydrogen Atom Transfer.” It is pointed out that *tert*-butylperoxyl radicals abstract hydrogen from phenol about 10^5 times faster than from toluene, even though the O–H and C–H bonds broken are about the same strength, around 370 kJ mol^{-1} . It is pointed out that, evidently, bond strengths are not the only determinant of hydrogen-atom transfer reactivity. The reasons for the generally slower H transfer between carbon radicals compared to H transfer between oxygen radicals is described as “having been discussed, but no simple picture has emerged.”¹⁴⁷ The fact is that bond strengths are a major factor in controlling energy barriers to H-atom transfer, but not the bond strengths that were mentioned in the account or one would usually consider.

In a lecture of a chemical kinetics class some time ago, specifically when energies of activation were being presented, a student piped up saying “You have no idea what controls energies of activation. Do you?” Students in Brooklyn will do this sort of thing. The fact of the matter is that it is not that difficult to get a feeling of what is going on. For the reaction $\text{X-H} + \text{Y}^\bullet \rightarrow \text{X}^\bullet + \text{H-Y}$, London had it right in 1929. It is simple: you have three species XH, HY, and XY. You have bonding and you have antibonding; that is all, except for the resonance. The latter is no problem. We know that the resonance stabilization of the allyl radical is about 59 kJ mol^{-1} for delocalizing one electron over three atoms. Similar delocalization over three atoms in TSs probably produces about the same stabilization. At the TS, the strength of the bond being broken must equal the strength of the bond being made. H is going from the potential energy curve of X–H to the potential energy curve of H–Y. The TS is where the two curves cross, the hydrogen is at that point, and both curves have the same zero of energy. Hence, the partial bonding of $\text{X}^\bullet \cdots \text{H}$ must be equal to the partial bonding of $\text{H}^\bullet \cdots \text{Y}$. Bonding at various X–H bond lengths can be approximated by the Morse equation for $\text{X}^\bullet \cdots \text{H}$. The bond length of $\text{H}^\bullet \cdots \text{Y}$ required to match the bonding of $\text{X}^\bullet \cdots \text{H}$ is easily obtained from the H–Y Morse curve. At the TS, there are three canonical forms that can be written for the three electrons: $\text{X} \uparrow \downarrow \text{H} \uparrow \text{Y} \uparrow$, $\uparrow \text{X} \text{H} \downarrow \uparrow \text{Y}$, and $\text{X} \uparrow \text{H} \downarrow \text{Y} \uparrow$. Because H is simultaneously bonded to both X and Y, the three electrons

must be either $\uparrow \downarrow \uparrow$ or $\downarrow \uparrow \downarrow$. It follows that the electron spins on X and on Y must be parallel. This is antibonding and it is implicit in London’s original equation, even though he did not point it out.¹⁴⁸ There is an approximate equation proposed by Sato for calculating antibonding (the anti-Morse curve). At any equibonding combination of X–H and H–Y bond lengths, the Sato function can be evaluated and its repulsive term can be added to the bonding term. A zero-point energy correction can be applied to the total energy. The TS is at the combination of stretched bond distances that produces the lowest barrier between reactants and products. This is the calculated energy barrier, similar to the Arrhenius activation energy. The computer program that does all this requires the information needed for constructing the empirical bonding and antibonding curves: For X–H, H–Y, and X–Y: BDE, equilibrium bond length, IR stretching frequency, and masses of the directly bonded atoms. The program executes in less than 0.1 s and its results match well experimentally determined energy barriers for hundreds of hydrogen abstractions involving many types of X–H and of Y.⁵⁴ The details of the calculation are not important. The lesson learned is that mostly, but not exclusively, the energy of activation goes into overcoming the triplet repulsion between X and Y.¹

Returning to the reaction $\text{tert-BuOO}^\bullet + \text{H-OPh}$ versus $\text{H-CH}_2\text{Ph}$, it is not the strength of the bonds broken and made that controls the height of the barrier in this case. In this essentially thermoneutral reaction, it is the X–Y antibonding that must be overcome, the triplet repulsion. Antibonding energy is proportional to BDE. With (21) and values from Table 7, $\text{BDE}[\text{CH}_3\text{OO-OPh}] = 35.8 + 7.5 + 96.23(3.303 - 3.377)^2 = 43.8$ and $[\text{CH}_3\text{OO-CH}_2\text{Ph}] = 35.8 + 139.3 + 96.23(3.303 - 2.506)^2 = 236.2 \text{ kJ mol}^{-1}$. Antibonding at the TS is almost nonexistent for $\text{ROO}^\bullet + \text{H-OPh}$ and this is why phenols are such a good hydrogen donors to the autoxidation chain-propagating species $\text{ROO}^\bullet$. There is a simple picture.

Phenol is not a particularly good free-radical trap for other radicals. In abstraction by benzyl radicals from phenol, the antibonding species is $\text{PhCH}_2\text{-OPh}$, with $\text{BDE} = 219.7 \text{ kJ mol}^{-1}$. This reaction will not be nearly as fast as abstraction by $\text{ROO}^\bullet$. It must not be forgotten that phenols do not inhibit the polymerization of styrene. Walling polymerized styrene in *m*-cresol solvent!¹⁴⁹ While the

molecular weight of the polymer was of the order of 33 000 rather than the 150 000 obtained in the absence of phenolic solvents, it clearly demonstrated that phenols are not particularly good inhibitors of all free-radical chain reactions.

Good antioxidants are not only those that easily transfer a hydrogen atom to peroxy radicals. The product radical formed must not be able to combine with $\cdot\text{OO}\cdot$ and thus continue the chain reaction. 1,4-Cyclohexadiene has C–H bonds about as weak as the O–H bond of α -tocopherol, but is not an antioxidant because it reacts with $\cdot\text{OO}\cdot$ to form $\text{ROO}\cdot$ that continues the chain. Table 7 has the information required for calculating the strength of the bond that $\text{PhO}\cdot$ will make with $\cdot\text{OO}\cdot$. $\text{BDE}[\text{PhO}-\text{OO}\cdot] = 7.5 + (-98.2) + 96.23(3.376 - 3.225)^2 = -88.5 \text{ kJ mol}^{-1}$. Bond formation is endothermic and it does not occur. O_2 would react with the ring carbons of phenoxyl radical to make hydroperoxyl radicals that continue the chain, but those positions are all blocked in α -tocopherol and other manmade antioxidants.

The simple picture of looking at the molecule that is never present in hydrogen abstractions, the chimera X–Y antibonding species, explains many types of reactions in which a stronger O–H bond is attacked in preference to a weaker C–H bond. *tert*-BuO $\cdot$ radicals abstract the phenolic hydrogen of *p*-HOC₆H₄CH₂C₆H₄-*p*-OH rather than the benzylic hydrogens where the C–H bond is 25 kJ mol^{−1} weaker than O–H.¹⁵⁰ The antibonding species is *tert*-BuO–OR in the preferred abstraction, much weaker with less triplet repulsion than *tert*-BuO–CHAr for the shunned abstraction. The experimental activation energy for H abstraction from the N–H group of dimethylamine is smaller than abstraction from a C–H, even though the latter is the weaker bond. The reason for this is that the preferred abstraction has an O–N antibonding group, while the less favored abstraction has O–C. O–N bonds are weaker with less triplet repulsion than O–C bonds and generate smaller energy barriers.¹⁵¹ Abstraction by hydroxyl radicals from methylamine occurred only 37% of the time from one of the three C–H bonds and 63% from the N–H bond, even though the latter is 35 kJ mol^{−1} stronger (Table 1) and has a statistical disadvantage of 3:1.¹⁵² Even though this aspect was not fully addressed, it is clear that a major, if not the controlling, factor is the relative BDEs of the antibonding

species; O–N bonds being weaker than O–C bonds cause smaller triplet repulsion and lower barrier.

Triplet repulsion explains the often reported “compensation effect” that is observed in hydrogen abstractions that are not particularly exothermic, but proceed with very low energies of activation. The pre-exponential Arrhenius term that is related to entropic effects tends to drop rather precipitously compared to similar reactions with higher activation energies. Although this has been observed several times, there is no broad acceptance of any particular explanation for the effect. If the low energy of activation is caused by low triplet repulsion at the TS, as it is for reactions of peroxy radicals abstracting H from phenols, then one should expect exactly such an effect. The low repulsion allows the X and Y terminal groups to approach more closely for a tighter TS structure and, therefore, more unfavorable entropy of activation.

Very similar thermoneutral reactions with similar X–H, H–Y, and X–Y BDEs can show significantly different energies of activation. CH₃–H + $\cdot\text{CH}_3$ has $E_a \approx 60 \text{ kJ mol}^{-1}$ while H–H + $\cdot\text{H}$ has E_a less than 38. Their BDEs are about the same. Another lesson learned is that, everything else being equal, the reaction that has the higher IR frequency for X–Y has the lower E_a . This is so because high frequencies produce narrower potential energy curves. At a given distance, antibonding will be smaller when the curve is narrow. In comparing the reactions CH₃–H + $\cdot\text{CH}_3$ and CH₃–H + $\cdot\text{OC}(\text{CH}_3)_3$, the abstraction by *tert*-butoxyl radical has a much lower energy of activation even though the bonds involved are fairly similar in BDE. However, the IR stretching frequency of the antibonding species CH₃–OC(CH₃)₃ is much higher than that of CH₃–CH₃ and this produces lower antibonding at the same distance and lower E_a .⁵⁴

6 SUBSTITUENT EFFECTS ON BDE AND ON RATES OF ATOM ABSTRACTIONS

Effects on BDE of Y substituents are of different types. Effects of meta and para ring substituents on benzylic BDE[YC₆H₄CH₂–X] and effects on BDE[YCH₂–X].

Abstractions of benzylic H from substituted toluenes by various radicals have been studied

extensively. All such abstractions occur with negative slopes in Hammett plots. Electron-withdrawing substituents retard the rate of abstraction. Some older reports of positive Hammett slopes were found to have been caused by then unsuspected radical additions to the ring.¹⁵³ Conversely, rates of abstraction of benzylic halogen atoms are always enhanced by electron-withdrawing substituents. Polar effects in the TS were routinely used to explain these facts, but it is now established that benzylic bond dissociation enthalpies are affected by ring substituents. When the bond dipole is toward the ring, $\text{ArCH}_2 \leftarrow \text{H}$, electron-withdrawing substituents stabilize the molecule, increasing the benzylic BDE, which results in slower rates of abstraction. That this is a BDE effect present in the parent molecule is shown by the dependence of $^{13}\text{C}-\text{H}$ coupling constants on the electron-donating or withdrawing ability of Y in the NMR of substituted toluenes, the magnitude of the coupling constant being proportional to the percent of s character of the bond and thus its strength.¹⁵⁴ The same trend of the effect of Y on reaction rates is also followed by quasi-benzylic bonds such as those of $\text{ArO} \leftarrow \text{H}$ and $\text{ArNH} \leftarrow \text{H}$, that have bond dipoles in the same direction. When the benzyl-X dipole is away from the ring, as in $\text{YC}_6\text{H}_4\text{CH}_2 \rightarrow \text{halogen}$, electron-withdrawing substituents destabilize the molecule and weaken the benzylic bond, which results in faster rates of halogen abstraction irrespective of the abstracting radical. This is an effect present in the parent molecules and is a net thermodynamic effect on the enthalpy of reaction, not an evanescent TS effect.^{155,156} In considering factors affecting in opposite ways the rates of abstraction of hydrogens versus halogens, the relative stabilization of the benzyl radicals formed is irrelevant because benzylic atom abstraction from $p\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{-H}$ or from $p\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{-Cl}$ produces the same radical.

For non-benzylic bonds, the most extensive work available consists of theoretical calculations at the level of G3(MP2)-RAD for a group of 64 YCH_2 radicals and their bonds to H, Cl, CH_3 , and the symmetrical $\text{YCH}_2\text{-CH}_2\text{Y}$; for the latter, there is no effect of bond dipoles on BDE.³¹ The most strengthened BDEs in the symmetrical compounds were those caused by the powerfully electron-withdrawing substituents $\text{Y} = \text{CH}_3\text{SO}_2$ and CF_3 . Electron-donating Y's cause a decrease in such BDEs. The range of BDE for the 64

Y is a substantial 112 kJ mol^{-1} . Some values of BDE in the upper and lower parts of this range are as follows: $\text{CH}_3\text{SO}_2\text{CH}_2\text{-CH}_2\text{SO}_2\text{CH}_3$, 403.4; $\text{CF}_3\text{CH}_2\text{-CH}_2\text{CF}_3$, 402.0; $\text{HOCH}_2\text{-CH}_2\text{OH}$, 361.8; $\text{HSCH}_2\text{-CH}_2\text{SH}$, 321.8; $\text{H}_2\text{NCH}_2\text{-CH}_2\text{NH}_2$, 318.2; $\text{CH}_3\text{NHCH}_2\text{-CH}_2\text{NHCH}_3$, 313.1; and $(\text{CH}_3)_2\text{NCH}_2\text{-CH}_2\text{N}(\text{CH}_3)_2$, 291.3. For comparison, $\text{BDE}[\text{CH}_3\text{CH}_2\text{-CH}_2\text{CH}_3] = 366.8$ and $\text{BDE}[\text{C}_6\text{H}_5\text{CH}_2\text{-CH}_2\text{C}_6\text{H}_5] = 277.0$. From the above evidence, one may infer that $(\text{CH}_3)_2\text{NC}^*\text{H}_2$ is more stable than $\text{CH}_3\text{SO}_2\text{C}^*\text{H}_2$ because it takes less energy to form it by cleaving the symmetrical bond. However, the same calculation showed that $\text{BDE}[(\text{CH}_3)_2\text{NCH}_2\text{-Cl}]$ is stronger than $\text{BDE}[\text{CH}_3\text{SO}_2\text{CH}_2\text{-Cl}]$ by 7.3 kJ mol^{-1} , not weaker as would have been expected from the above inference. This is because the substituent does not only affect the inherent bonding ability of the carbon radical or its stability/instability, but it also affects its electronegativity: $\chi[(\text{CH}_3)_2\text{NC}^*\text{H}_2] = 2.28$ and $\chi[\text{CH}_3\text{SO}_2\text{C}^*\text{H}_2] = 2.80$; from Table 7, $\chi[\text{Cl}^*] = 3.174$. As a result, the C-Cl bond dipole in $(\text{CH}_3)_2\text{NCH}_2\text{-Cl}$ contributes 76.9 kJ mol^{-1} to the BDE, while the C-Cl dipole in $\text{CH}_3\text{SO}_2\text{CH}_2\text{-Cl}$ contributes only 13.5. The interplay of both DE and of electronegativity must be considered as is done with the DE and χ values of Table 7.

7 CONCLUSION

A wealth of thermodynamic information, both experimental and theoretical, has become available. This has helped increase dramatically our understanding of radical reactions and has facilitated their use in many areas of chemistry, biology, and technology. Both experimental and theoretical contributions have been described in this article. Their impact on our understanding radical reactivities has been significant, but much still remains unclear and differences of opinion in rationalizing the known facts still exist.

END NOTES

^a See Ref. 36. The authors report high level theoretical calculations yielding $356.1 \text{ kJ mol}^{-1}$ for the enthalpy of formation of the ground state triplet ethylidene.

^b. See Ref. 37. Values calculated by a group additivity scheme fashioned on the basis of CBS-QB3 theoretical calculations. The reported GAV values are reduced here by 6 kJ mol^{-1} because the calculated values are invariably too high by an average of 6 kJ mol^{-1} when compared to available experimental values.

^c. See Ref. 43. The authors report $\Delta_f H^\circ$ [1-ethylcyclohexanol] = $\Delta_f H^\circ$ [cyclohexanol] – 28.6 = $(-290 \pm 8) - 28.6 = -321.8 \pm 8 \text{ kJ mol}^{-1}$.

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Radical Kinetics and Clocks

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1 INTRODUCTION

The interest in organic radical chemistry increased tremendously in recent decades as synthetic methods for using radicals in fine chemical synthesis were refined and the occurrence of radical intermediates in productive biological processes became better understood. Both for synthetic planning with radicals and for mechanistic understanding of processes involving radical transients, the rate constants of radical reactions are critically important. Most radicals are highly reactive transients that couple with one another with diffusion-controlled rates, but most productive radical reactions require that the radicals react with closed-shell molecules with velocities that minimize the extent of radical–radical reactions. In order to achieve that condition in a preparative reaction, one must control velocities by the concentrations of reagents, and synthetic planning is greatly simplified when the rate constants for the radical reactions are available. The concept of applying radical kinetics for synthetic planning is well accepted by all contemporary organic chemists, and many radical rate constants were determined by organic chemists for that specific objective.

Radical rate constants can be measured directly in physical chemistry laboratories equipped with fast detection methods, typically by UV–visible spectroscopy, and pulse irradiation methods such as laser flash photolysis (LFP) or pulse radiolysis for generation of radicals. Alternatively, indirect kinetic methods can be accomplished in most organic chemistry preparative laboratories. In an indirect

method, products from competitive reactions are quantified after work-up by a spectroscopic or chromatographic technique, and the ratio of products, concentrations of reagents, and the known rate constant for one of the competing reactions, the so-called basis reaction, is used to determine the rate constant for the reaction of interest. This simple approach requires no special instrumentation, and it has been widely applied, often by chemists who wish to use the information in designing new conversions, and most of the radical kinetic data used in synthetic planning has come from indirect studies.

Radical reaction rate constants are an integral part of the description of radical reactions, and they are contained in most of the sections of this encyclopedia for the specific radicals of interest in each article. A comprehensive listing of radical kinetics is beyond the scope of this article, but absolute rate constants are listed here for representative values for some common reactions to demonstrate trends. The major focus of this article is on the application of competition kinetic studies that can be applied for a wide range of radical reactions and a cataloging of various types of “radical clocks” that can be used in competition studies.

When a radical process used as a basis reaction in indirect studies is a first-order rearrangement, the reaction is commonly termed a *radical clock*, an appellation used by Griller and Ingold in a seminal review published in 1980.¹ That report established guidelines for competition kinetic studies and can be credited with generally informing the organic community of the availability and utility of the methods. Radical clocks provide an obvious advantage

in experimental design because the basis reaction is self-contained, and one does not need to control concentrations of a trapping reagent. Nonetheless, the range of kinetics for which any given radical clock can be applied is limited because one cannot alter the rate constant of the clock reaction. Therefore, a collection of radical clocks with a wide range of rate constants is desired for studies of new reactions with various reactivities. In practice, such a repertoire of radical clocks exists for alkyl radicals,² but clocks for carbon-centered radicals with stabilizing groups and for heteroatom-centered radicals are less well established. In this article, radical kinetics and indirect kinetic methods are described with an emphasis on radical clocks. Direct kinetic studies are discussed in **Analysis of Radicals by EPR and Structures and Reactivity of Radicals Followed by Magnetic Resonance**.

2 CHAIN AND NONCHAIN RADICAL REACTIONS

2.1 Examples of Chain and Nonchain Radical Reactions

Productive radical methods can involve either chain reactions or nonchain reactions, which are described briefly here for reference in the kinetic discussions that follow. Most chemists are familiar with chain reaction applications, which are the most common. Nonchain radical reactions are less familiar, but they can be very useful for fine chemical synthesis and highly controlled radical polymerizations.

A radical chain reaction sequence is composed of three parts, initiation, propagation, and termination, as exemplified in the tin hydride reaction of an alkyl bromide shown in Figure 1. Radicals are formed in the initiation reactions, typically by thermolysis or photolysis of an initiator (see **Overview of**

Radical Initiation). The initiation sequence can be a single reaction that gives radicals that enter into a subsequent propagation reaction or a sequence of reactions as shown in Figure 1. The productive steps in the chain sequence are the propagation reactions. In each individual propagation reaction, the product radical is a reactant radical for another propagation step. The propagation sequence can be simple, involving only one or two elementary reactions, or it can be complex with many competing reactions. The termination reactions involve radical–radical reactions, either couplings or disproportionations, that give closed-shell products. In principle, a variety of radical–radical termination reactions could be occurring in a chain sequence, but that is seldom the case. Because many chain termination reactions occur at diffusion control, the major termination pathway will be radical–radical reactions between the most abundant radical at steady state, which is controlled by the relative rate constants of the elementary propagation steps. For example, in the chain sequence in Figure 1, the $\text{Bu}_3\text{Sn}^\bullet$ radical reacts with RBr with a second-order rate constant that is about 100 times larger than that for the reaction of radical $\text{R}^\bullet$ with Bu_3SnH . An absolute condition of the chain sequence is that the two propagation reactions have the same velocity, and, in the case where the concentrations of alkyl halide and tin hydride are equal, this requires that the $\text{R}^\bullet$ concentration at steady state is 100 times as great as the $\text{Bu}_3\text{Sn}^\bullet$ concentration. Therefore, if all radical–radical reactions occur at diffusion control, then 99% of the termination events will involve reactions of two $\text{R}^\bullet$ radicals.

Nonchain radical reactions also can be applied productively for synthesis. The hallmark of a non-chain sequence is that one of the radical intermediates is persistent under the reaction conditions, a condition that arises because self-termination of that radical is slow or reversible. For example,

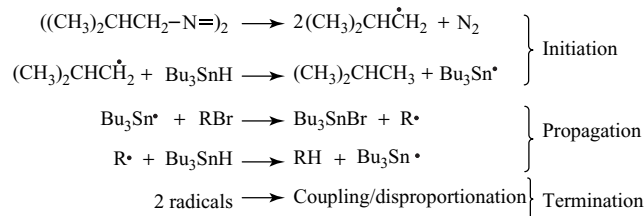


Figure 1 Tin hydride reduction of an alkyl bromide. Elementary steps in the radical chain reduction of an alkyl bromide with tin hydride.

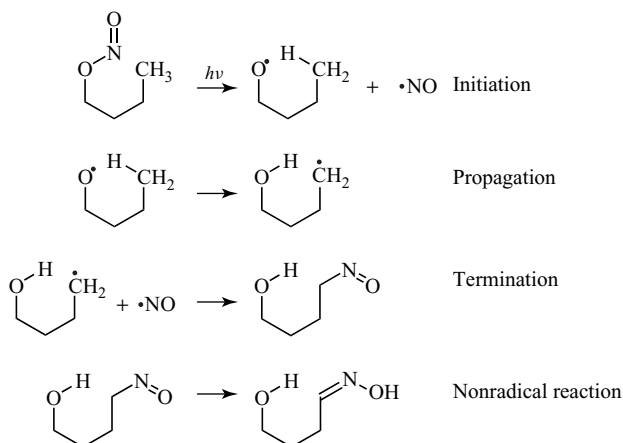


Figure 2 The Barton reaction. Photolysis of the nitrite ester gives an alkoxy radical and the NO radical, which is persistent. Internal hydrogen atom transfer of the alkoxy radical gives the carbon-centered radical that is trapped by NO to give the nitroso compound. Rearrangement of the nitroso compound to an oxime is a nonradical reaction.

nitroxyl radicals lacking β -hydrogen atoms such as the 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) radical have small equilibrium constants for dimerization, and the $\cdot\text{NO}$ radical is stable with respect to coupling. The persistent radical is reactive with other radicals, however, and when it accumulates to a relatively high concentration, it captures all other radicals in cross-termination reactions because of its high concentration. The general phenomenon where all radicals cross-couple without multiple propagation steps is termed the *persistent radical effect* or the *Ingold–Fischer effect* for the authors who initially described it succinctly (see **Nitroxides in Synthetic Radical Chemistry and Fundamentals of Controlled/Living Radical Polymerization**).^{3,4}

The Barton reaction,⁵ illustrated in Figure 2, is a nonchain radical reaction that involves the $\cdot\text{NO}$ radical. In this reaction, photolysis of a nitrite ester gives the $\cdot\text{NO}$ radical and an alkoxy radical, which can recombine in a nonproductive step. The alkoxy radical can abstract a hydrogen atom from a neighboring carbon atom to give an alkyl radical, and the alkyl radical formed in this process will react with the $\cdot\text{NO}$ radical in a termination reaction to give a nitroso compound that rearranges to an oxime in a nonradical process.

2.2 Kinetics of Radical Chain Reactions

Chain reactions have a unique set of rate expressions, and an understanding of radical chain reaction

kinetics can be useful in the design of efficient conversions. The key points in a chain reaction are that (i) each propagation step in the chain sequence must have the same velocity and that (ii) under steady-state conditions that are obtained in a chain sequence, the velocity of the initiation sequence is equal to the velocity of the termination sequence. Because of these equalities, a series of steady-state assumptions can be made that result in the rate law for the chain reaction in terms of a few key rate constants for elementary reactions. Importantly, the rate constant for the slow step in the chain reaction, termed the *rate-controlling step*, is the only elementary propagation rate constant that appears in the rate law. For the radical chain reduction of an alkyl bromide with tin hydride shown in Figure 1, an alkyl radical reacts with tin hydride with a rate constant of about $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at room temperature,⁶ and the $\text{Bu}_3\text{Sn}\cdot$ radical reacts with an alkyl bromide with a rate constant that is about 100 times greater.⁷ If the reaction is initiated by thermal decomposition to azo-*bis*-isobutyronitrile (AIBN), then the total rate law for the chain reaction is given in (1). In (1), k_{init} is the first-order rate constant for the initiator homolysis step,⁸ f is the fraction of initiator radicals that escape from the solvent cage, k_{SnH} is the second-order rate constant for the rate-controlling reaction of alkyl radical with tin hydride, and k_{term} is the second-order rate constant for termination, often equal to 25% of the diffusion control rate constant due to the spin statistical requirement that radicals have proper

spin orientations to form singlet products, which occurs in 25% of the encounters of two odd-electron species.⁹ The rate law will be similar for photochemical initiation, but the k_{init} and f terms are replaced by the photon flux and quantum yield of the photolysis and, if the solution is not opaque, the absorbance.

$$\frac{d[\text{RX}]}{dt} = \frac{k_{\text{init}} f [\text{AIBN}]^{1/2} k_{\text{SnH}} [\text{Bu}_3\text{SnH}]}{2k_{\text{term}}^{1/2}} \quad (1)$$

With general knowledge of the rate constants for the elementary processes, one can predict the velocity of chain reaction. Consider the reduction of RBr with Bu_3SnH using AIBN initiation in refluxing benzene with the following concentrations: $[\text{RBr}]_0 = [\text{Bu}_3\text{SnH}]_0 = 0.2 \text{ M}$; $[\text{AIBN}]_0 = 0.005 \text{ M}$. The rate constants at 80°C are $k_{\text{init}} = 2 \times 10^{-4} \text{ s}^{-1}$ for AIBN homolysis, $k_{\text{SnH}} = 6.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{term}} = 1 \times 10^{10} \text{ s}^{-1}$, and $f \approx 0.5$. Under these conditions, the velocity of the chain reaction is about $3 \times 10^{-4} \text{ M s}^{-1}$, and the reaction would be complete in about 15 minutes. Substituting the slower reacting $(\text{Me}_3\text{Si})_3\text{SiH}$ ($k_{\text{SiH}} = 1.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 80°C) for the tin hydride would increase the reaction time to about 1 hour.

The importance of the rate-controlling reaction is readily understood by example. If one replaced RBr with RI as a radical precursor in the tin hydride example, the rate of reaction of $\text{Bu}_3\text{Sn}\cdot$ with RI would be increased to the diffusion-control limit, but the reaction of $\text{R}\cdot$ with Bu_3SnH would be unchanged. Therefore, the transient concentration of $\text{Bu}_3\text{Sn}\cdot$ would be reduced, but the overall velocity of the process would not be affected provided that the initiation reaction was unchanged. Alternatively, replacing the tin hydride with tris(trimethylsilyl)silane would result in a reduced rate for the overall reaction as noted above. In addition, the overall reaction also would be slowed if RBr was replaced with RCl as the radical precursor. In this case, the rate constant for the reaction of $\text{Bu}_3\text{Sn}\cdot$ with RCl is appreciably smaller than that for the reaction of the stannyl radical with RBr and, in fact, even smaller than that for the reaction of $\text{R}\cdot$ with tin hydride.⁷ The rate law for the overall reaction (1) would now contain the rate constant for the reaction of the stannyl radical with the alkyl chloride, and the velocity of the reaction would be reduced if other experimental details were unchanged.

2.3 Radical Chain Initiation Kinetics

In many conversions, radical chain reactions are initiated thermally by decomposition of an added initiator. For reactions conducted at elevated temperatures, Walling reported the following temperatures that gave 1-hour half-lives for decomposition of commercial or synthesized radical initiators (see **Overview of Radical Initiation**)⁸: di-*tert*-butyl peroxyoxalate, 45°C ; di-*tert*-butyl hyponitrite, 55°C ; AIBN, 81°C ; benzoyl peroxide, 91°C ; *tert*-butyl peroxybenzoate, 125°C ; and di-*tert*-butyl peroxide, 150°C . As a general rule, these temperatures can be considered to be typical reaction temperatures for the use of the particular initiator or a closely related initiator. A variety of thermal initiators exist, but it is noteworthy that Barton's PTOC (pyridine-2-thioneoxycarbonyl) ester radical precursors (see below for an example) decompose thermally in refluxing solvents such as tetrahydrofuran (THF) or toluene.¹⁰ Barton's PTOC esters also decompose when irradiated with visible light, which provides a convenient method for radical chain initiation at reduced temperatures.

A relatively new method of thermal initiation involves addition of a small amount of Et_3B to a reaction mixture that has not been degassed thoroughly.¹¹ The borane reacts with oxygen, apparently to generate ethyl radicals. The kinetics of this reaction are not available, but the reaction is known to be efficient at low temperatures, and this is an attractive method for initiation of radical reactions when one wishes to maintain low reaction temperatures to achieve selectivity in the conversions.

3 COMPETITION KINETICS AND RADICAL CLOCKS

3.1 Overview of Competition Kinetics

Although sophisticated instrumentation is needed for measuring radical kinetics due to the short lifetimes and small concentrations of radicals in typical reactions, kinetic studies can be accomplished in most wet chemistry laboratories without any special instrumentation by the use of competition experiments. The concept of the study is that a reaction with a known rate constant competes with

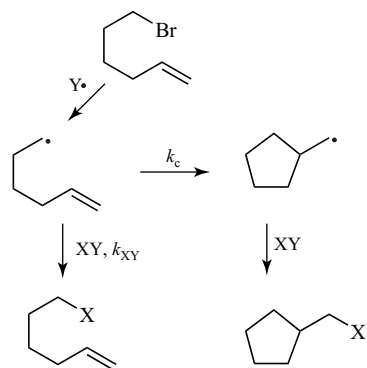


Figure 3 Reactions in a competition kinetic study. The 5-hexenyl radical cyclization competes with trapping by reagent XY, and the rate constant for the trapping reaction can be determined from the ratio of acyclic to cyclic products, the concentration of XY, and the known rate constant for cyclization.

the reaction with the unknown rate constant, and the unknown rate constant can be calculated from the product ratio obtained after the reaction, the concentrations of reagents employed, and the known rate constant. An example of a competition kinetic study is shown in Figure 3. In this sequence, the radical precursor, 6-bromo-1-hexene, reacts with Y[•] to give the 5-hexenyl radical, which is a “radical clock.” The clock cyclizes to the cyclopentylmethyl radical with a known rate constant (k_c), and the rate constant of interest is that for the reaction of trapping agent XY with the primary radical (k_{XY}). Because the cyclization reaction in this example is effectively irreversible, the rate constant for trapping the cyclic radical is not important. The ratio

of products is determined after the reaction, and the rate constant k_{XY} is calculated from that ratio, the concentration of trapping agent XY, and the known cyclization rate constant k_c .

3.2 Kinetic Expressions in Competition Kinetics

In a competition kinetic study, the products formed in the competing reaction are quantified, and the rate constant for the reaction of interest is determined from this product ratio, the concentrations of reagents, and a known rate constant for the basis reaction. If a unimolecular radical reaction (i.e., a radical clock, see below) is employed, the reaction is a first-order process by definition. From a practical perspective, it is most convenient to use large excesses of reagents in bimolecular processes such that pseudo-first-order conditions are maintained. Nonetheless, true second-order kinetics with changing concentrations of reagents can be handled with the correct kinetic expression. Table 1 contains the kinetic expressions that apply to some of the more common experimental designs.

The precision necessary for a rate constant is a function of the desired application. When high precision is needed, one should study the reaction with a variety of concentrations of the radical trapping agent to prevent errors due to reversibility of the clock reaction. Many first-order radical reactions are effectively irreversible, but the following example

Table 1 Kinetic expressions for competition kinetic experiments.^a

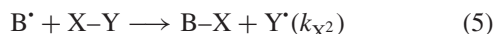
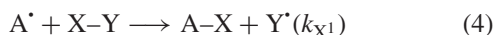
Type of study	Kinetic expression
First-order (k_1) vs pseudo-first-order (k_2)	$k_1/k_2 = ([R^1X]/[R^2X])([XY]_m)$
First-order (k_1) vs second-order (k_2)	$k_1/k_2(\ln([XY]_i + k_1/k_2) - \ln([XY]_f + k_1/k_2)) = [Sub]_i ([R^2X]/[R^1X]) (1 + ([R^2X]/[R^1X]))^{-1}$
Pseudo-first-order (k_1) vs pseudo-first-order (k_2)	$k_1/k_2 = ([RX^1]/[RX^2]) ([X^2Y]_m/[X^1Y]_m)$
Second-order (k_1) vs second-order (k_2)	$k_1/k_2 = (\ln([X^1Y]_i)/([X^1Y]_i - [RX^1]))/(\ln([X^2Y]_i)/([X^2Y]_i - [RX^2]))$
Reversible first-order(k_1) vs pseudo-first-order (k_2)	$(k_1/k_2)(k_2/(k_{-1} + k_2[XY]_m)) = [R^1X]/[R^2X]$

^aIn these expressions, the trapping agent is XY, which reacts by transfer of X to the radical. The subscript in $[XY]_i$ indicates initial concentration, that in $[XY]_f$ indicates final concentration, and that in $[XY]_m$ indicates average concentration. The rate constants k_x in the kinetic expressions are shown in the type of study column in parentheses. Products with superscripts 1 and 2 are those formed in the first and second reaction, respectively, in the type of study column.

illustrates the potential problem of reversibility. Ring opening of the cyclopropylcarbinyl radical (see Section 4) is a well-recognized fast radical reaction, and this reaction has been used as a competition reaction in many indirect kinetic studies. The equilibrium constant for the cyclopropylcarbinyl radical at 20 °C strongly favors the ring-opened product ($K \approx 10\,000$ at room temperature).¹² In the phenyl-substituted analog, the cyclopropylbenzyl radical, the ring opening of the cyclopropyl group is reasonably fast ($k = 6 \times 10^4 \text{ s}^{-1}$ at 20 °C¹²), but the ring-opened product is disfavored ($K = 0.012$ at room temperature).^{12,13} Nonetheless, the benzylic radical can still be used as a competing reaction in a competition study with appropriate caution.

A determination of a second-order rate constant at a single concentration of reagent would not provide a unique rate constant unless the trapping reaction of the ring-opened radical was fast relative to the back-reaction. However, this problem is avoided if one conducts a series of reactions at a variety of concentrations. Figure 4 illustrates the situation for the

case where radical $A^\bullet$ equilibrates with $B^\bullet$, and both radicals react with trapping agent XY to give products AX and BX. In this case, the ratio of products will change with the concentration of the trapping agent as shown in the idealized plot in Figure 4. The rate constants in this situation are described by (6). Note that the rate constants for the back-reaction and trapping reaction of the rearranged radical are not needed to obtain the rate constant for the trapping reaction of radical $A^\bullet$ with XY.



$$\frac{AX}{BX} = \frac{k_{X1}k_{R2}}{k_{X2}k_{R1}} + \frac{k_{X1}}{k_{R1}}[X-Y]_m \quad (6)$$

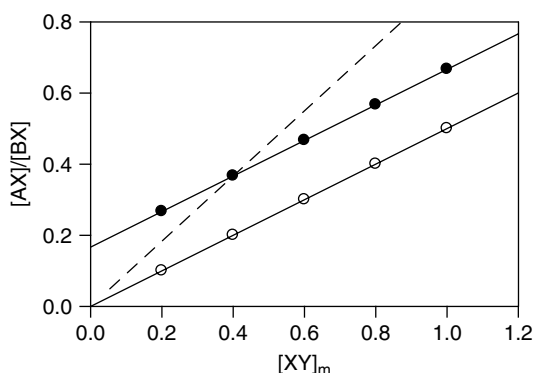


Figure 4 Results from hypothetical competition kinetics experiments for a radical clock reacting in the presence of bimolecular trapping reagent XY used in excess where the rearrangement has $k_{R1} = 1 \text{ s}^{-1}$, and the trapping reaction has $k_{X1} = 0.5 \text{ M}^{-1} \text{ s}^{-1}$. When the rearrangement is effectively irreversible, $k_{R2} \approx 0 \text{ s}^{-1}$, then the plot with an intercept at the origin (open symbols) is obtained. If the clock rearrangement is reversible with rate constant $k_{R2} = 3 \text{ s}^{-1}$ and the trapping rate constant for the rearranged radical is $k_{X2} = 1 \text{ M}^{-1} \text{ s}^{-1}$, then the plot with the solid symbols is obtained. The slopes of the lines give k_{X1}/k_{R1} , which is the same for both cases. If the reversible clock was studied only at 0.4 M concentration of XY with the assumption that the reaction was not reversible, however, then the dashed line would be obtained, and the derived trapping reaction rate constant would be in error by nearly a factor of 2.

3.3 Basis Reactions for Radical Clocks

Any kinetic method could be used to calibrate a radical clock, and several clocks were calibrated by direct EPR or UV-visible spectroscopy with flash lamp or LFP methods to generate the radicals. However, many carbon radical clocks were calibrated indirectly with a limited number of trapping agents. The two most common methods, the tin hydride method and the PTOC-thiol method, can be used for a wide range of radicals and are illustrated in this section.

3.3.1 The Tin Hydride Method

In the tin hydride method, the radical precursor is a halogen or pseudo-halogen and tributyltin hydride or another group 14 hydride is used as the trapping agent (see **Tin Hydrides and Functional Group Transformations**). Group 14 metal hydrides are the most completely calibrated family of radical trapping agents, and rate constants for reactions of Bu_3SnH , Ph_3SnH , $(\text{Me}_3\text{Si})_3\text{SiH}$, and Et_3SiH with many carbon-, nitrogen-, and oxygen-centered radicals are known.¹⁴ The most widely used reagent for calibration has been Bu_3SnH , which reacts with

alkyl radicals with rate constants that were determined using LFP methods in the early 1980s.^{6,15} These directly measured rate constants were combined with previously determined relative rate constants to give absolute rate constants for clock reactions. For example, cyclization of the 5-hexenyl radical in competition with tin hydride trapping was quite well studied by Walling in the late 1960s and early 1970s,¹⁶ and combination of the relative rate constants for those processes with the absolute tin hydride values gave absolute rate constants for cyclization of the 5-hexenyl radical and launched contemporary radical clock chemistry.

The experimental design for a tin hydride competition study is illustrated in Figure 3. The radical precursor typically is an alkyl halide or pseudohalide, although other radical precursors can be used. Tin hydride or other group 14 hydride is used in excess so that pseudo-first-order reaction conditions are maintained. In early studies, reactions were usually initiated by thermolysis of AIBN or a similar initiator at temperatures between 70 and 110 °C. In more recent studies, radical initiation by reaction of triethylborane with oxygen at room temperature or reduced temperatures has been common.

As in synthetic applications of radical chemistry, a competition kinetic study requires an efficient chain reaction sequence. For group 14 hydrides, tin and germanium hydrides react fast enough with alkyl radicals to maintain chain conditions, but

trialkylsilanes such as Et₃SiH do not. The substituted (Me₃Si)₃SiH (see **Silanes as Reducing Reagents in Radical Chemistry**) reacts considerably faster with alkyl radicals than common silanes, and this reagent is an excellent hydrogen atom trapping agent for alkyl radicals. For trapping more reactive radicals such as aryl, vinyl, and oxyl radicals, Et₃SiH is adequately reactive to propagate chain reactions.

In regard to the radical precursor limitations, the group 14 trialkylmetal radical must react efficiently with the precursor. Silyl radicals are highly reactive with various halides or pseudohalides, but stannyl radicals react only sluggishly with alkyl chlorides. For aryl and vinyl radical generation, iodides are recommended as the radical precursors. There is no direct counterpart for heteroatom radical generation in the tin hydride protocol.

3.3.2 The PTOC thiol method

The PTOC thiol method is a kinetic adaptation that employs Barton's PTOC esters (anhydrides of a carboxylic acid and the thiohydroxamic acid *N*-hydroxypyridine-2-thione) as radical precursors (Figure 5). In this method, the PTOC ester reacts to give an acyloxyl radical, and decarboxylation of the acyloxyl radical gives the target radical. The target radical can react with a wide range of

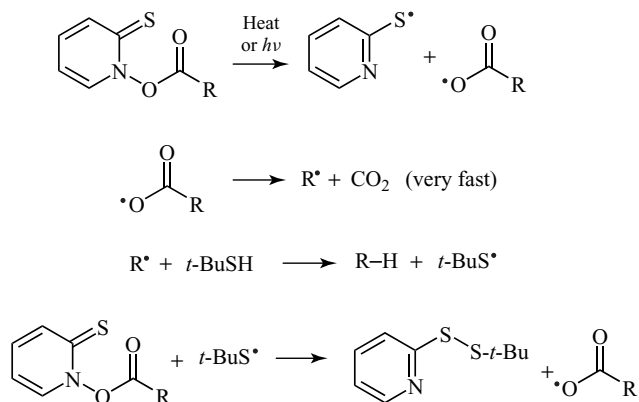


Figure 5 Fundamental reactions in the PTOC thiol method. The radical precursor is a mixed anhydride of a carboxylic acid and the thiohydroxamic acid, *N*-hydroxypyridine-2-thione, termed a PTOC ester. The PTOC ester decomposes thermally or photochemically with visible light irradiation to give an acyloxyl radical that rapidly decarboxylates to give the radical of interest. Reaction of that radical with a thiol competes with a rearrangement (not shown). The thiyl radical reacts with another PTOC ester molecule to give the disulfide product and another acyloxyl radical.

hydrogen atom donors including the highly reactive thiophenol and benzeneselenol (selenophenol), and the radicals formed from the hydrogen atom transfer step react with another molecule of PTOC ester in a propagation step.

The PTOC thiol method has two significant advantages over the tin hydride method as well as two significant disadvantages. Owing to the high reactivity of the thione group in the PTOC ester and related radical precursors, a wide range of propagating radicals can be used including any group 14 atom centered radical and the group 16 thio- and seleno-centered radicals. This feature opens the kinetic method to the use of highly reactive H-atom transfer agents, such as benzeneselenol. In addition, the PTOC ester methodology has been extended to the production of nitrogen- and oxygen-centered radicals, which were not readily available in the tin hydride method. On the negative side, the high reactivity of the thione group results in relatively efficient reactions of the precursors with carbon-centered radicals,¹⁷ and it is difficult to “time” a slow carbon radical reaction by this method because the radical precursor will intercept the carbon-centered radicals in a “self-trapping” reaction. The other disadvantage of the method is due to the requisite intermediacy of the acyloxyl radicals; acyloxyl radical precursors to aryl and vinyl radicals will not decarboxylate rapidly enough to avoid some trapping of these radicals by many H-atom trapping agents.

4 RADICAL CLOCKS

Competition kinetic methods commonly employ radical clocks,¹ which are calibrated unimolecular radical reactions. The clock reactions are cyclizations, fragmentations including ring openings, or migrations that involve initial cyclizations and subsequent ring openings. The primary advantage of a radical clock is that the competition reaction is self-contained and additional reagents are not necessary, but this property works to limit the useful dynamic range of a clock.

4.1 Carbon Radical Clocks

Alkyl radical clocks are the most numerous, with calibrated clocks ranging in rate constants at room

temperature from 300 s^{-1} to greater than $3 \times 10^{11}\text{ s}^{-1}$. Table 2 contains a representative selection of alkyl radical clocks.^{6,15,16,18–30} This collection is intended to show the breadth of calibrated clocks employing examples that are not especially difficult to prepare and whose products are reasonably easy to characterize. The Arrhenius functions should be considered operational equations that predict rate constants reasonably well but do not necessarily provide highly accurate entropies and enthalpies of activation. Most of the kinetic values were determined from competition kinetic studies using the rate constant for the reaction of Bu_3SnH as the basis reaction, which illustrates the fundamental importance of the tin hydride rate constants.^{6,14}

Substituted alkyl radical clocks are well represented in the context of 5-exo cyclizations with rate constants in the range of 1×10^5 to $1 \times 10^8\text{ s}^{-1}$ at room temperature (Table 3).^{6,16,31–35} A noteworthy point of these rate constants is the similarity of the values for both series of monosubstituted (i.e., secondary) radicals. For the tertiary radicals, however, significant reductions in rate constants were observed for the planar conjugated radicals (carboethoxy and cyano substituents), and this effect is most likely due to steric compression in obtaining the transition state for cyclization as opposed to stabilization due to the substituent.³⁴

Some benzyl radical clocks are available. A problem with these clocks is that the high stability of the benzyl radical limits the number of reactions possible. For example, the 5-exo cyclization shown in Figure 6 is slow,²¹ and the ring opening of the cyclopropylbenzyl radical, while reasonably fast, is reversible with the cyclic product favored.^{12,13} For the (2-phenylcyclopropyl)benzyl radical, the phenyl

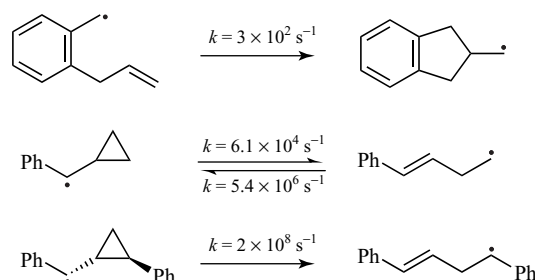
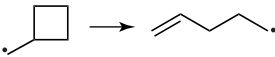
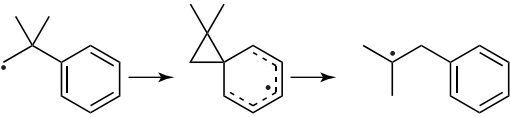
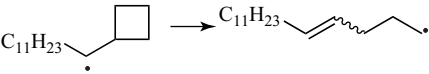
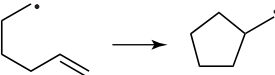
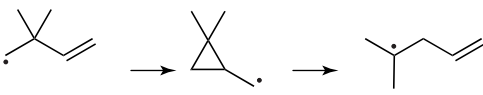
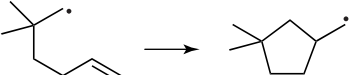
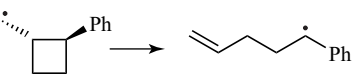
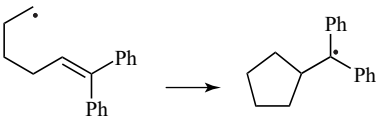
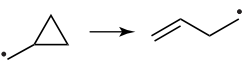
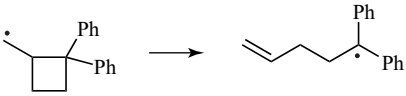
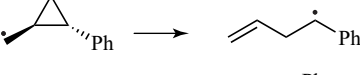
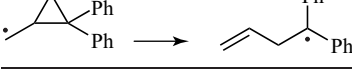


Figure 6 Examples of benzyl radical clocks. The rate constants are for reactions at room temperature.

Table 2 Representative alkyl radical clocks.^a

Reaction	Arrhenius function	$k_{(20\text{ }^{\circ}\text{C})}$ (s ⁻¹) ^b	Basis ^c	References
	12.6 – 12.2/θ	300	Tin hydride	18–20
	11.55 – 11.82/θ	500	Tin hydride	21
	13.2 – 13.5/θ	1300	Tin hydride	22
	10.37 – 6.85/θ	1.8 × 10 ⁵	Tin hydride	6, 16
	11.00 – 5.88/θ	4.1 × 10 ⁶	Tin hydride	6
	9.9 – 4.4/θ	4.1 × 10 ⁶	Tin hydride	15, 23
	13.1 – 8.0/θ	1.3 × 10 ⁷	Direct	24
	10.40 – 3.63/θ	4.9 × 10 ⁷	Direct	25
	13.15 – 7.05/θ	7.8 × 10 ⁷	Various	26
	12.7 – 5.04/θ	2.5 × 10 ⁸	Direct	27
	13.0 – 5.2/θ	1.3 × 10 ⁹	PhSeH	28, 30
	13.9 – 3.3/θ	2.7 × 10 ¹¹	PhSeH	29
	13.1 – 2.0/θ	5 × 10 ¹¹	PhSeH	29

^a Arrhenius function in which the activation energy is in kcal mol⁻¹; θ = 2.3RT in kcal mol⁻¹.

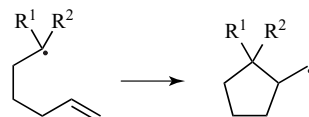
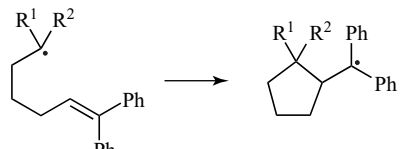
^b Rate constant at 20 °C.

^c Basis method for measuring the clock reaction; tin hydride competition, direct studies via laser flash photolysis, or benzeneselenol competition.

groups at the radical center and incipient radical center cancel one another, and the rate constant for ring opening is similar to that for ring opening of the unsubstituted parent, the cyclopropylcarbonyl

radical.³⁶ It is noteworthy that all three of the benzyl radical reactions shown in Figure 6 are about 3 orders of magnitude slower than the reactions of the corresponding primary alkyl radicals.

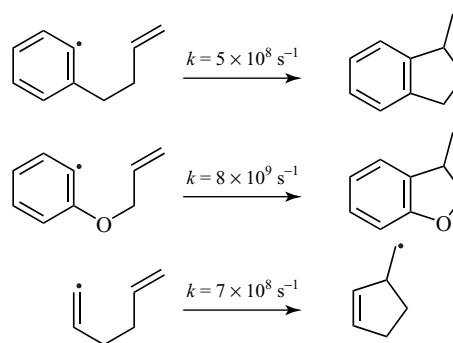
Table 3 Rate constants for substituted alkyl radical clocks

			
R ¹	R ²	<i>k</i> _(20 °C) (s ^{−1}) ^a	References
H	H	1.8 × 10 ⁵	6, 16
CH ₃	H	1.1 × 10 ⁵	31
CH ₃	CH ₃	2.6 × 10 ⁵	31
CO ₂ Et	H	1.4 × 10 ⁵	31
C(O)NEt ₂	H	0.9 × 10 ⁵	32
OCH ₃	H	1.6 × 10 ⁵	31
			
H	H	3.7 × 10 ⁷	25, 33
CH ₃	H	2.2 × 10 ⁷	33
CH ₃	CH ₃	1.1 × 10 ⁷	33
CO ₂ Et	H	5 × 10 ⁷	34
C(O)NEt ₂	H	2 × 10 ⁷	32
OCH ₃	H	4 × 10 ⁷	34
OH	CH ₃	9.1 × 10 ⁷	35
CO ₂ Et	CH ₃	3.3 × 10 ⁵	34
C(O)NEt ₂	CH ₃	3 × 10 ⁵	32
CN	CH ₃	2.1 × 10 ⁵	34

^aRate constants at 20 °C in units of s^{−1}.

Aryl and vinyl radical clocks are not well represented. In early studies, diacylperoxide precursors to the phenyl and 2,2-dimethylvinyl radical were irradiated with laser light with the intention of producing the corresponding acyloxyl radical that could decarboxylate. Rate constants for reactions of tin hydride were determined in these studies,¹⁵ but it was later learned that the initially formed acyloxyl radicals did not decarboxylate completely before reaction with the tin hydride.

In more recent studies, a rate constant for the reaction of an aryl radical with tin hydride at room temperature was determined to be $k = 7.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.³⁷ If this value is used with previous competition kinetic results, the rate constants at 25 °C for cyclization of the aryl radicals shown in Figure 7 are 5×10^8 and $8 \times 10^9 \text{ s}^{-1}$ at room temperature.¹⁵ The relative rate constant

**Figure 7** Examples of aryl and vinyl radical clocks. The rate constants are for reactions at room temperature.

for cyclization of vinyl radical in Figure 7 and trapping by tin hydride is 0.9 M at 80 °C.³⁸ If one assumes that the rate constant for tin hydride

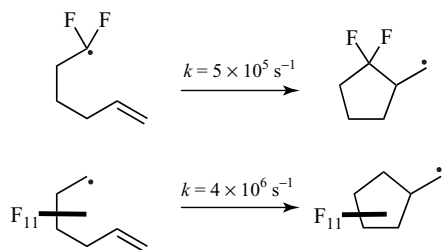


Figure 8 Examples of fluorocarbon radical clocks. The rate constants are for reactions at 30 °C.

reaction with the vinyl radical is equal to that for reaction with the aryl radical, then the rate constant for cyclization of the vinyl radical clock in Figure 7 is $7 \times 10^8 \text{ s}^{-1}$; the assumption is based on the fact that vinyl and alkene C–H bond energies are quite similar.

Products from fluorocarbon radical reactions are of high commercial interest owing to the stability of the polymers and the low refractive index of fluorocarbons. Cyclizations of a series of fluorine-containing 5-hexenyl radicals³⁹ and other fluorine-containing radical cyclizations⁴⁰ have been studied. Two examples are shown in Figure 8.³⁹

4.2 Nitrogen Radical Clocks

A number of nitrogen-centered radical clocks have been calibrated, most by direct LFP. Some early nitrogen radical clock calibrations were attempted by the kinetic EPR method,⁴¹ but the method is difficult to interpret when no comparative values are available. The advantage of the direct LFP approach is that absolute kinetic values can be obtained with good accuracy and precision in many cases, but the disadvantage is that the clocks might not be appropriate for a wide range of studies. In order to detect the products in LFP studies, many of the clocks were designed to give UV–visible detectable benzylic or diphenylalkyl radicals. In indirect studies with these clocks, these relatively stable product radicals might not react efficiently with trapping agents in follow-up reactions, which can result in high radical concentrations that interfere with an indirect kinetic study. Nonetheless, with appropriate control reactions, these clocks can be used in indirect kinetic studies when the trapping agents are

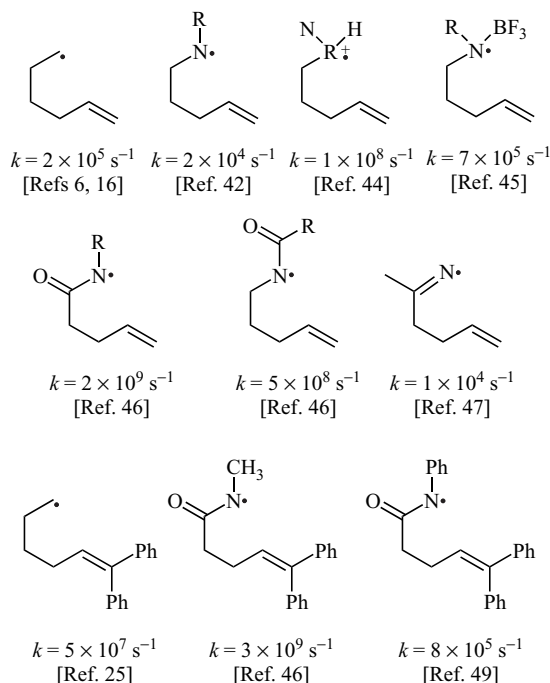


Figure 9 Nitrogen radical clocks that react by cyclizations. The rate constants for 5-exo cyclizations at room temperature are listed.

highly reactive as in reactions of tin hydrides or thiols.

Figure 9 shows a number nitrogen-centered radical clocks involving 5-exo cyclizations, and Figure 10 shows nitrogen radical clocks that react by fragmentations. In both figures, appropriate carbon radical clocks are provided that permit comparisons with carbon radical analogs. Aminyl radicals are relatively low reactivity species in addition to alkenes,⁴² but fragmentations that produce a relatively stable imine π -bond are fast.^{42,43} Protonated dialkylaminium radical cations have long been known to be highly reactive,⁴⁴ and Lewis acid complexed aminyl radicals lie between the extremes of the neutral and protonated forms.⁴⁵ Amidyl radicals are much more reactive species than α -carbonyl carbon radicals,⁴⁶ but iminyl radicals are much less reactive than the carbon analog vinyl radicals.⁴⁷ In a predictable manner, phenyl substitution to give the nitrogen equivalents of benzyl radicals results in apparent low reactivity in a cyclopropane-substituted aniline radical cation⁴⁸ and in a variety of anilidyl radicals.⁴⁹

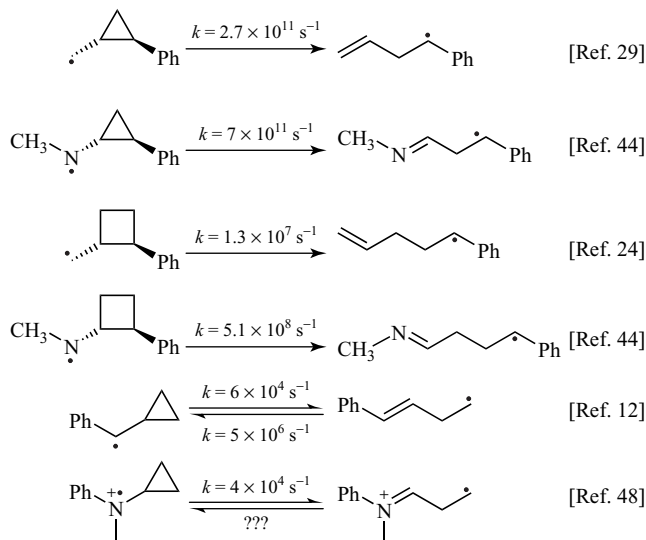


Figure 10 Comparisons of nitrogen radical fragmentations to carbon radical reactions. The rate constants are for reactions at room temperature.

4.3 Oxygen Radical Clocks

Oxygen-centered radicals are highly reactive species in comparison to carbon-centered radicals. The archetypal oxygen radical clock reaction is fragmentation of the *tert*-butoxyl radical to give acetone and a methyl radical, which has been studied for half a century.⁵⁰ Relative rate constants for competing fragmentation and reaction of the oxyl radical with solvent were reported long ago,⁵¹ and precise absolute rate constants were later determined by LFP methods.⁵² Most of the calibrated oxygen radical clocks are fragmentations similar to the *tert*-butoxyl radical reaction,^{53–55} but cyclizations,⁵⁶ intramolecular hydrogen abstraction,⁵⁷ and rearrangements⁵⁸ have also been calibrated.

Figure 11 shows examples of oxyl radical clocks. One noteworthy point is that oxygen radical kinetics is sensitive to solvent polarity effects; for example, the rate constant for fragmentation of the *tert*-butoxyl radical in water is more than 100 times greater than that for fragmentation in CCl_4 .⁵² Another important point is that an oxyl radical ring opening can be reversible, as seen in the cyclopentanoxyl radical,⁵⁵ although the carbon-centered radical product is favored thermodynamically.

4.4 Acyl Radical Clocks

Fragmentations of acyl radicals give alkyl radicals and carbon monoxide, and these decarbonylation reactions are reversible when conducted at high CO pressure. Several kinetic studies were conducted, and a number of results were collected in an overview published in 1987.⁵⁹ Some examples of acyl radical clocks are shown in Figure 12.^{60–64} The kinetics of these reactions was obtained over a wide temperature range and should be among the more accurate values available.

5 KINETIC TABLES

Radical reaction rate constants are presented in many of the articles in this encyclopedia in conjunction with the other details of the chemistry of the radicals. In this section, some of the more commonly encountered second-order rate constants are collected for convenient reference. These include rate constants for hydrogen atom transfer reactions from the more common radical reducing agents and addition reactions of carbon-centered radicals to various alkenes.

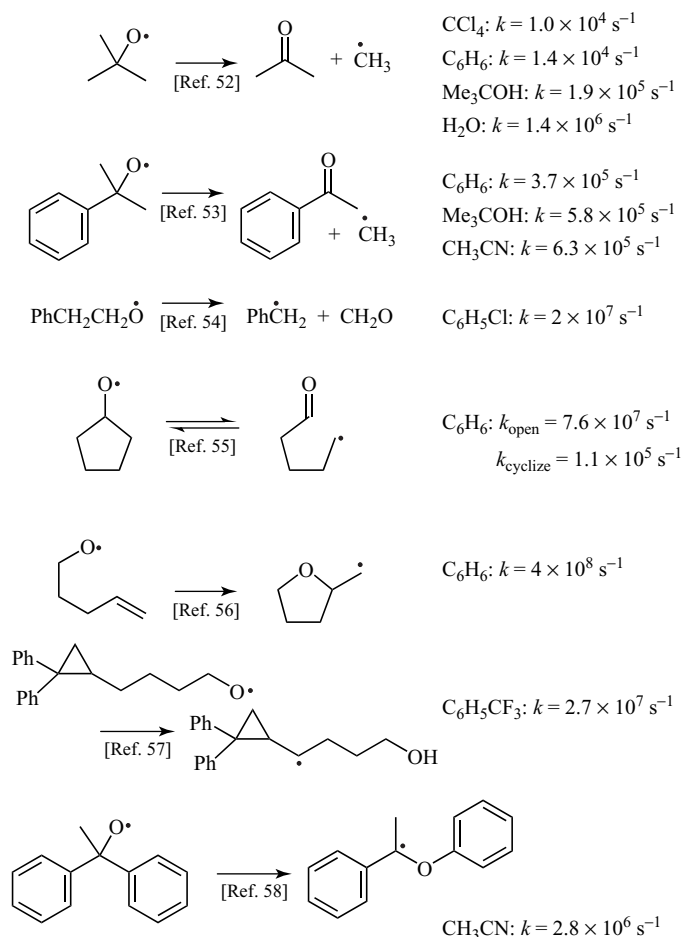


Figure 11 Examples of oxygen-centered radical clocks. The rate constants in units of s^{-1} are for reactions at approximately room temperature.

5.1 Hydrogen Atom Transfer Kinetics

Table 4 contains rate constants for the reactions of some of the more commonly employed hydrogen atom transfer reactions. Hydrogen atom transfer reactions of group 14 hydrides and group 16 hydrides are the best characterized radical reactions kinetically, and Table 4 lists values for the most commonly employed reagents.

The most commonly employed radical reducing agent has been tributyltin hydride, Bu_3SnH , which has been used extensively for half a century and is the species referred to as *tin hydride*. Triphenyltin hydride, Ph_3SnH , is more reactive than Bu_3SnH .

Tributylgermanium hydride is somewhat less reactive than Bu_3SnH ; it can be used in many radical reactions, but it seldom has been. Simple trialkylsilanes such as Et_3SiH react too slowly with alkyl radicals to propagate a chain reaction sequence, but the activated silane *tris(trimethylsilyl)silane*, $(\text{CH}_3\text{Si})_3\text{SiH}$, reacts fast enough with carbon radicals to be useful (see **Silanes as Reducing Reagents in Radical Chemistry**). A contemporary review of group 14 hydride reagents and their radical reactions contains the most comprehensive collection of kinetics for these reagents.¹⁴

For comparisons with the other group 14 hydrides, the rate constants for reactions of the

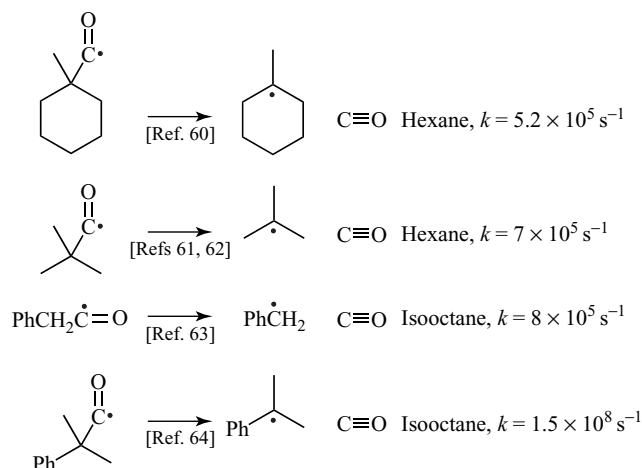


Figure 12 Examples of acyl radical clocks. The rate constants are for reactions at room temperature.

Table 4 Rate constants for hydrogen atom transfer reactions at room temperature.^a

Radical	(Me ₃ Si) ₃ SiH	Bu ₃ SnH	<i>t</i> -BuSH	PhSH	PhSeH
<i>t</i> -BuO•	1.1×10^8	2.0×10^8			
R ₂ NH ^{•+}		2.4×10^{8b}	3.4×10^{6c}	4.3×10^7	
RC(O)N [•] R'		1.3×10^9		1×10^8	
R ₂ N•	Circa 34 ^d	4.3×10^5	6×10^6	1.1×10^8	2×10^9
R ₇ CF ₂ •	5.1×10^7	2.0×10^8		3×10^5	
C ₆ H ₅ •	3×10^8	7.8×10^8			
RCH ₂ •	3.9×10^5	2.5×10^6	6×10^6	9×10^7	1.2×10^9
PhCH ₂ •		3.2×10^4		2.8×10^5	
RC(O)•	1.8×10^4	3.9×10^5	2×10^{6e}		Circa 4×10^9

^aRate constants in units of M⁻¹ s⁻¹ at room temperature unless noted. References: for alkyl radicals with group 14 hydrides, Ref. 14; for alkyl radicals with group 16 hydrides, Ref. 33; for aminyl radical, Refs 14, 42; for amidyl radicals, Ref. 46; for benzyl radical, Ref. 65; for fluorocarbon radicals, Ref. 66; for acyl radicals, Refs 14, 67, 68.

^bFor reaction of Ph₃SnH.

^cFor reaction of octanethiol.

^d2,2,6,6-tetramethylpiperidine radical.

^eReaction with “*tert*-dodecanethiol” at 80 °C.

silane hydrogen of Et₃SiH with *tert*-butoxyl radical and a simple alkyl radical at room temperature are 4.6×10^6 and $3.2 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, respectively.^{14,69,70} Note that the methylene hydrogens in Et₃SiH also are transferred to radicals, resulting in somewhat larger overall rate constants than those quoted here. Also for comparison purposes, Bu₃GeH reacts at room temperature with *tert*-butoxyl and alkyl radicals with rate constants of 9.2×10^7 and $9.5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, respectively.^{14,70–72} Triphenyltin hydride has been well studied and the rate constants for reactions

with many radicals have been collected¹⁴; Ph₃SnH reacts somewhat faster than Bu₃SnH.

Group 16 hydrides are well-known hydrogen atom donors. Phenols have long been used as inhibitors for spoilage, but thiols are more commonly applied in synthetic applications, and benzeneselenol is a highly reactive trapping agent. Thiols are highly reactive hydrogen atom transfer agents with nucleophilic radicals such as alkyl radicals. Many thiols are readily available, and *tert*-butylthiol rate constants are relatively well

studied. Thiophenol is highly reactive, and benzeneselenol reacts at close to diffusion control at room temperature.^{21,25,26,29,30,33,65–67}

The group 16 hydrides are limited to some extent in their applications in that the thiyl and selenyl radicals will not abstract halogen atoms from an alkyl halide radical precursor, although they can be used with the PTOC class of radical precursors developed by Barton and coworkers.¹⁰ Nonetheless, it is possible to use a group 16 hydride as fast radical trapping agents with an alkyl halide radical precursor if a group 14 hydride is added as a sacrificial reductant, a method termed *polarity reversal catalysis*.⁷³ For example, Et₃SiH and *t*-BuSH can be used in combination to reduce an alkyl halide. The thiol reacts rapidly with the alkyl radical, the thiyl radical thus formed will not react with the alkyl halide but does react with the silane to give a silyl radical, and the silyl radical then reacts efficiently with the alkyl halide. This method was also applied with (Me₃Si)₃SiH as sacrificial reductant in a calibration of rate constants for a collection of thiols reacting with alkyl and acyl radicals.⁶⁸ In a similar manner, one can generate PhSeH *in situ* by reaction of PhSeSePh with Bu₃SnH and use the combination of the diselenide and tin hydride as an efficient reducing agent with alkyl halide radical precursors.⁷⁴ In passing, one should note that chalcogenide (or pseudohalide) radical precursors such as RSPH or RSePh can be contaminated with impurities of dichalconides PhSSPh and PhSeSePh, respectively, which are reduced by Bu₃SnH to give the highly reactive hydrides PhSH and PhSeH; thus, it is possible to generate a highly reactive radical reducing agent unintentionally when pseudohalide radical precursors are employed.⁷⁴

A new aspect of hydrogen atom transfer to alkyl radicals is evolving at the time of this writing. Owing to the toxicity of tin-containing compounds, chemists have sought “tin-free” alternatives for many years. For example, Derek Barton noted that the family of PTOC ester radical precursors he and his coworkers developed in the 1980s¹⁰ were aimed in part at removing the need for tin hydride in radical applications in synthesis. More recently, there has been progress in using water and simple alcohols as hydrogen atom donors toward radicals. The strong OH bond in water is significantly weakened by complexation with Lewis acids, and water and alcohols complexed

with boron species have been shown to react with carbon radicals.^{75,76} A kinetic study of the reactions of triethylborane-complexed water and methanol found the rate constants for reactions on the order of $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at room temperature,⁷⁷ but an unusual entropic term was found, indicating that an equilibration preceded the rate-determining hydrogen atom transfer step. Recently, Renaud and coworkers (private communication from Dr. G. Povie for results from G. Poive, M. Marzorati, P. Bigler, and P. Renaud) found that the equilibrium constant for binding water and Et₃B was quite small at room temperature, a result consistent with the unusual entropic term obtained in the kinetic studies. This observation suggests that the measured rate constant for hydrogen atom transfer reactions of Et₃B complexed water and alcohols might be only a small fraction of the true rate constant, which might be nearly as great as that for tin hydride. One is encouraged to refer to contemporary studies reported after this review was written for recent progress in this area.

5.2 Additions to Alkenes

The rates of reactions of radicals with alkenes provides insight into the reactivities of the radicals and the substrates. A large collection of background data was accumulated by the late Hans Fischer and coworkers who studied reactions of radicals that can be classified as nucleophilic (α -oxygen substituted),⁷⁸ electrophilic (α -ester substituted),⁷⁹ and mixed (ambiphilic, alkyl)⁸⁰ reactivity. Table 5 contains collections of data that show the reactivities of various radicals with different alkenes. The table includes data from Dolbier and coworkers for reactions of the perfluoropropyl radical.⁸¹

A relative complete collection of rate constants for reactions of alkyl radicals with other unsaturated substrates is collected in Table 6.^{82–87} This data is presented in terms of relative rate constants because it was derived from both inter- and intramolecular reactions. It can be used as a predictor of radical reactivity for a given substrate in reactions with alkyl radicals and possibly other nucleophilic radicals, but one must be cautious about using this table for electrophilic radicals such as alkoxyl or perfluoroalkyl radicals.

Table 5 Rate constants for addition reactions of radicals to substituted alkenes at room temperature.^a

	CH ₂ =CHOEt	CH ₂ =CHR	CH ₂ =CHCO ₂ Me	CH ₂ =CHPh
(CH ₃) ₂ C(OH) [•]	32	1.1 × 10 ³	> 1 × 10 ⁷	2.2 × 10 ⁶
H ₃ C [•]	1.4 × 10 ⁴	7.6 × 10 ³	3.4 × 10 ⁵	2.6 × 10 ⁵
<i>t</i> -BuO ₂ CCH ₂ [•]	1.5 × 10 ²	54	4.9 × 10 ²	1.9 × 10 ³
C ₃ F ₇ [•]		6.2 × 10 ⁶	2.2 × 10 ^{6b}	4.3 × 10 ⁷

Data from Refs 78–81.

^aReactions at room temperature, rate constants in units of M⁻¹ s⁻¹.^bSubstrate was acrylonitrile.**Table 6** Relative rate constants for additions of alkyl radicals to unsaturated substrates at room temperature.^a

Substrate	Relative <i>k</i>	References
RCH=CH ₂	1.0	
R-C≡CH	0.075	82
R-C≡N	0.025	82
RCH=O	0.56	83
RCH=NR	3.75	84
C≡O	18	85
RCH=NOCH ₃	24	86
RCH=NNR ₂	39	86
CH ₂ =CHCH ₂ Si(CH ₃) ₃	40	87

^aRelative rate constant at room temperature determined by comparing kinetics of pairs of inter- or intramolecular reactions.

5.3 Radical Fragmentation Reactions

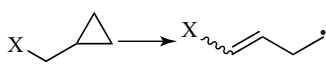
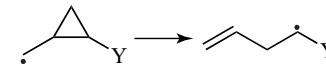
Radical fragmentations display kinetic effects that are similar to those observed in radical additions. The stability of the incipient radical center is the dominant feature in the kinetics for a series of fragmentations. Table 7 contains rate constants for a series of cyclopropylcarbinyl ring opening reactions that are collected from various sources.^{12,28,29,33,88–91} The entropic terms are quite similar for these reactions, and the enthalpic terms provide the major effects on the

kinetics. For the series of radical center-substituted cyclopropylcarbinyls, the rate constants are similar except in the case of the highly stabilized benzyl radical. On the other hand, the rate constants for the series of cyclopropylcarbinyl radicals that give substituted product radicals vary widely.

6 CONCLUSION

This overview of radical kinetics is intended to provide a foundation for designing indirect kinetic studies and the application of radical clocks in addition to background kinetic information on some of the more common radical reactions. Kinetic information is an integral part of the description of any radical reaction, and much kinetic information is presented in this encyclopedia in the specific articles describing various types of radicals. Radical kinetic studies have been a focus of interest for many years, and kinetic results fill volumes. Nonetheless, one should appreciate that most radical-based synthetic methods were developed without complete knowledge of absolute rate constants, which highlights the importance of a qualitative understanding of radical kinetics and reactivities.

Table 7 Rate constants for cyclopropylcarbinyl radical fragmentations.^a

			
X	<i>k</i> (s ⁻¹)	Y	<i>k</i> (s ⁻¹)
H	7 × 10 ⁷	H	7 × 10 ⁷
CH ₃	4 × 10 ⁷	CH ₃	1 × 10 ⁸
OCH ₃	2 × 10 ⁷	OCH ₃	1 × 10 ⁹
CO ₂ CH ₂ CH ₃	2 × 10 ⁸	CO ₂ CH ₃	7 × 10 ¹⁰
Ph	6 × 10 ⁴	Ph	1.5 × 10 ¹¹

Data from Refs 12, 28, 29, 33, 88–91.

^aRate constants in units of s⁻¹ for reactions at room temperature.

ACKNOWLEDGMENTS

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Structures and Reactivity of Radicals Followed by Magnetic Resonance

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1 INTRODUCTION

In most cases, radicals are rather short-lived and appear at low steady-state concentrations. One way of detecting them is to provide an inert environment, which precludes their quenching. Accordingly, radicals are often generated in rigorously dried solvents and the exclusion of air is substantial. Moreover, reaction partners, being able to convert radicals to diamagnetic species (e.g., by recombination reactions or electron transfer), have to be excluded. With such precautions, radicals can exist for several minutes or even hours and can be preferentially investigated by standard electron paramagnetic resonance (EPR) techniques. Such reaction conditions, however, cannot be met in all cases and, moreover “real time” detection and a kinetic analysis at a short timescale are highly desirable (Scheme 1).

Time-resolved EPR (TR-EPR) also denoted as CIDEF (chemically induced dynamic electron polarization) and CIDNP (chemically induced dynamic nuclear polarization) spectroscopy ideally meet these requirements. Both techniques rely on a trigger, which starts the generation of radicals (e.g., a laser or rapid mixing), and take advantage of magnetic-field effects (which are explained below).

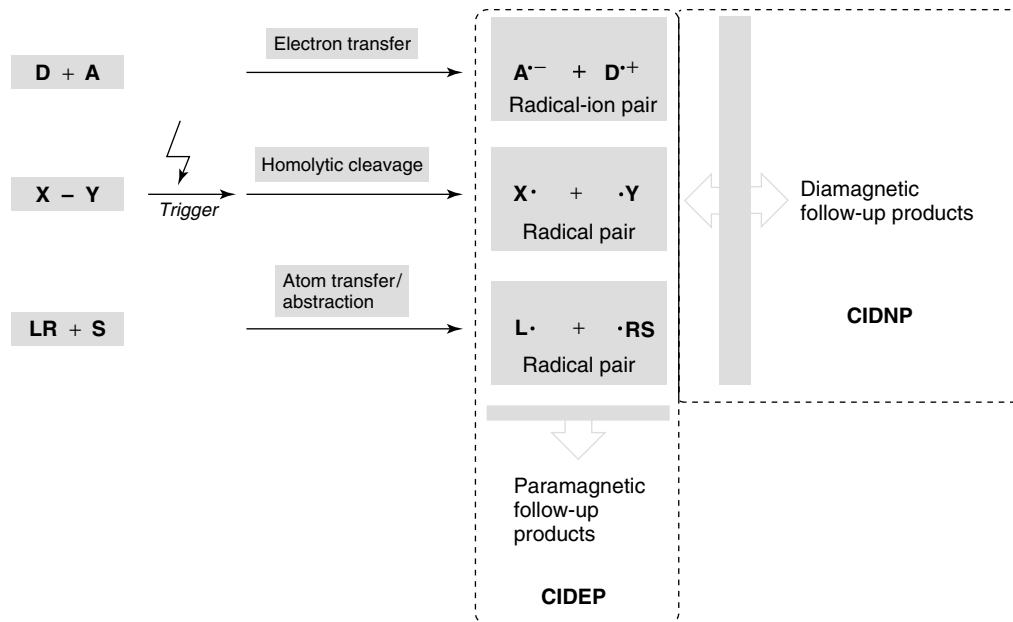
This article presents an elementary introduction to the principles underlying the detection of radicals at a nanosecond–microsecond timescale and introduces a couple of representative examples for the application of TR-EPR (CIDEF) and CIDNP. The common feature of these techniques is that they take advantage of “radical-pair” effects, which are active at applied magnetic field and lead to a substantial enhancement of EPR and nuclear magnetic resonance (NMR) lines, thereby making it possible to detect short-lived radicals generated at rather low concentrations (in the micromolar range).

The aim of this article is to introduce the principles underlying these techniques (see **Analysis of Radicals by EPR**) and present typical examples. The basic chemical reactions are presented in more detail and the applications of these fundamental reactivity patterns are sketched to illustrate the scope of CIDNP and CIDEF.

2 CIDNP

2.1 The Effects of Radical Pairs

During the last few decades, NMR spectroscopy has been established as a powerful analytical method in physics, materials science, chemistry, medicine, and biochemistry known for its high content of



Scheme 1 Radicals at short timescales and their detection by CIDNP and CIDEP.

information. Even highly complicated secondary, tertiary, and even quaternary structures become accessible by the application of advanced techniques. One major drawback is its comparatively low sensitivity resulting from the small energy gaps between the involved spin states, which leads to the necessity of developing high-field instruments, thereby limiting the application of NMR in many fields.

However, samples, in which fast free-radical reactions are taking place, often show substantially (up to three orders of magnitude) enhanced NMR signals. Moreover, such NMR spectra show perturbed intensities and phases for lines belonging to reaction products formed via paramagnetic intermediates. This phenomenon of nuclear hyperpolarization is called *chemically induced dynamic nuclear polarization (CIDNP)*.

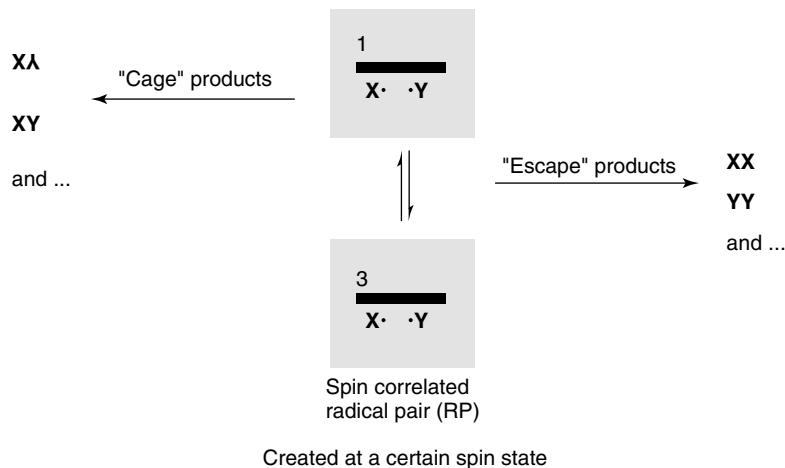
How can nuclear spins be involved in free-radical chemistry? The answer is based on the interaction between electron and nuclear spins and the total spin conservation in chemical reactions together with their spin selectivity. It is simple and easy: a chemical reaction is allowed only if the total spin of reactants coincides with the spin of the product (generally closed-shell singlet). Chemical reactions produce diamagnetic species from intermediate

radical pairs (RPs, Scheme 2). An RP has four states: one singlet state with antiparallel orientation of electron spins and three triplet states with their parallel mutual orientation.

Usually, only the singlet RP can form a product, while the triplet can not. Transition between triplet and singlet states is induced by the local magnetic field via *hyperfine interaction (HFI) of the unpaired electron with nuclei* and by magnetic interaction with the external static magnetic field. These phenomena are reflected in the NMR signals of the products formed via RPs at short timescales. Thus, CIDNP provides an indirect way for detecting elusive short-lived radicals, to determine their structure and reaction mechanisms. Several aspects of CIDNP spectroscopy were reviewed recently.¹

2.2 CIDNP—The Scope

The combination of pulsed Fourier transform-NMR (FT-NMR) and nanosecond pulsed lasers made a breakthrough in developing the method of time-resolved CIDNP (TR-CIDNP) detection that opens the way to monitor chemical reactions of radicals on the microsecond timescale by NMR. Here,



Scheme 2 The formation of radical pairs and their spin-selected follow-up reactions.

we first present an overview of the quantitative treatment of CIDNP to demonstrate the high potential and ability of the TR-CIDNP technique as analytical and informative tool in free-radical chemistry. The first part provides the reader with some phenomenological background and helps in understanding the TR-CIDNP technique and observations described thereafter. The experimental technique is a subject of the second section. Herein, the experimental setup for the acquisition of time-resolved spectra is depicted, applications of TR-CIDNP methods to the analysis of fast reactions and characterization of short-lived reaction intermediates are discussed, and the proportionality of CIDNP intensity to hyperfine coupling constants (HFCCs) is introduced. Experimental examples include photoinduced reactions of amino acids, nucleotides, peptides, and proteins. CIDNP as a tool to study intra- and intermolecular electron-transfer reactions is also considered in detail. The application of CIDNP to probe accessibility of the amino acid residues in proteins and protein folding is reviewed. The final part presents examples of determination of g -factors of radicals and electronic exchange interaction in biradicals from CIDNP field dependence.

2.3 CIDNP: Phenomenological Description

The term *chemically induced dynamic nuclear polarization* (CIDNP) is used for hyperpolarization

observed in the NMR spectra of reaction products resulting from a radical reaction that exhibit anomalous intensities and phases in their spectral lines. The CIDNP phenomenon illustrates the importance of the spin degrees of freedom in the chemistry of RPs. The origin of CIDNP is the spin-selective recombination of RPs, resulting from spin conservation during chemical reactions. CIDNP effects arise when the electronic triplet–singlet conversion of an RP is the bottleneck for the reaction. The leading mechanisms of its formation are well understood^{2–5} and shall be reviewed only briefly. Several tutorials,^{6–8} reviews,^{1,9,10} and monographs^{11–14} have appeared on the theory and CIDNP applications to organic chemistry.

Since its first report by Bargon *et al.*,¹⁵ CIDNP has been studied in detail and turned into a widely used tool for the investigation of chemical reactions with radical intermediates. Kaptein and Oosterhoff first developed the theory of the so-called radical pair mechanism (RPM),^{2,3} which is valid for CIDNP and for electron polarization (CIDEP; see Section 6). This mechanism depends on the existence of a stage of interaction between two radicals in a “cage,” when they constitute an RP (Scheme 2). The “cage” is, in principle, a time regime at which an efficient reaction between two radicals forming the pair occurs. In this region, the radicals react only within the RP, whereas the probability of their reaction with other radicals is negligible.

Two radicals constituting the RP diffuse with respect to each other; a reaction between them takes

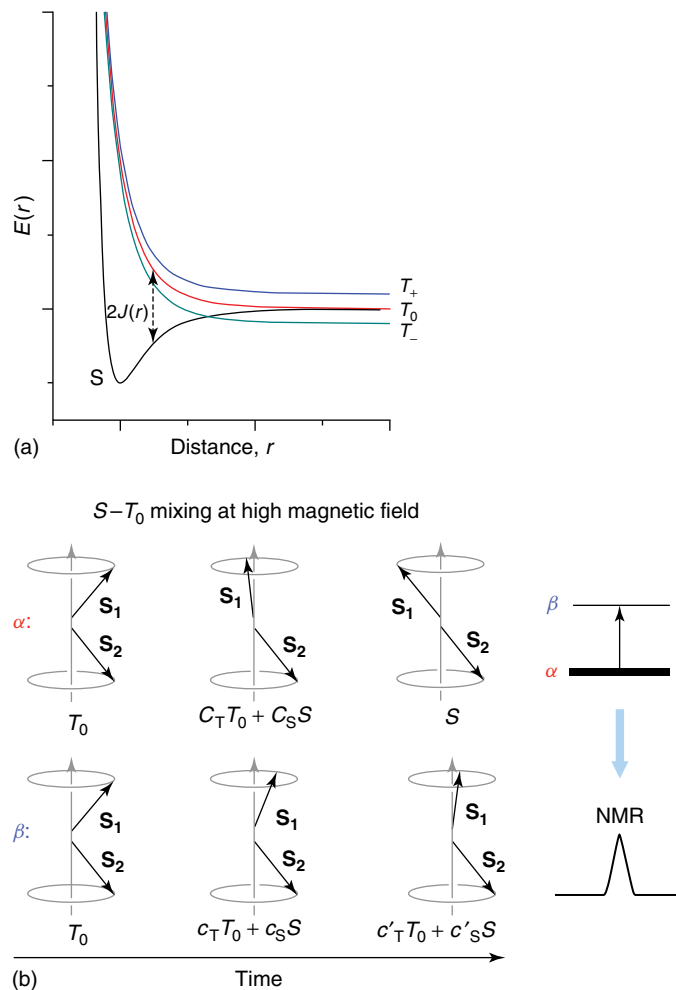


Figure 1 (a) Potential energy of a radical pair in a magnetic field as a function of interrational distance r . (b) Precession of electron spin vectors $\mathbf{S}_1$ and $\mathbf{S}_2$ of triplet-born radical pairs with α nuclear spin projection (upper row) and β nuclear spin projection (lower row) viewed in a frame rotating with $\mathbf{S}_2$. The recombination from singlet state is permitted, leading to enhanced absorption in the NMR spectrum of product.

place only at their direct contact. While caged, there is little mixing of the spin states because of the large electronic exchange energy, that is, the large singlet–triplet splitting in the spin-correlated pair at close distance. In addition, at high magnetic field, the energy levels of a triplet RP are split by Zeeman interaction into three sublevels: T_+ , T_0 , T_- (Figure 1). The magnitude of this splitting equals $g\mu_B B$, where g is the electron g -factor, μ_B is the Bohr magneton, and B is the magnetic-field strength. However, the exchange interaction, J , decreases exponentially with distance so that once the radicals are separated by the solvent molecules,

J becomes negligible and the energy difference between the S and T_0 spin states becomes small. In this case, the spin multiplicity of the RP can change under the influence of Zeeman and HFI as shown in Figure 1a. The electron spin state of the two radicals initially forming the RPs starts oscillating between triplet and singlet multiplicity because of their different Larmor frequencies, which depend on the electron g -factors of the two radicals and HFI. As a consequence of HFI, when the partner radicals in the spin-correlated RP re-encounter, they have different degrees of electronic singlet and triplet character depending on their nuclear spin states.

However, the lifetime of the RP is short compared to the oscillation frequency and, thus, only the beginning of the oscillations is seen. Consequently, the rate of multiplicity mixing is proportional to the difference in the Larmor precession frequencies, which is different for nuclear spin states (α and β) of the radicals (Figure 1b). For a positive HFI constant and a g -factor higher for the first spin S_1 than for the second S_2 , the Larmor frequency is higher for the RP with the nuclear spin oriented along the field (α -projection). For zero J , the rate of multiplicity mixing for RPs with α -projection is proportional to difference in g -factors and HFI constant, A , and equal to

$$\Delta_{\alpha,\beta}\omega = \left| \frac{\Delta\delta\mu_B B}{\hbar} \pm \frac{1}{2}A \right| \quad (1)$$

where A is the HFI constant. With the assumption that the reaction product formed at a re-encounter is a diamagnetic molecule in its singlet state, the probability of formation is proportional to the singlet character of the spin-correlated pair. Thus, the recombination product will be enriched in α nuclear spin states and depleted in β states (Figure 1b).

For RP at high magnetic field, (1) is extended readily to include as many nuclei as desired. Let the first radical have N magnetic nuclei with the HFCCs a_i and the second radical N' nuclei with the HFCCs b_j . Then the rate of singlet–triplet conversion ω for the certain nuclear spin state $\{M_1, \dots, M_N; M_1, \dots, M_{N'}\}$ is given by the expression¹⁶

$$\omega(M_1, \dots, M_N; M_1, \dots, M_{N'}) = \frac{1}{2}(g_1 - g_2)\mu_B B_0 + \frac{1}{2} \sum_{i=1}^N a_i M_i - \frac{1}{2} \sum_{j=1}^{N'} b_j M_j \quad (2)$$

Here, $\{M_i, M_j\}$ is the set of the z -projections of the nuclear spins in the selected spin state.

A simple analysis of CIDNP spectra detected at high field can be obtained by the empirically developed Kaptein's rules,¹⁷ which allow to predict the sign of the polarization (absorption or emission). For the net effect, the sign can be determined by four decisive parameters, according to the equation

$$\Gamma_i = (\mu)(\varepsilon)(\Delta g)(A_i) \quad (3)$$

where μ denotes the initial electron multiplicity of the RP at its formation (+ for triplet, – for singlet), ε the type of reaction leading to the observed products (+ for cage product, – for escaped products), $\Delta g = g_1 - g_2$ the sign of difference in g -factors of the two radicals (g_1 is the g -factor of the radical with nucleus under observation), and A_i the sign of the HFI constant. The sign product of these four parameters determines whether the sign, Γ_i , of the polarization for nucleus i indicates absorption (+) or emission (–).

The relative line intensities in the “geminate CIDNP” detected at high field can be calculated in the frame of Adrian's model.¹⁶

In fact, if an RP contains more than one magnetic nucleus, the above-described mechanism can give rise to two types of CIDNP effects: net and multiplet ones. In the case of two nuclei, there is a difference in the rate of electron multiplicity mixing for parallel and antiparallel mutual alignment of the two nuclear spins. The net effect occurs in the case of $\Delta g \neq 0$ as shown in Figure 1b. If $\Delta g = 0$, there can be no net polarization in any product but there can be a mixture of emissive and enhanced absorptive polarization—multiplet effect. This effect can be seen only if spins are scalar coupled in the diamagnetic product.

Here, we consider only the net CIDNP effect describing the net alignment of individual spins along the magnetic-field axis, and do not discuss more subtle effects such as the multiplet CIDNP effect that represents mutual ordering of spins. For the multiplet effect of two nuclei, there is the Kaptein's rule¹⁷ as well. The multiplet effects of higher orders can be revealed by their characteristic dependences on the detection flip angle.¹⁸ For high magnetic field of modern NMR spectrometers used for CIDNP detection, the term $\Delta g\mu_B B$ is not negligible in comparison with HFCCs; therefore, multiplet effects are usually weakly pronounced. Here, no multiplet CIDNP effect is further discussed.

Importantly, the above-mentioned effects are typically produced at a (sub) nanosecond timescale. However, the relaxation of the non-Boltzmann populated nuclear states is substantially slower, between hundreds of microseconds to seconds. This is the reason, why radical-pair-based reactions can be readily detected via the analysis of the reaction products with (essentially) standard NMR instruments.

2.4 Time-Resolved CIDNP

2.4.1 CIDNP Kinetics

CIDNP is a time-dependent effect. Nuclear polarization is formed in short-lived RPs and stored during relaxation times in diamagnetic reaction products, where it can be detected by NMR. Under continuous radical generation, only time-averaged or steady-state CIDNP spectra are detectable. In such conditions, CIDNP effects originating from primary RPs on nanosecond timescale cannot be discriminated from the radical reactions on microsecond timescale. Moreover, apparent polarization is heavily influenced by nuclear relaxation of the product. For photochemical reactions, submicrosecond time resolution in photo-CIDNP detection is achievable by the application of flash photolysis and by detection of polarization by FT-NMR at various delay times after the photolysis flashes.^{6,19–21} Although RPs can be formed in different ways, here only laser-induced photoreactions are discussed.

A liquid solution containing two types of molecules is considered, a dye (D) and a quencher (Q). For simplicity, the quencher molecule is assumed to have a single magnetic nucleus with spin 1/2 while the other molecule does not have any magnetic nuclei with HFI. Under light irradiation, the dye molecule absorbs a photon and is excited into a higher singlet state. After internal conversion followed by intersystem crossing (ISC) due to spin–orbit interactions, it reaches its lowest triplet state (Figure 2). The triplet formation in a molecule is usually fast ($\ll 1$ ns) compared to the laser pulse duration (5–15 ns). The next step is quenching of the triplet excited dye (3D) by the quencher molecule

(Q). This process strongly depends on the nature of the reactants and under the assumption that bimolecular reactions take place usually via electron (e) or, for example, hydrogen atom (H $\cdot$) transfer from Q to D or vice versa. Depending on the structure of the starting molecule and the quenching mechanism, the radicals formed can be charged or neutral. Another important factor influencing the quenching reaction is the nature of the solvent.

Since the total spin multiplicity does not change in the quenching process, the primary “geminate pair” is generated in a well-defined spin state (spin-correlated radical pair (SCRPs) denoted by an over bar). In the case considered, the RP is born in its triplet state (Figure 2). Subsequently, the RP can react to give geminate diamagnetic products or the radical partners can leave the “cage” by diffusing apart. The probability that the components of such a separated geminate pair re-encounter is finite, but falls off with time, and in low-viscosity solvents it becomes negligible after $\sim 10^{-7}$ s.

Let us assume that the RP is terminated by back e $^-$ or (H $\cdot$) transfer and can proceed only from an SCRPs with the same multiplicity as the subsequent ground state, which usually has singlet multiplicity. The rate of multiplicity mixing is proportional to the difference in the Larmor precession frequencies, which is different for nuclear spin states (α and β) of the radicals. For a positive HFI constant and a g -factor higher for Q $\cdot$ than for D $\cdot$, the Larmor frequency is higher for the RP with the nuclear spin oriented along the field (α -projection, denoted by “ $\uparrow$ ” in Figure 2). With the assumption that the reaction product formed at a re-encounter is a diamagnetic species in its singlet state, the probability of formation is proportional to the singlet character of the spin-correlated pair. Thus, the

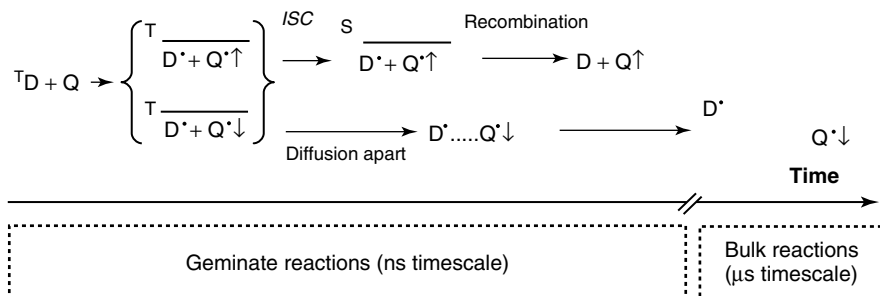


Figure 2 Radical pair mechanism of CIDNP formation in a low-viscosity solution at high magnetic field. Here, SCRPs are denoted by a bar. For details see the text.

geminate products will be enriched in α nuclear spin states, $Q\uparrow$, and depleted in β states, $Q\downarrow$ (Figure 2). This process termed *spin sorting* leads to nuclear spin polarization in the geminate products and to an equally large polarization of opposite sign in the remaining radicals. The spin-sorting process in typical organic radicals with HFCCs of 15–60 MHz takes no more than 10 ns, and geminate product formation stops after 100 ns. The number of radicals that react in the geminate stage is usually small, whereas most of them diffuse into the bulk. Escaped radicals can re-encounter and form escape products with opposite to geminate polarization (Scheme 2, Figure 2).

After the geminate stage, the polarization formation in RPs in the bulk, so-called F-pairs, continues until all radicals react to diamagnetic products (not shown in Figure 2). According to spin-sorting process described above, the time evolution of CIDNP has the shape depicted in Figure 3a. After a fast rise of the geminate stage, a slow decay of equal amplitude during escape reactions leads to compensation of CIDNP (black line). During the radical lifetime, nuclear spin lattice relaxation under influence of the unpaired electron (paramagnetic nuclear relaxation) is operative reducing the polarization in the radicals. Electron spin relaxation times are of the order of 10^{-6} s, while nuclear spin relaxation in

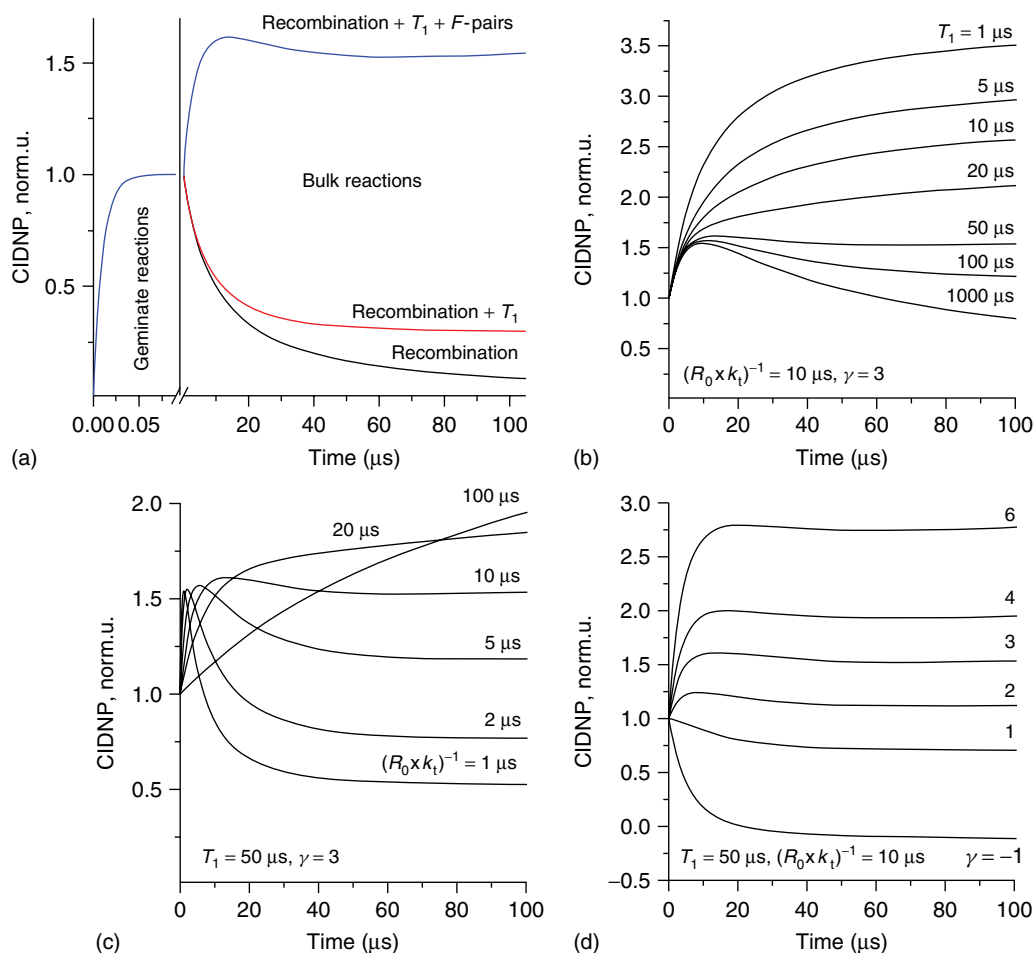


Figure 3 Kinetics of CIDNP, taking into account second-order radical recombination with the parameter $(R_0 \times k_t)^{-1} = 10 \mu s$ (black line), plus nuclear relaxation in radicals with $T_1 = 50 \mu s$ (red line), plus polarization generation in F-pairs with $\gamma = 3$ (blue line). All kinetics start with fast formation of the geminate polarization (a). Kinetics of CIDNP calculated at different values of T_1 (b), $R_0 \times k_t$ (c), and γ (d).

free radicals takes approximately 10^{-4} s. In contrast, the polarization in the diamagnetic reaction product relaxes at a much slower pace (diamagnetic relaxation). The paramagnetic relaxation leads to non-compensated polarization of the products at the end of the radical reaction (red line). Radicals form RPs in the bulk (so-called F-pairs) either in singlet or triplet state. For F-pairs in triplet T_0 state, the same rules of spin sorting as for the geminate RP are valid. Thus, F-pair polarization adds an increasing contribution into CIDNP (blue line).

In the case of cyclic reactions, the procedure of evaluating the CIDNP kinetics is described in Refs 22, 23. It is based on the set of differential equations suggested by Fischer.^{24,25} The polarization of one of the products in cyclic reaction (Figure 2) after the geminate stage is given by the following set of equations:

$$R(t) = \frac{R_0}{1 + k_t R_0 t} \quad (4)$$

$$\frac{dP(R)}{dt} = -k_t P(R)R - k_t \beta R^2 - \frac{P(R)}{T_1} \quad (5)$$

$$\frac{dP(\text{Pr})}{dt} = k_t P(R)R + k_t \beta R^2 \quad (6)$$

The formation of geminate RPs via triplet quenching is assumed to be instantaneous. Here, R_0 is the initial RP concentration, $R(t)$ the concentration of radicals (of the dye D or quencher Q) in the cyclic reaction, $P(R)$ the polarization of the radicals, $P(\text{Pr})$ the polarization of the diamagnetic products (which coincide with the initial species), k_t the rate constant of radical termination, and T_1 the paramagnetic nuclear relaxation time. Parameter β denotes the polarization per RP created in the so-called F-pairs. It is related to the geminate polarization P^G via the quantity γ , which denotes the ratio of polarization created in F-pairs with respect to the geminate polarization: $\beta = \gamma P^G / R_0$.²⁵ For a triplet precursor and a purely random statistics, $\gamma = 3$ is expected. In accordance with literature,^{24,25} $\gamma = 2.8$ was generally used.

In Figure 3, plots b, c, and d show how different parameters determine CIDNP kinetics. With the set of equations (4–6), CIDNP kinetics were calculated at different values of paramagnetic relaxation time T_1 (Figure 3b), of second-order termination reaction parameter $R_0 \times k_t$ (Figure 3c), and of different γ

values (Figure 3d); the CIDNP amplitudes formed after geminate stage of the reaction are set to unity. Thus, the shape of the kinetics is determined by three parameters: T_1 , $R_0 \times k_t$, and γ . The value of stationary CIDNP relative to the geminate polarization depends on the ratio of paramagnetic relaxation time and the radical lifetime. Relaxation destroys “escape” nuclear polarization during the radical lifetime. The more efficiently this CIDNP is destroyed, the higher is the stationary value of polarization (Figure 2).

The above considerations are valid for the case of triplet precursor. If the RP is born in singlet state, $\gamma = -1$. In this case, stationary CIDNP is much lower than the geminate one; its value and sign depend on nuclear paramagnetic relaxation time and radical lifetime. An example of such kinetics is shown in Figure 3d. However, CIDNP resulting from singlet precursor is very low, and there are no relevant examples in the literature. That is why CIDNP from singlet SCRPs is not described in details.

In noncyclic reactions, the equations become more complex and must be derived according to the reaction scheme.^{24,26,27} Below, CIDNP kinetics for cyclic and noncyclic reactions are presented using photoreactions of guanosine-52-monophosphate as an example. Before that, let us describe TR-CIDNP experimental setup.

2.4.2 The Time-Resolved CIDNP Experiment

In Figure 4, the typical TR-CIDNP setup is shown. It consists of FT-NMR spectrometer and pulsed laser. A probe head contains light guide for light irradiation of the sample from the side. The light of the laser is focused on the end of a light guide inserted in the probe head by an optical system, for example, by a quartz lens and a prism. The light guide is a cylindrical quartz rod with the upper end cut under 45° . This surface acts as a mirror to deflect the light by 90° , as it is done in the prism. The convex surface of the quartz rod acts as a cylindrical lens. After reflection on upper surface, the light beam is concentrated to achieve the optimal irradiation conditions of the sample. Another possibility of irradiation with a system of mirrors or prisms to route light to the NMR sample from above²⁸ is applicable for shared NMR

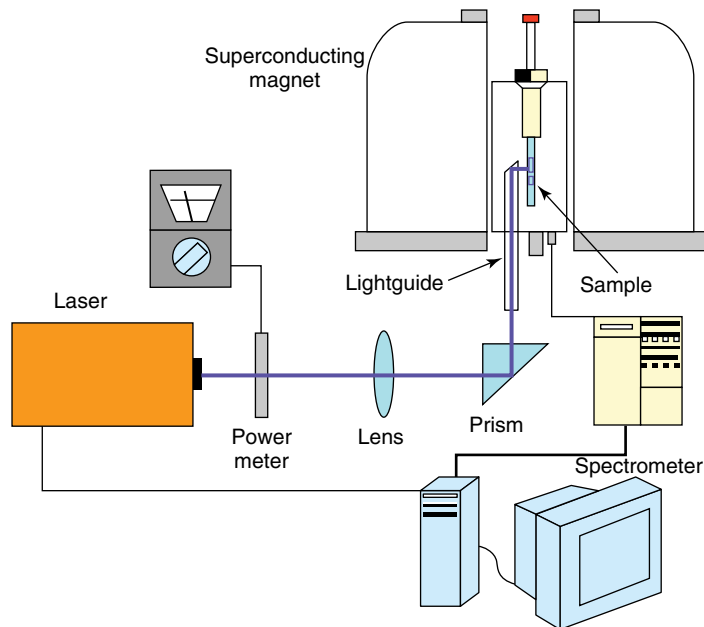


Figure 4 Scheme of the time-resolved CIDNP setup with side irradiation.

spectrometers equipped with multiuser multinuclear probes that could not be modified to permit sample irradiation.²⁹

The time sequence of the measurements is shown in Figure 5. The sample in the NMR spectrometer is irradiated by the laser. Before applying the laser pulse, it is advantageous³⁰ to remove any equilibrium polarization or residual CIDNP from the preceding sequence by a train

of homonuclear saturation pulses provided by the instrument's decoupler. This presaturation takes a few seconds and has the advantage that only pure CIDNP signals appear in the final spectrum. Shortly after the laser pulse is fired to initiate the RP reaction, and during an appropriate and variable delay, τ , the light-induced reactions evolve. Then a radiofrequency (RF)-pulse is applied to measure the magnetization of

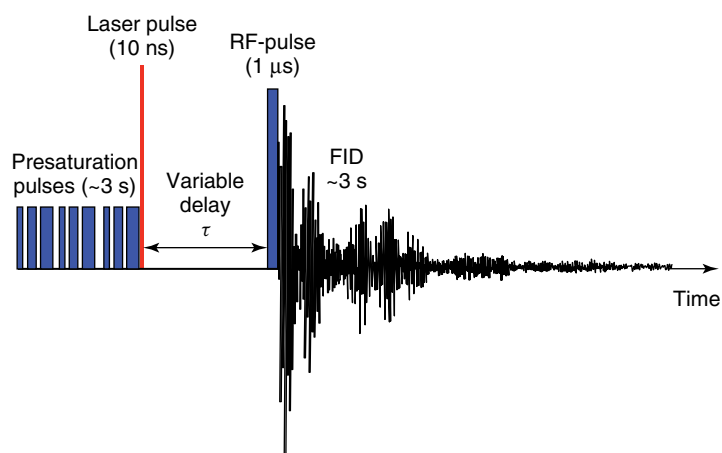


Figure 5 Pulse diagram of the TR-CIDNP experiment. The time axis has a nonlinear scale.

the diamagnetic polarized products formed during τ . For increasing the time resolution, although usually the duration of the pulse is much smaller than the duration of a $\pi/2$ flip angle, signal intensity is sacrificed. The free induction decay (FID) is acquired in the normal way and the experiment is repeated to obtain the desired signal-to-noise ratio. A kinetic profile of the appearance of the polarized products is obtained by varying τ .

This experiment monitors only the rates of formation of the final diamagnetic products. The paramagnetic intermediates cannot be seen as their spectral lines are much wider and shifted out of the excitation range. A “snapshot” picture of the reaction is taken at the time τ , representing the polarization of the products at that particular time. Any products formed after the RF-pulse are not seen because their magnetization remains parallel to the main applied field B_z and does not induce any voltage in the probe coil. The nuclei in the free radicals are not excited by the RF-pulse because their resonance frequencies are shifted by the HFI as compared to diamagnetic molecules.

The time resolution of the experiment depends on both the excitation and probing pulse widths. Here, the laser pulse is short (~ 10 ns) and the limit is determined by the length of the RF-pulse. In the examples given below, an RF-pulse of $1\ \mu\text{s}$ was used. The timing usually refers to the center of the RF-pulse, that is, $0.5\ \mu\text{s}$ for $\tau = 0$, and so on on all CIDNP plots below.

2.4.3 Proportionality Relation Between Geminate CIDNP and Hyperfine Coupling Constant (HFCC)

Since ISC in RPs (which is the cause of CIDNP effects) is conditioned by HFIs in the RPs, CIDNP of the diamagnetic products of radical reactions is exploited for the purpose of determination of the HFCCs of the radical intermediates. Thus, CIDNP gives an NMR method to determine the EPR parameters of elusive radical species. Individual nuclei in the radicals are polarized according to their HFI with the unpaired electron and, thus, to the spin density distribution. Together with high-resolution NMR detection, it allows atomic resolution and permits elucidation of the reaction mechanisms and a straightforward assignment of

HFCCs to the structure of reactive intermediates. If the nuclear spins in the reaction product are weakly coupled, the NMR lines belonging to different nuclei do not overlap and net CIDNP of each nucleus is exactly given by integration over all lines of the corresponding spin multiplet. A simple proportionality relation between net geminate CIDNP of a nucleus and its HFCC at the radical stage was established theoretically for short-lived RPs in low-viscosity solution.³¹ The applicability range of this relation was determined: the relation is fulfilled in the case of large difference in g -factor between the radicals involved and for the situation where the number of magnetic nuclei in the system is sufficiently large. The validity of the relation was confirmed by TR-CIDNP experiments on RPs with precisely known HFCCs.³¹ An important extension of the method is a way to determine not only the relative HFCCs but also the absolute ones by analysis of the geminate CIDNP. This becomes possible if one of the partner radicals has precisely known HFCCs and therefore can be used for calibrating the CIDNP dependence. As an example, Figure 6a shows ^1H CIDNP spectrum taken with zero delay after laser pulse in the photoreaction of 3,3',4,4'-tetracarboxybenzophenone (TCBP) and L-methionine–L-glycine (Met–Gly). Polarization of methionine is detected for protons in α , γ , and δ positions of methionine residue, but not in β position, which is characteristic pattern for cyclic transient radical.³² Since integrated over individual signals, net CIDNP formed in a pair of anionic radical of TCBP and cyclic radical of amino acid shows perfect linear dependence on HFCCs of the former (Figure 6b) that are known very precisely from time-resolved EPR; this dependence allows one to determine HFCCs with the protons on the counterpart cyclic transient radicals of methionine moiety using their CIDNP signals. The determined HFCCs are 0.87, 0.78, and 0.72 mT for α , δ , and γ protons, respectively.

The proportionality relation described here is applicable only to analysis of geminate spectra and if the nuclear spins in the reaction product are weakly coupled. In this case, the NMR lines belonging to different nuclei do not overlap and net CIDNP of each nucleus is exactly given by integration over all lines of the corresponding spin multiplet. For strongly coupled nuclei, their CIDNP pattern strongly depends on flip angle of magnetization vector, and information about the

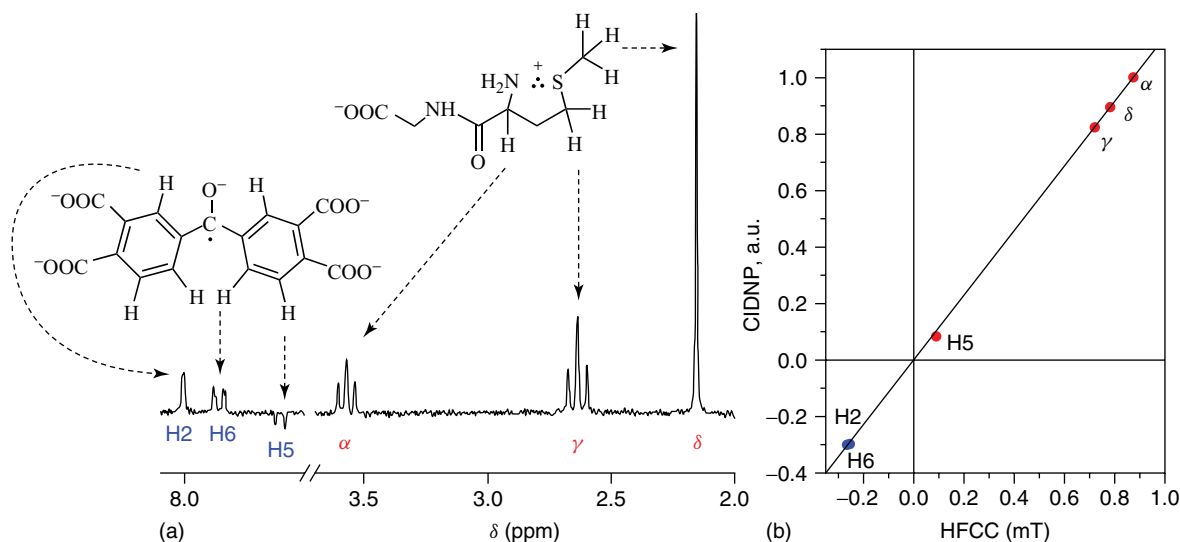


Figure 6 (a) Geminate CIDNP spectrum obtained in electron-transfer reaction between triplet TCBP and Met-Gly; the compliance between NMR signals of diamagnetic products and the protons in intermediate radicals is shown by arrows. (b) Linear dependence HFCCs of TCBP anion radical on CIDNP intensity that allows determination of HFCC with protons in cyclic radical of the methionine moiety in peptide.

sum of HFCCs of the coupled nuclei only can be extracted without analysis of the flip angle dependence used for FT-NMR detection.^{6,7,33}

2.4.4 Kinetic Considerations—Cyclic Reactions

As an example, let us consider the hydrogen atom transfer from guanosine-5'-monophosphate (GMP) to triplet excited 2,2'-bipyridyl (DP) where, at pH 7.5, the neutral radical of guanosine G(−H)• is formed³⁴:



No transformation of this radical occurs at neutral pH, and it is converted back to diamagnetic molecule in the reaction with DP radical. In this case, CIDNP kinetics of GMP could be described by (4–6).

The structures of the initial compounds and of the guanosyl radicals at different pH are shown in Figure 7a. The only nonexchangeable proton of guanyl is H8. CIDNP spectrum obtained immediately after the laser pulse in photoreaction of GMP and DP is shown in Figure 7b. Emission is

observed for H8 of GMP while enhanced absorption is observed for H3, H4, and H5 of DP. The signs of CIDNP are in accordance with Kaptein's rules. CIDNP kinetics shown in Figure 7c (black circles) was simulated using (4–6). The following parameters resulted in best fit (black line): $T_1 = 20 \mu\text{s}$, $(R_0 \times k_t)^{-1} = 45 \mu\text{s}$. The parameter $\gamma = 2.8$ was used.

2.4.5 Cyclic Reaction with Degenerate Electron Exchange

The reaction of degenerate electron exchange (DEE) is operative under the conditions when the radical and its parent molecule represent a system where one of the particles is an electron deficient analog of the other. Matching these conditions requires that the radical is created by electron transfer in the primary photochemical step, and that it is neither protonated nor deprotonated. Another possibility is the radical formation via hydrogen atom transfer and subsequent protonation or deprotonation. Here, to illustrate the influence of the DEE reaction on CIDNP kinetics photoreaction of DP with GMP at pH 1.3 is chosen. At this pH, positively charged GMP (GH^+) quenches positively charged triplet

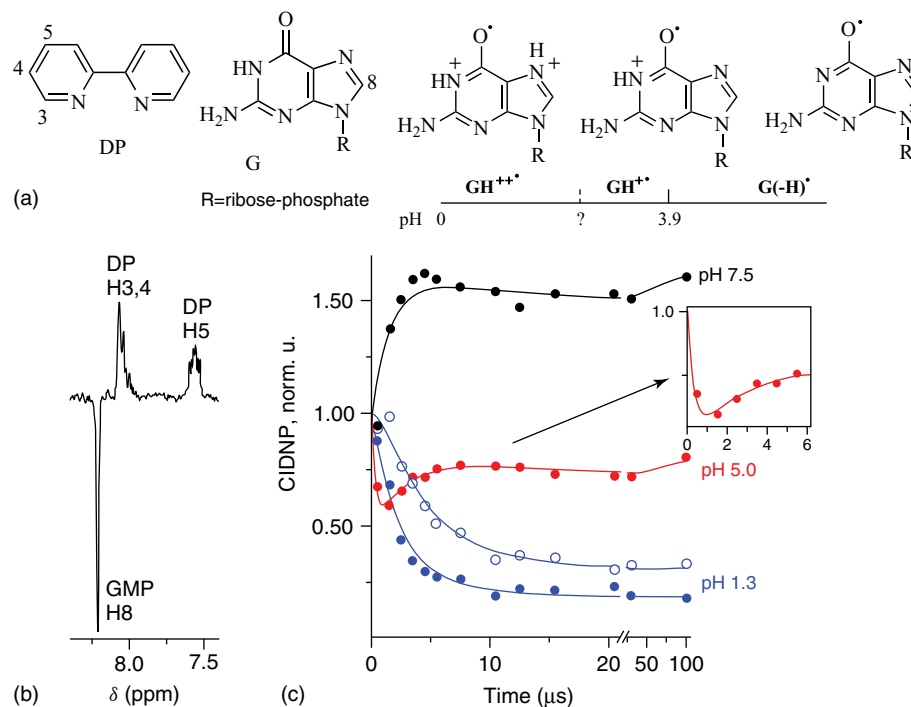
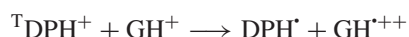
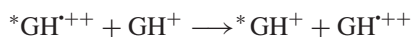


Figure 7 (a) The structures of 2,2'-bipyridyl and guanosine-5'-monophosphate, and the radicals of guanosine-5'-monophosphate at different pHs. (b) 200 MHz ¹H CIDNP spectrum, obtained in the photoreaction of 2,2'-bipyridyl and guanosine-5'-monophosphate at pH 7.5 with a detecting RF-pulse of 1 μs immediately after the laser pulse. (c) ¹H CIDNP kinetics of H8 of guanosine-5'-monophosphate, obtained during the photoreaction of 2,2'-bipyridyl and guanosine-5'-monophosphate at the concentration of 20 mM at pH 7.5 (black circles), 6 mM at pH 5.0 (red circles), 3 mM at pH 1.3 (blue open circles), and 6 mM at pH 1.3 (blue solid circles). Solid lines—model simulations (see text for details).

excited DP via electron transfer. Guanosine dication radical is formed³⁴:



In the reaction of DEE, no net chemical transformation occurs. However, in this reaction nuclear polarization (denoted by asterisk below) is transferred from the radical to a diamagnetic molecule.



This polarization, which is opposite in sign to the geminate one, superimposes the latter, leading to efficient CIDNP cancellation. For the description of CIDNP kinetics in the presence of DEE, an additional term should be incorporated into equations for nuclear polarization in the radical and in the product. Since the concentration of radicals is usually much smaller than that of

parent molecules, DEE is treated as irreversible pseudo-first-order reaction with the rate proportional to the concentration of molecules (*C*) involved in the exchange reaction with second-order rate constant *k_{ex}*:

$$\frac{dP(R)}{dt} = -k_t P(R)R - k_t \beta R^2 - \frac{P(R)}{T_1} - k_{\text{ex}} CP(R) \quad (7)$$

$$\frac{dP(\text{Pr})}{dt} = k_t P(R)R + k_t \beta R^2 + k_{\text{ex}} CP(R) \quad (8)$$

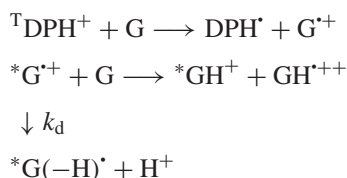
CIDNP kinetics obtained at different concentrations of GMP are shown in Figure 7c by blue symbols. The typical decay is seen, with the decay rate and stationary CIDNP value proportional to the concentration of the starting compound. CIDNP kinetics was simulated with the following parameters: *T₁* = 20 μs, (*R*₀ × *k_t*)^{−1} = 40 μs, *k_{ex}* = 1.3 × 10⁸ M^{−1} s^{−1}.³⁴

2.4.6 Cyclic Reaction with Degenerate Electron Exchange and Deprotonation

When the radical formed in the primary photochemical reaction step and involved in DEE is not an equilibrium particle, equilibration reaction (protonation of deprotonation) locks DEE. The ratio of equilibration time and the characteristic times of the bulk reactions determines CIDNP kinetics. Below, two cases are considered.

“Slow” Deprotonation

At pH 5, triplet excited DP is quenched by GMP via electron transfer. Cation radical of guanosine G^{+} is formed, which is involved into DEE with the parent molecule G. The rate constant of DEE is $k_{\text{ex}} = 1.3 \cdot 10^8 \text{ M}^{-1} \text{ s}^{-1}$. The radical cation G^{+} has $pK_a = 3.9$, and at pH 5 deprotonates to form neutral radical $G(-H)^{\bullet}$:



Neglecting the difference in recombination rate constants in two pairs of radicals, the concentrations of the dye R_D , cation radical of GMP R_1 , and neutral radical R_2 are as follows:

$$R_D(t) = \frac{R_0}{1 + k_t R_0 t} \quad (9)$$

$$R_1(t) = \frac{R_0 e^{-k_d t}}{1 + k_t R_0 t} \quad (10)$$

$$R_2(t) = \frac{R_0(1 - e^{-k_d t})}{1 + k_t R_0 t} \quad (11)$$

Here, k_d is the rate constant of deprotonation reaction.

The following equations describe polarization in two types of quencher radicals and in corresponding products:

$$\begin{aligned} \frac{dP(R_1)}{dt} &= -k_t P(R_1) R_D - k_t \beta_1 R_1 R_D \\ &\quad - \frac{P(R_1)}{T_1} - k_{\text{ex}} CP(R_1) \end{aligned} \quad (12)$$

$$\frac{dP(\text{Pr}_1)}{dt} = k_t P(R_1) R_D + k_t \beta_1 R_1 R_D + k_{\text{ex}} CP(R_1) \quad (13)$$

$$\frac{dP(R_2)}{dt} = -k_t P(R_2) R_D - k_t \beta_2 R_2 R_D - \frac{P(R_2)}{T_1} \quad (14)$$

$$\frac{dP(\text{Pr}_2)}{dt} = k_t P(R_2) R_D + k_t \beta_2 R_2 R_D \quad (15)$$

In the CIDNP experiment, the sum $P(\text{Pr}_1) + P(\text{Pr}_2)$ is detected. Since CIDNP enhancement coefficients formed in the two types of RPs may differ, two parameters R_1 and R_2 were used. No difference in nuclear paramagnetic relaxation times for different guanosine radicals was found, so only one value of T_1 is taken into account.

CIDNP kinetics obtained in photoreaction of GMP and DP at pH5 is shown in Figure 7c (red symbols). It is seen that initial decay is changed to a growth, indicating DEE termination upon deprotonation. The parameters of simulation are as follows: $T_1 = 20 \mu\text{s}$, $(R_0 \times k_t)^{-1} = 114 \mu\text{s}$, $k_{\text{ex}} = 3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $\gamma_1 = 2.8$, $\gamma_2 = 2.2$, $k_d = 1.6 \times 10^6 \text{ s}^{-1}$.

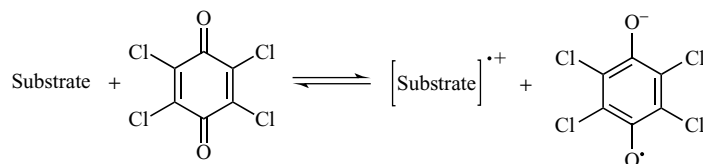
“Fast” Deprotonation

The example of CIDNP kinetics detected in case of fast deprotonation of the radical is given in the section “Applications of CIDNP,” where photoinduced reaction between triplet excited 4-carboxybenzophenone and glycylglycine dipeptide is described.

3 CIDNP—EXAMPLES

3.1 Steady-State CIDNP of Organic Radicals and Radical Ions

Photo-triggered reactions have been utilized for the generation of short-lived species in a variety of fields. A frequently followed procedure to attain reactive organic radical cations is light excitation of mixtures of efficient electron acceptors, for example, benzoquinone, its derivative chloranil (2,3,5,6-chloro-1,4-benzoquinone) or DDQ (2,3-dichloro-5,6-dicyanobenzo-1,4-quinone) together with the oxidizable substrate. Such reaction mixtures result in the formation of radical (ion)



Scheme 3 Formation of radical-ion pairs.

pairs. Obviously, electron-transfer procedures also can lead to neutral, or differently charged radicals, depending on the character of the parent reactants (Scheme 3).

In most cases, electron transfer proceeds after ISC from an excited singlet to the triplet state. In terms of organic radical cations, pioneering work was contributed by H. D. Roth.^{35–37} Out of many radical cations investigated by Roth and coworkers, a few representative examples are introduced here, to show the scope of this method. One such example is the question of whether homoaromaticity exists; that is, can non-directly bonded molecular moieties carrying a double bond interact “through space”? One of the classical examples in this respect is norbornadiene (ND). A ¹H-CIDNP experiment performed with chloranil or 1-cyanonaphthalene yields a polarization pattern indicating that the radical cation ND^{•+} possesses two indistinguishable ethene moieties, thus indicating a homo-delocalized π system. It is even more remarkable that photolysis of the ND isomer quadricyclane QC leads to ND; however, the intermediate radical cation QC^{•+} reveals a different electronic structure than ND^{•+} (Figure 8; one could also call them homo σ - and homo π -aromatic, respectively).

A wide variety of functional molecules like drugs or antioxidants contain amino groups. Since, the primary reaction of the amino moiety generally is electron transfer leading to the formation of

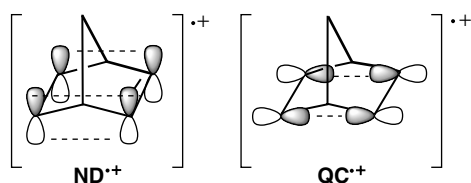
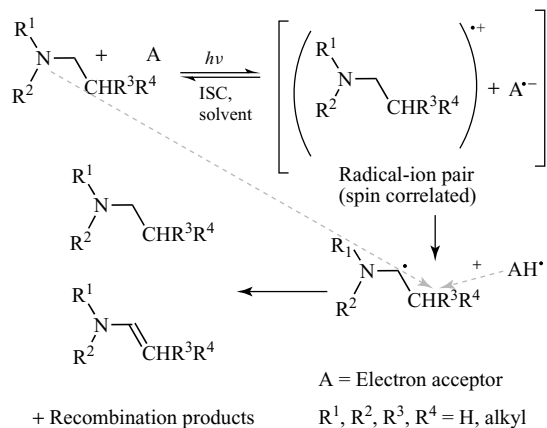


Figure 8 Different structures of the radical cations generated from norbornadiene and quadricyclane.

a (predominately) nitrogen-centered radical cation, CIDNP is a very well-suited method for the investigation of the follow-up reactivity of the short-lived amino radical cations. Already in the early years of CIDNP, the reactions between (tertiary) amines and electron acceptors were investigated.^{38,39} Generally, an initial amine radical cation deprotonates forming an α amino carbon-centered radical, which further leads to the parent amine and an alkene via well-established radical disproportionation as well as recombination products (depending on the steric situation) as shown in Scheme 4.

Several research groups have investigated the reactivity of amines with a variety of electron-transfer agents. Besides electron transfer, also hydrogen abstraction can occur. The nature of the solvent and the acceptor A (e.g., 9,10-anthraquinone or benzophenone derivatives) play a decisive role for the lifetime of the initially formed radical-ion pair (Scheme 4) and its follow-up reactivity. A more detailed account on these reaction patterns was elaborated by Roth.⁴⁰



Scheme 4 Simplified reaction sequence for the electron-transfer reaction between an amine and an electron acceptor (A). The reactions at the triplet and singlet domain are omitted; see text.

3.2 Photoinitiators and Radical Polymerization

It is obvious that the CIDNP technique is also rather helpful for the investigation of systems, which show α -cleavage (or a Norrish type I reaction). In the predominant number of cases, such molecules consist of a (substituted) benzoyl moiety attached to a molecular entity, which is able to form short-lived reactive radicals. If such a compound is irradiated at a wavelength where $n - \pi^*$ transitions are excited, homolytic bond cleavage occurs after ISC. The subsequently formed RP is able to initiate follow-up radical reactions (Scheme 5). Accordingly, such photo-triggered reactions can be utilized as photoinitiating systems for polymerizations.

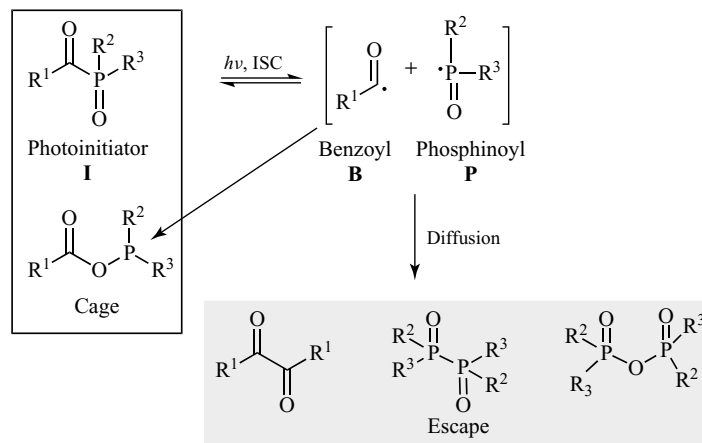
In the early days of CIDNP, it was shown that photolysis of benzyl derivatives leads to well-distinguishable CIDNP patterns.⁴¹ Subsequently, many industrially applied photoinitiators also were investigated.^{42,43} Here, we present an example based on rather efficient photoinitiators consisting of a benzoyl and a phosphinoyl moiety (Scheme 5). On photolysis and ISC, initiator **I** undergoes α -cleavage and the carbon-centered benzoyl radical **B** and phosphorus-centered radical **P** are created. Both radicals are able to act as starters for radical polymerization if an appropriate quencher (e.g., an acrylate) is present.⁴⁴

The reaction sequence displayed in Scheme 5 holds for a variety of initiators.⁴⁵

In the presence of polymerizable molecules, the escape products (Scheme 5) are no more detected. Apart from the CIDNP resonances of “cage” recombinations, polarized signals stemming from products formed during the growth of the polymer chain become visible.⁴² Two predominate features are detected, when benzoyl-based initiators are utilized in the presence of monomers. This is shown in Figure 9.

The first feature, which becomes visible is a well-pronounced polarization of the acrylate and can be rationalized by a reversible addition–elimination of the monomer, a feature observable with a variety of substrates.^{46,47} The second feature is the occurrence of the absorptive resonance at circa 10.5 ppm, indicative of the formation of an (aromatic) aldehyde. Since the aldehyde is formed as an escape product, the initially formed benzoyl radical has to obtain the hydrogen atom from a species that stems from an “escaped” radical. The CIDNP spectra are in line with the assumption that the H atom stems from a growing-chain radical as shown in Scheme 6.

Accordingly, the formation of aldehydes from benzoyl radicals can not be omitted since the bond dissociation energies of the transferable β -protons in PM $\cdot$ and BM $\cdot$ are low.⁴⁶ The reversibility of the initial addition of monomers to initiator radicals can give insights into the molecular basis of depolymerization procedures, which is macroscopically characterized by the ceiling temperature. Moreover, the inclusion of the polymerizable products PM



Scheme 5 α -Cleavage of a phosphine oxide-based photoinitiator and follow-up products (in the absence of a quencher).

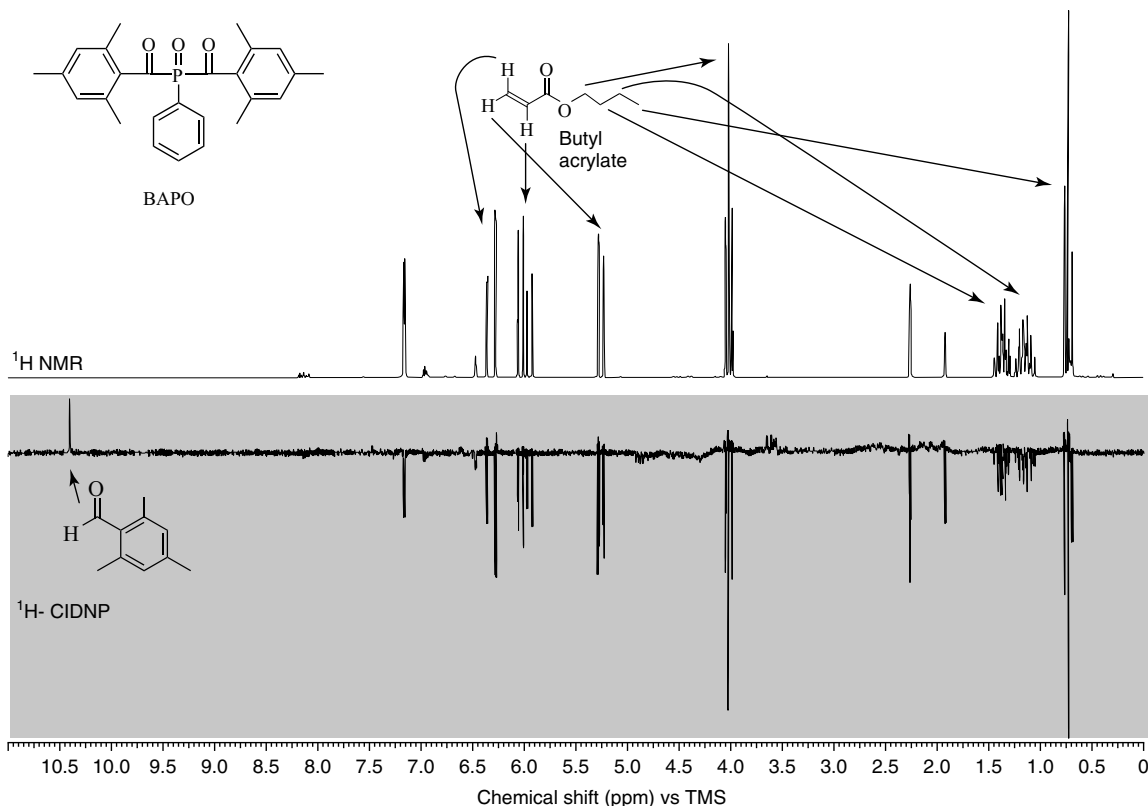


Figure 9 ^1H NMR and ^1H CIDNP spectrum obtained after photolysis of bisacylphosphin oxide (BAPO) and butyl acrylate.

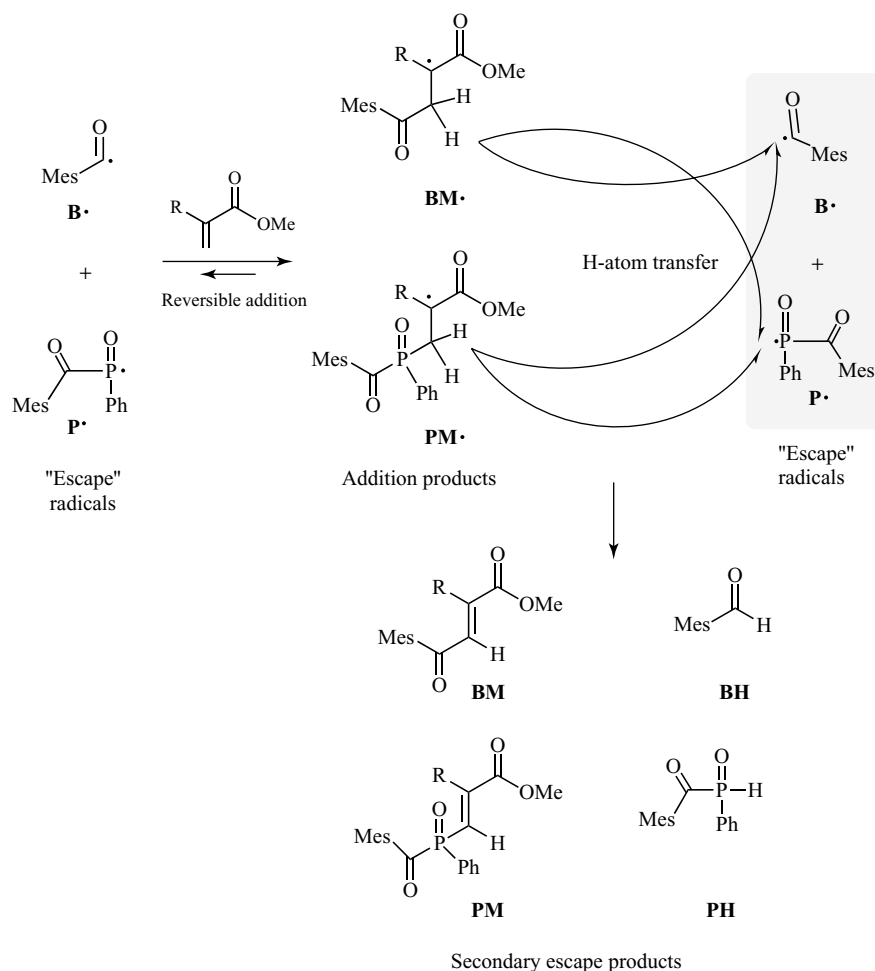
and BM can lead to additional functionalization of polymers.

CIDNP can also be utilized to investigate stereo-electronic effects on chemical reactivity. Molecules endo-N and exo-N are stereoisomers. While the benzoyl substituent is oriented at an axial position in endo-N, the axial position of this substituent leads to the orientation of the aromatic moiety away from the bicyclic system in exo-N. These different orientations of the photoactive benzoyl moieties cause dramatic reactivity differences between endo-N and exo-N, whereas no CIDNP effects can be established on photolysis of endo-N (the polycyclic skeleton K can be identified by NMR techniques). As illustrated above, the RP, consisting of the 6-hydroxy-bicyclo[2.2.2]oct-2-en-6-yl ($\text{NR}^\bullet$) and the benzoyl radical, leads to cage and escape products. Besides recombination, rearrangement and disproportionation products are observed. Since $\text{NR}^\bullet$ is essentially planar at the radical center, recombination with the benzoyl radical leads not only to the

restitution of the exo-N but also to the endo isomer (Scheme 7).

3.3 Application of Time-Resolved CIDNP

The examples above demonstrate that CIDNP kinetics is highly sensitive to the rates and mechanisms of radical reactions. Thus, it was successfully used to investigate radical reactions pathways and radical structure. Individual atoms in the radicals are polarized according to spin density distribution that, together with NMR technique of detection allowing atomic resolution, permits elucidation of the reaction mechanisms and the structure of reactive intermediates. The polarization pattern is detected by pulsed NMR method that leads to submicrosecond time resolution. With this time resolution, investigation of such processes as paramagnetic nuclear relaxation for individual nuclei is possible that gives



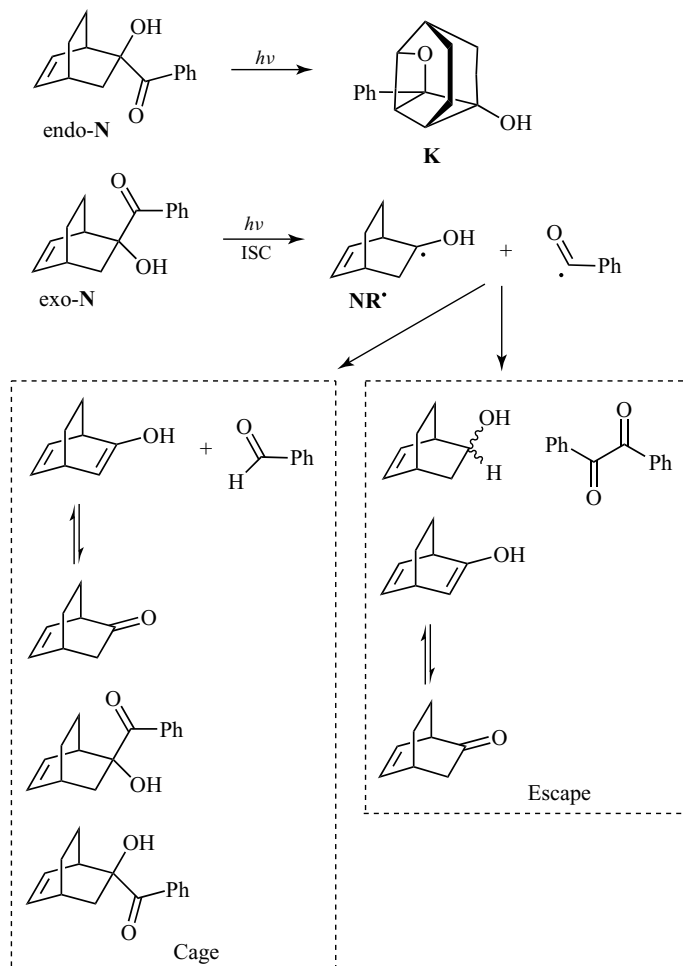
Scheme 6 Reaction pathway derived from the CIDNP spectra displayed in Figure 8 (for clarity, the addition of further acrylates to $PM\cdot$ and $BM\cdot$ leading to the polymer—still, the dominating reaction—is omitted).

information on intramolecular mobility of polarized parts of the radicals. In addition, CIDNP is one of the few methods that are sensitive to intramolecular electron transfer (IET) and DEE.

3.3.1 Photoreactions of Glycylglycine

Electron transfer from the lone pair on the nitrogen atoms of the peptide backbone to oxidizing agents is recognized as one of the major contributions to protein degradation. The oxidation process primarily leads to formation of aminium radical cations. These are highly reactive and very short-lived intermediates, and as a result they have

eluded electron spin resonance (ESR) detection in numerous studies of aqueous solutions of amino acids at room temperature.^{48–51} Instead, the more stable secondary aminyl radical or α -aminoalkyl radicals and products of their decomposition were detected.^{48–51} The quenching mechanism that is electron transfer from the amino group was found to be responsible for the main channel of the reaction of triplet 4-carboxybenzophenone (CBP) with aliphatic amino acids.⁵¹ Evidence for this came from the emergence of the transient absorption spectra of the carboxybenzophenone radical anion on the nanosecond timescale after photoexcitation, but not of the aminium radical. The lack of a suitable chromophore in the aminium radical precludes its

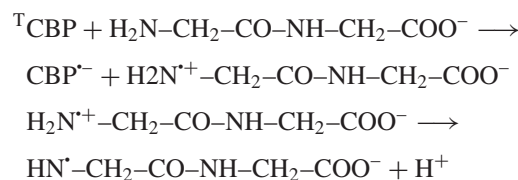


Scheme 7 Photoreactivity of endo- and exo-N.

detection by transient optical absorption. A source of experimental information on such radicals is TR-CIDNP.⁵²

Since oxidized glycine undergoes fast decarboxylation, glycyglycine (Figure 10a) was the simplest and probably the best model system to study this electron-transfer reaction involving the lone pair on nitrogen and photoinitiation with triplet sensitizer (4-carboxybenzophenone, CBP). In the pH range 6–13, nuclear polarization of the dipeptide Gly–Gly was observed only for the α -protons of the glycine residue at the N-terminus (Figure 10b). This observation provides irrefutable evidence that the excited triplet state of 4-carboxybenzophenone reacts with Gly–Gly in aqueous solution via a reductive quenching mechanism from the terminal NH_2 group, and

no quenching reaction takes place from the other residue at the C-terminus. As in the case of glycine, the aminium radical, formed as a result of quenching, undergoes fast deprotonation:



The characteristic deprotonation time τ_d could be estimated using the $\text{p}K_a$ value 2.6 reported for the aminium radical derived from glycine,⁵³ and a typical value of the protonation rate constant

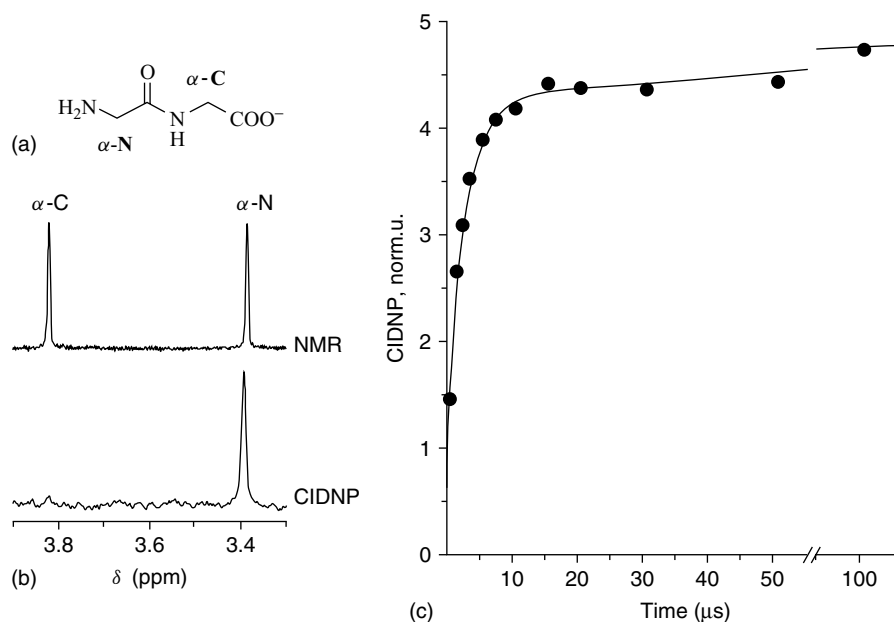


Figure 10 (a) The structure of glycylglycine. (b) 200-MHz ^1H NMR spectrum of glycylglycine and 200-MHz ^1H CIDNP spectrum, obtained in the photoreaction of 4-carboxybenzophenone and glycylglycine at pH 12 with a detecting RF-pulse of 1 μs immediately after the laser pulse. (c) Circles: ^1H CIDNP kinetics of the α -protons at the N-terminus of glycylglycine, obtained during the photoreaction of 4-carboxybenzophenone and glycylglycine at pH. Solid line: model simulation (see text for details).

$k_p = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$; $\tau_d = K_a^{-1} k_p^{-1} \approx 40 \text{ ns}$. Thus, the characteristic time of deprotonation falls in between the characteristic times of geminate reactions and bulk reactions. The kinetic data obtained are in agreement with a fast deprotonation to the aminyl radical; otherwise, a fast decay of the CIDNP kinetics would be expected which is determined by DEE.^{23,54} In the present case, the geminate RP and RPs in the bulk are different due to deprotonation of the aminium radical. In order to take this into account in the kinetic simulations, the intensities of polarization of α -protons at the N-terminus were calculated using the Adrian model⁵ for the two types of RPs with triplet precursor. Both pairs contain the anion radical of carboxybenzophenone, and aminium radical or amino radical as a partner. The CIDNP intensity for the α -protons in the pair with an aminyl radical was found to be 3.4 times higher than that with the aminium one; therefore, $\gamma = 3.4 \times 2.8 = 9.6$ was used. Such a high value provides more than fourfold CIDNP growth. Variation of T_1 in the range 20–40 μs resulted in good coincidence between experiment

and simulation. Other parameters of simulation are $T_1 = 25 \mu\text{s}$, $(R_0 \times k_t)^{-1} = 63 \mu\text{s}$ (Figure 10c).

3.3.2 Photoreactions of Sulfur-Containing Biologically Important Molecules

TR-CIDNP was successfully applied to study of the reactions of radical intermediates of methionine,⁵⁴ 3-(methyl)thiopropylamine,⁵⁴ Met–Gly,³² and Gly–Met³² with 4-carboxybenzophenone, 3-carboxybenzophenone, 3,3',4,4'-benzophenone-tetracarboxylic acid, and 9,10-anthraquinone-2-sulfonate in aqueous solution at different pHs (6.7–13.3). The obtained results give clear evidence that two oxidative quenching mechanisms formally attributed to electron abstraction from sulfur and nitrogen atoms are operative in reactions with excited triplet states of suitable acceptor molecules. Thus, the structure of the methionine radical cations derived from the free amino acid or the dipeptides depends on the pH. After electron transfer from the sulfur atom to the triplet excited dye molecule, two structures of the radical cation having different

distributions of spin density are formed. At pH values above the pK_a of the amino group, the Met radical cation exists in a cyclic form with a two-center, three-electron bond between the nitrogen and sulfur atoms, while in solutions below pK_a the Met radical cation has an “open form” structure. The same behavior is observed for 3-(methylthio)propylamine. The comparison of the TR-CIDNP results with literature data obtained by steady-state CIDNP measurements⁵⁵ casts doubt on the hypothesis that interconversion between three types of methionine cation radicals occurs. Instead, a competitive channel for oxidative quenching of the triplet sensitizer by direct electron transfer from the nitrogen atom leading to formation of the aminium radical cation was revealed that is operative in strongly basic solution. The study of the CIDNP kinetics formed in the photoreaction of 3-(methylthio)propylamine and methionine at strongly basic condition shows a much higher efficiency of polarization in the aminyl radical than in the two other species, the aminium and cyclic radicals.⁵⁴

In the case of the dipeptides, the reactions are more complex.³² Gly–Met form S-centered radicals at all pHs, whereas the Met–Gly only at a pH below 4.5. At a pH above 4.7, a cyclic radical with a two-center, three-electron bond between the N and S atoms is formed for the case of Met–Gly, but not for Gly–Met. In neutral solution, at a pH above 4.5 but below the pK_a of the amino group Met–Gly forms first S-centered radicals, which undergo deprotonation on the microsecond scale with formation of the cyclic radical. In basic solution (pH > 11), the existence of a channel of oxidative quenching via electron transfer from the lone electron pair of nitrogen of the amino group was revealed for both Met and Gly allowing to suggest that it is a common feature of all amino acids and proteins. The CIDNP kinetics of Met–Gly and Gly–Met showed that in basic solution the aminium radical deprotonates on the submicrosecond timescale forming the aminyl radical.³²

The TR-CIDNP measurements also allow demonstrating the crucial influence of the DEE between cationic radicals (or dimers) and diamagnetic molecules on the intensity of the CIDNP signals in the pH range below the pK_a of the amino group of methionine.⁵⁴ The rate constant for the electron exchange was obtained. The kinetics of the polarization in the 3-(methylthio)propylamine chosen as a

model compound to study magnetic resonance properties in cyclic five-membered ring radicals allows to determine the paramagnetic nuclear relaxation time T_1 for α and γ protons and to show that protons in the vicinity of the nitrogen have a much faster relaxation than the other protons. Kinetic parameters were also obtained for both dipeptides in neutral and basic solutions.³²

The polarization of the Gly residue occurs only when it is located at the N-terminus of the protein. The position of the Met residue, whether it at the N-terminus, the C-terminus or in the middle of the protein, can be derived from the polarization pattern: the α proton is polarized only at the N-terminus and not polarized in the other cases.

3.3.3 Time-Resolved CIDNP as a Tool to Study Inter- and Intramolecular Electron-Transfer Reactions

Among processes that are important in biological systems is charge migration in the oxidized species. To understand the factors that govern such processes, monitoring the radicals during their lifetime is necessary. Transient optical spectroscopy is not always applicable for that since not all the radicals are good chromophores. CIDNP offers a good alternative: enhancements are observed for NMR signals of nuclei that have nonzero HFI constants in transient radicals. The essence of TR-CIDNP method in investigation of the reductive electron-transfer reactions is in spin-sorting nature of $S-T_0$ mechanism of CIDNP formation. As described in detail above, the geminate stage of the reaction, nuclear-spin-dependent ISC, and spin-selective recombination give rise to the geminate CIDNP. Radicals that escape geminate termination are “marked” by nuclear polarization that is opposite in sign to the geminate one. When the reductive electron transfer takes place, this CIDNP superimposes the geminate polarization leading to CIDNP decay. This CIDNP cancellation effect is very similar to that observed in the CIDNP kinetics when DEE is operative. The difference from DEE is that in the type of the reaction considered not only the polarization is transferred from the radical to a diamagnetic molecule, but the radical itself decays that closes the possibility for the formation of additional CIDNP in the F-pairs. This is taken into

account in the equations describing CIDNP kinetics. As shown below, CIDNP kinetics is highly sensitive to the rate of the reductive electron transfer so that it is possible to study this reaction quantitatively by analyzing CIDNP kinetics.

3.3.4 Intramolecular Electron Transfer in Dipeptides His-Tyr and Tyr-His

Indirect evidence for the proton coupled electron transfer from tyrosine to the histidyl radical was drawn only from optical detection of tyrosyl radicals. The CIDNP technique allows one to follow the reactions of transient histidyl radical using NMR detection of histidine signal.^{22,56} The CIDNP-detected kinetics of H2 of His residue is shown in Figure 11a. The polarization decay is typical of reductive electron transfer to the radical the product of which is observed.^{23,57–60} For comparison, the kinetics of the photoreaction between DP and the peptide histidine-phenylalanine (His-Phe) is shown. The CIDNP of H2 of the histidine residue in His-Phe is observed to increase in time (black circles in Figure 11a). Therefore, the CIDNP

decay observed for H2 proton of His residue in the photoreactions of the peptides His-Tyr and Tyr-His can be attributed to the reaction of IET from the tyrosine residue to the histidyl radical. The rate constant of IET from tyrosine residue to histidine radical is denoted as k_e . The general reaction is



The equations describing the observed CIDNP kinetics are the following:

$$R_D(t) = \frac{R_0}{1 + k_t R_0 t} \quad (18)$$

$$R_1(t) = \frac{\alpha R_0 e^{-k_e t}}{1 + k_t R_0 t} \quad (19)$$

$$\begin{aligned} \frac{dP(R_1)}{dt} = & -k_t P(R_1) R_D - k_t \beta R_1 R_D \\ & - \frac{P(R_1)}{T_1} - k_e P(R_1) \end{aligned} \quad (20)$$

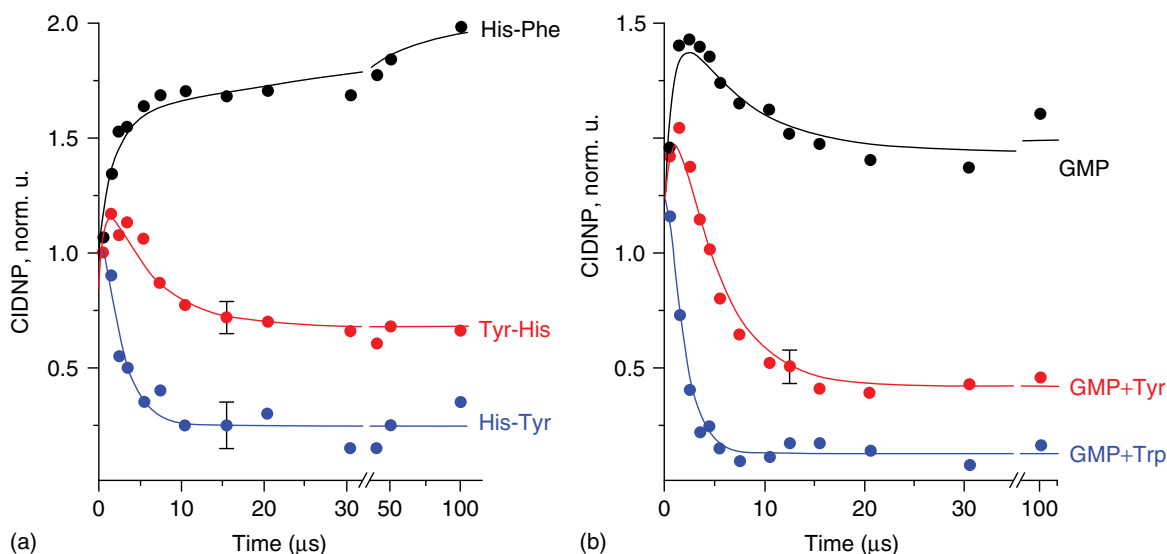


Figure 11 (a) ^1H CIDNP kinetics for the H2 proton of histidine residue in His-Phe (black circles), Tyr-His (red circles), and His-Tyr (blue circles), obtained during the photoreaction between 2,2'-bipyridyl and the corresponding dipeptide at pH 7.3. (b) ^1H CIDNP kinetics for the proton H8 of GMP obtained at pH 7.5 in the photoreactions of 2,2'-bipyridyl with GMP (black circles), with GMP in the presence of 2.5 mM of *N*-acetyl tyrosine (red circles), and with GMP in the presence of 2.5 mM of *N*-acetyl tryptophan (blue circles). Solid lines—model simulations (see text for details).

$$\frac{dP(\text{Pr}_1)}{dt} = k_i P(\text{R}_1) R_D + k_i \beta R_1 R_D + k_e P(\text{R}_1) \quad (21)$$

Since both residues, His and Tyr, participate in the quenching reaction with the formation of corresponding radicals, the parameter α is used, which is the share of histidyl radicals.

The best-fit simulations are shown in Figure 11a by solid lines. The best-fit values of $(R_0 k_i)^{-1}$ are 23 μs for Tyr–His and 34 μs for His–Tyr. The rate constants of IET are $(7.5 \pm 1.5) \times 10^4 \text{ s}^{-1}$ and $(3.8 \pm 0.8) \times 10^5 \text{ s}^{-1}$ for the oxidized Tyr–His and His–Tyr, respectively.⁶¹

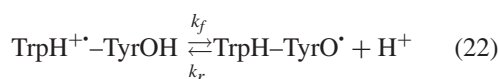
3.3.5 Modeling of Non-Enzymatic DNA Repair by Electron Transfer from Amino Acids to Guanosyl Radicals

Electronic vacancies on the guanyl base in DNA produced by oxidizing agents or by ionizing radiation may be refilled rather fast via electron transfer from the surrounding protein pool, thus preventing the radical chemistry to evolve into pathological DNA damage. As a model of chemical DNA repair, the reductive electron transfer to the free radical of the GMP from *N*-acetyl derivatives of amino acids tyrosine and tryptophan was studied.^{23,60} The guanosyl radicals were photochemically generated in the quenching reaction of the triplet excited dye 2,2'-bipyridyl.

The kinetic data for the reductive electron transfer between photochemically generated GMP radicals and *N*-acetyl tryptophan or tyrosine demonstrate that for both amino acids the reaction rate constants are dependent on the protonation state of the reacting species.^{23,60} The example in Figure 11b shows CIDNP kinetics, obtained in photoreaction of GMP in the presence of *N*-acetyl derivatives of tyrosine and tryptophan at pH 7.5. The decay observed in CIDNP kinetics of GMP in the presence of the amino acids compared to CIDNP kinetics of GMP when no amino acid is added unambiguously proves that electron transfer to guanosyl radical takes place. The rate constants of this reaction obtained from the simulation of CIDNP kinetics are $(6.0 \pm 1.0) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (*N*-acetyl tyrosine)²³ and $(2.6 \pm 0.4) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ (*N*-acetyl tryptophan).⁵²

The detailed kinetic investigation of four forms of elusive radical intermediates of GMP subject to the reductive electron transfer from the amino acids in aqueous solution at ambient temperature was possible because of the very strong enhancement of NMR signals by chemically induced dynamic nuclear polarization in the reaction of the triplet dye DP with both GMP and each of the two amino acids. For both amino acids, our data show that the different forms of GMP radicals, namely, $\text{GH}^{++\cdot}$ (pH 1.3), $\text{G}^{+\cdot}$ (pH 2.9), $\text{G}(-\text{H})^{\cdot}$ (pH 7.5, 11.0, 11.3), and $\text{G}(-2\text{H})^{-\cdot}$ (pH 13.3), are characterized by a different oxidative property with rate constants changing from $(1.0 \pm 0.3) \cdot 10^9 \text{ M}^{-1} \text{ s}^{-1}$ as obtained for $\text{G}^{+\cdot}$ and $\text{GH}^{++\cdot}$ with *N*-acetyl tryptophan⁶⁰ to a value of less than $6.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the reduction of $\text{G}(-2\text{H})^{-\cdot}$ by *N*-acetyl tyrosine.²³ The common feature for reductive electron transfer is that the reaction proceeds with much higher efficiency in acidic conditions. For tryptophan, the reaction proceeds with a higher efficiency than that for tyrosine, and is of much higher efficiency at neutral and basic conditions.

A quantitative analysis of photoinduced bidirectional IET between tryptophan and tyrosine moieties at strongly acidic conditions using the high potential of TR-CIDNP is used in determination of radical reaction mechanisms and absolute rate constants. The CIDNP kinetics obtained in photoreactions of 2,2'-bipyridyl with the tryptophan–tyrosine peptide proved to be very sensitive to the IET in the peptide.⁶²

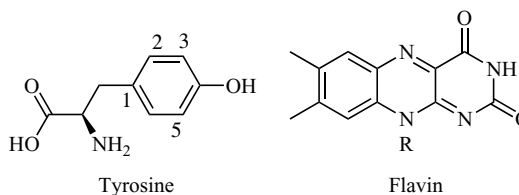


In reactions with the two residues, the sign of the dye polarization (emissive in the pair with tryptophanyl and absorptive in pair with tyrosyl) is a characteristic and sensitive indicator that allows one to elicit the direction and efficiency of IET. It was possible to extract the rate constants of IET in both directions, k_f and k_r , from the tyrosine to the tryptophan radical moiety, and from the tryptophan to the tyrosine radical moiety, respectively. In acidic solutions with pH varying from 1.6 to 2.4, k_f remains constant, while k_r changes. The differences between the one-electron reduction potentials of the tryptophanyl and tyrosyl radicals in the peptide were obtained from the value of the equilibrium

constant $K = k_f/k_r$, which showed a good linear dependence on pH with a slope equal to unity.⁵⁴ Application of TR-CIDNP to photoreactions of protein, hen egg white lysozyme, allowed to reveal that intramolecular electron transfer between tyrosine residues and tryptophan radicals in denatured lysozyme is highly efficient and partially reversible; also, there is a reaction of electron transfer from tryptophan residues to tryptophan radicals (this electron exchange is not fully degenerate).⁶³ These reactions affect the CIDNP kinetics so that tyrosine signals increase in time, and tryptophan signals decay rapidly.⁵⁹ Thus, geminate CIDNP spectra differ substantially from stationary spectra. It therefore appears that it is IET that leads to the observation of low CIDNP intensity for tryptophan residues relative to tyrosine residues in steady-state spectra rather than hydrophobic clustering as suggested earlier, although observation of IET does not exclude the existence of hydrophobic clustering. CIDNP spectra recorded immediately after a short laser pulse may thus allow a more reliable assessment of the surface accessibility of amino acid residues in proteins.

3.3.6 Interactions in Biomacromolecules

The principles of creating polarized NMR spectra can be advantageously utilized to gain insight into the fluid-state behavior of biomacromolecules. Here, we present illustrative examples from many investigations to indicate the scope of this experimental approach. Generally, proteins contain tyrosine, tryptophan, and histidine residues. Particularly, these amino acids are able to undergo reactions compatible to those shown in the previous chapters. On irradiation in the presence of a suitable dye (flavin derivatives are frequently used here), these amino acids can undergo electron or hydrogen atom transfer reactions, which lead to RPs as intermediates. Importantly, the spin distribution and the electronic structures of the amino acids lead to well-distinguishable polarizations in their NMR spectra. Moreover, specific chemical shifts of, for example, the tyrosine proton resonances help to identify the exact location at which radical formation takes place (particularly, the 3 and 5 positions of tyrosine). Pioneering work for establishing this principle was reported by Kaptein and coworkers.⁶⁴ Accordingly, this procedure has been utilized in many investigations.



Particularly valuable information on the accessibility of specific residues in complex biological structures can be gained by CIDNP since these experiments are performed on fluid samples at ambient conditions. Therefore, the limitations of solid-state-based methods like X-ray structure analysis do not exist and dynamic properties of, for example, proteins can be accessed.^{9,65}

This includes the (surface) accessibility of specific domains,^{66,67} protein structure,^{9,68,69} and folding^{70–74} and, rather recently, it was shown that well-selected Ru(II) complexes can be utilized as sensitizers.⁷⁵

For such protein studies, CIDNP is created by reactions involving reversible electron or hydrogen atom transfer between a photo-excited dye molecule (see above) and CIDNP-active amino acid residues. The polarization of the CIDNP-active residues in the protein depends on their accessibility for the probing dye molecule. The assumption underlying the photo-CIDNP technique is that only residues accessible to the dye molecule acquire substantial polarization. Therefore, one can analyze CIDNP of the protein in order to obtain the accessibilities of residues on the protein surface. However, it should be pointed out that CIDNP in proteins depends not only on the accessibility of the amino acid residues and on the mechanism of photochemical reactions but also on the reactivity of the intermediates and the efficiency of IET.⁵⁷ In the case of real time protein folding detection by CIDNP at the millisecond timescale, the spin polarization does not reflect the folding in a straightforward way since it depends also on the change of the efficiency of IET on the folding and on the dynamics of CIDNP formation on the microsecond timescale. In particular, we want to stress that only geminate, and not stationary, CIDNP should be used to draw conclusions about structural changes in denatured and molten globule states. However, with proper precaution taken, the combination of TR-CIDNP with the initiation of folding in the probe of the NMR spectrometer opens the possibility to follow the protein folding process

by high-resolution NMR selectively enhanced by CIDNP.

4 FIELD DEPENDENCE OF CIDNP

The mixing of the RP state and, hence, the efficiency of the sorting depends on the competition between hyperfine and difference in Zeeman interaction, $|g_1 - g_2|\mu_B B$ (see Figure 1b); thus, the CIDNP effect varies with the external field. In return, this dependence on the magnetic field can be exploited for determining HFI couplings in the radicals as well as differences in their g -factors. Roughly speaking, the maximum NMR enhancement in RP with a single nucleus spin 1/2 is expected when the Zeeman term $|g_1 - g_2|\mu_B B$ is equal to half of the hyperfine coupling, $A/2$. RP can contain many nuclear spins whose hyperfine couplings increase the local magnetic field. Consequently, the position of CIDNP maximum is shifted to higher field and maximum broadening by additional HFCCs.

Field-dependent CIDNP measurements were carried out using a mechanical field cycling setup driven by a computer-controlled step motor device positioning of the whole NMR probe⁷⁶ or irradiation cell combined with injection device within the bore of NMR magnet⁷⁷ that can be utilized for magnetic field from 0.05 to 14 T. Although time resolution is not possible in such experiments and only steady-state polarization is detected, high sensitivity of the CIDNP field dependence with respect to Δg makes the analysis of CIDNP very suitable for characterizing short-lived paramagnetic reaction intermediates. For example, at large g -factors of two methionine radicals, 2.0064 for cyclic radical and 2.0100 for S-centered radical, CIDNP maxima were found at around 2.1 T and 0.7 T, respectively.^{32,78} Examples of radicals of amino acids methionine,⁷⁸ histidine, and⁷⁹ tyrosine,^{18,80,81} and of peptides Met-Gly and Gly-Met³² show that the high field part of CIDNP field dependence when $B \gg A$ is described very well in frame of Adrian model,⁵ allowing to determine Δg value quite precisely.

For RPs with restricted mobility that are being in confined media or connected by chemical bonds forming biradicals, the electronic exchange interaction is important for spin evolution. Field dependence of CIDNP offers the possibility of a direct determination of electronic exchange interaction, J . Depending on the sign of J , the RP singlet level

crosses one of the triplet levels, with T_+ or T_- for positive and negative J , respectively, at magnetic fields $g\mu_B B = 2|J|$ where a resonance-like maximum is formed.^{82–84} Since the total electronic and nuclear spin is conserved in singlet–triplet conversion, the electronic and nuclear spins are flipping together in allowed transitions $S\alpha \rightarrow T_-\beta$ and $S\beta \rightarrow T_+\alpha$. Thus, the sign of nuclear polarization in this case is determined by the multiplicity of precursor μ and by the sign of J , $\Gamma = (\mu)(J)$, and does not depend on the sign of HFCC, in contrast to $S-T_0$ transition at high field for the short-lived RPs. If the multiplicity of the precursor is known from optical data, the sign of J can be determined from the sign of nuclear polarization.⁸³ While position of the maximum can be directly related to the electronic exchange interaction for rigid biradicals, $g\mu_B B = 2|J|$,⁸³ for flexible biradicals that, for instance, are resulting from the photolysis of cyclic aliphatic ketones^{82,85} the situation is much more complex. The spin evolution and molecular dynamics are coupled via modulation of the distance-dependent exchange interaction $J(r)$ by motion of radical centers.^{86,87} As a consequence, the position of CIDNP maximum is dependent on molecular mobility and in gas phase, it is considerably shifted to higher magnetic field.⁸⁴

The theory of RP mechanism of CIDNP predicts that while the high field part of the CIDNP depends on both the difference of g -factors and the HFIs of the radicals, the CIDNP formation in RPs at low field is conditioned solely by the HFI and J . However, quantitative analysis of CIDNP in low field is very complex, because observed polarization depends also on the spin evolution in the diamagnetic molecules, which is a function of the magnetic-field strength. One consequence of this evolution is polarization transfer among nuclei in the molecule,^{88–90} taking place once the nuclei are strongly coupled in the studied magnetic field. (Two spins are considered weakly coupled if the nuclear spin–spin interaction between them is much smaller than the difference in their Zeeman interaction with the external field. In other cases they are considered strongly coupled.) Thus, not the absolute, but only the relative strength of the coupling with respect to difference in Larmor frequency of nuclei is important for fulfilling the strong coupling condition, which therefore depends on the external magnetic field. In addition, nuclear relaxation of scalar coupled of diamagnetic molecules is also field

dependent,^{91,92} even if conditions of fast motion are met. Fast and coherent redistribution of polarization among spins strongly coupled by scalar interactions in diamagnetic products is an inevitable obstacle for low-field CIDNP experiments and plays a negative role since after polarization redistribution unraveling information on reaction pathways and intermediates is obscured and its analysis becomes problematic and ambiguous. Anyway, information about the field dependence of CIDNP is a valuable addition to the data obtainable in the time-resolved mode of CIDNP as considered above. It provides supportive information to interpretation of CIDNP patterns detected in high field.

5 SOLID-STATE CIDNP

In 1994, it was reported, that CIDNP phenomena can be established also in the solid-state magic angle spinning-NMR (MAS-NMR).⁹³ It has been mainly observed in photosynthetic reaction centers (¹³C and ¹⁵N nuclei), which are modified to allow a reversible electron transfer ("cyclic electron transfer").^{94–99} Recently, the MAS CIDNP effect was observed on a blue-light photoreceptor.¹⁰⁰

This technique allows insight into the photochemical background of the reaction in light-harvesting proteins. The theory behind this effect is still under development and relies on different spin-related mechanisms, which exceed the scope of this article^{101–104} and were briefly summarized.¹⁰⁵ Apart from its, yet, limited usability, it will be of interest to follow the development of this method.

6 CIDEP (TIME-RESOLVED EPR)

The phenomenon of CIDEP was reported prior to the discovery of CIDNP.¹⁰⁶ First developed connected to the pulse-radiolytic generation of radicals, it is now predominately used in connection with laser-flash photolysis. Compared with the "usual" continuous wave EPR (cw-EPR), the signals are detected in a nonmodulated manner. In a similar way as described in Section 1.2 of this article, the radicals (RP) are created in a polarized state and, accordingly, non-Boltzmann effects on the applied timescale dominate the signal intensities. Two predominant factors are responsible for the

perturbed intensities, the triplet mechanism (TM) and the RPM. The RPM in CIDEP is analogous to that established in Section 1.2 of this article, but here in contrast to CIDNP, the recombination of the radicals is not required.

The TM is generally detected in systems where radicals are generated by photolysis. After excitation to the excited singlet state, the polarization is built up during ISC to the triplet state. ISC depends on spin–orbit coupling and this interaction is related to the relative orientation of the orbitals involved. On the basis of the nondegeneracy of the triplet components at high magnetic field, each of the three triplet energy levels becomes populated to a different extent (Figure 12); thus, remarkably, the polarization is created even before the radicals are formed.

While the TM leads to identical phases and intensity enhancements of the EPR lines, RPM provides emission *and* absorption contributions. Since both phenomena are time dependent, often different polarization patterns are observed at varying delays of signal acquisition.

The origin of TM and RPM for CIDEP has been developed and reviewed.^{107–112} In the last few decades, additional mechanisms for the creation of polarization have been developed such as the RTPM (radical triplet pair mechanism)^{113,114} and the SCRPM mechanism^{115–118} with the latter being particularly active in confined environments displaying high viscosity.

CIDEP has been frequently utilized as a tool to establish photophysical processes and details of molecular arrangements in the solid state with many contributions in systems with charge-separated states (e. g., photosynthesis¹¹⁹).

In terms of the instrumental effort, commercial EPR spectrometers have to be modified to allow the acquisition of EPR spectra in the nanosecond–microsecond time domain. The microwave bridge has to be adjusted (amplifier), the spectral acquisition has to be synchronized with the source triggering the generation of radicals, and the transfer of data has to be interfaced between the components of the spectrometer. Such experiments can be performed on spectrometers based on a conventional continuous wave (cw-X) band EPR spectrometer, at W-band (10 MHz, high field), or pulsed spectrometers.

Here, we will restrict ourselves to examples contributing to the understanding of chemical reactivity

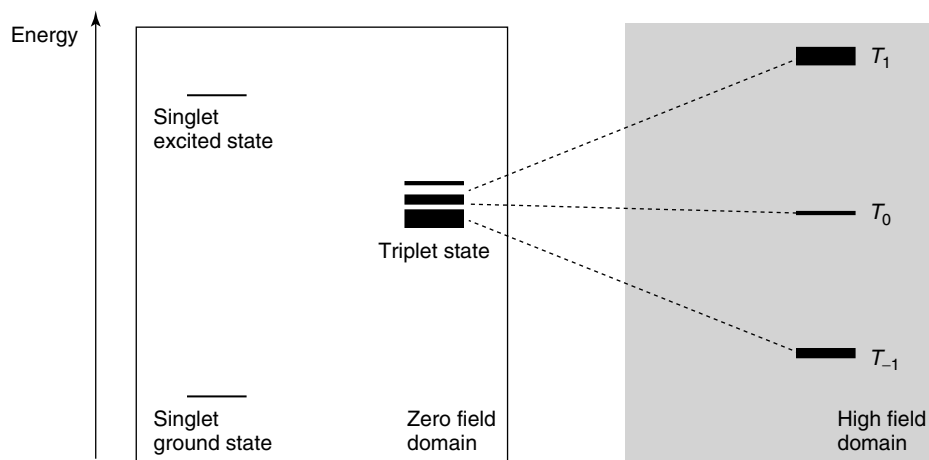


Figure 12 The triplet mechanism of CIDEP.

of (organic) radicals taking advantage of the substantial time resolution of CIDEP (radical lifetimes in the 50 ns to μ s region) and of the increased sensitivity caused by the “physical” mechanisms sketched above.

6.1 CIDEP and Radical Polymerization

With the general principle of the photolytic generation of radicals, and follow-up of formation of carbon-centered radicals and reactions on a nanosecond–microsecond timescale, photoinduced radical polymerization is an ideal paradigm for demonstrating the power of CIDEP. Accordingly this technique will be illustrated by choosing examples from photoinitiators.

Photolysis of aliphatic or aromatic ketones often leads to the homolytic cleavage of the bond in α -position to the keto group. This has been utilized to produce biradicals¹²⁰ starting with cyclic ketones. Hydrogen abstraction reactions by excited states of carbonyl compound can as well be utilized as starting reactions to observe radicals based on acrylates at a short timescale.^{121,122}

Many (also commercially applied) initiators for radical polymerization rely on such α -cleavage reactions (Section 3.2)¹²³; with the lifetime of the initiating species being short, CIDEP is the method of choice to observe the primary radicals. An example for a bisacylphosphineoxide is shown in Figure 13. The three signals stem from two

radicals: the central line represents an unresolved EPR spectrum of the 2,4,6-trimethylbenzoyl radical and the two outer lines are due to the P-centered substituted phosphinoyl radical (which also do not show additional resolution here). The dominating interaction here is that between the unpaired electron and the ^{31}P nucleus, which leads to the considerable isotropic HFCC of 25.8 mT (the distance between the two outermost lines). In contrast to steady-state EPR, here the two lines representing the ^{31}P coupling do *not* possess identical intensities. This reveals the presence of both, TM *and* RPM, being responsible for the polarization. Accordingly, particularly when these mechanisms contribute to the line intensities, the decay of the EPR signal does not represent the lifetime of the radical.

When a monomer is added to the reaction solution, the spectra undergo significant alterations. This is displayed in Figure 14 for a mixture of phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide and butyl acrylate in toluene. Immediately after photolysis, the three lines corresponding to those shown in Figure 12 are visible. After circa 300 ns, additional signals start to grow in the center of the spectrum. They unambiguously stem from growing-chain radicals of the polymer at a very early stage (addition of a first acrylate to the initiating radicals). Then, at 700–800 ns the signals of the initiating radicals disappear, and also the intensity of the central signal stemming from the C-centered radicals CP and CC (Scheme 8) starts to fade in the spectrum although this type of radicals is

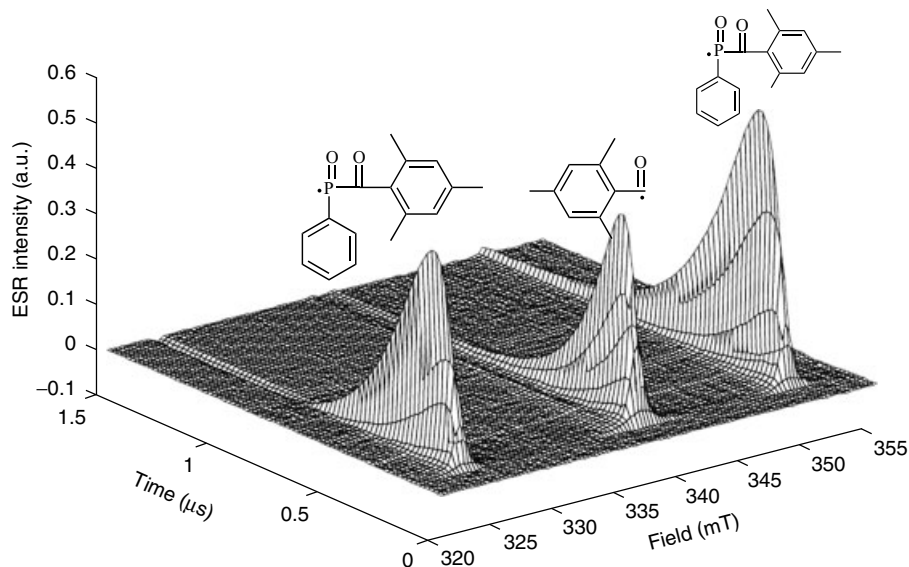


Figure 13 CIDEF spectrum obtained after laser-flash photolysis of phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide. [Reproduced with permission from I. Gatlik, PhD thesis, Univ. Basel, 2001.]

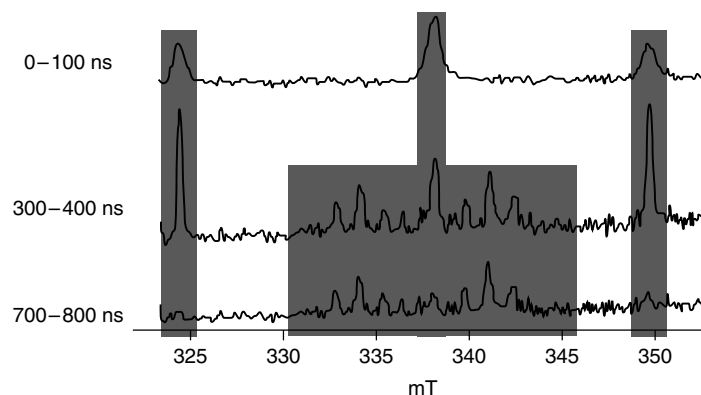
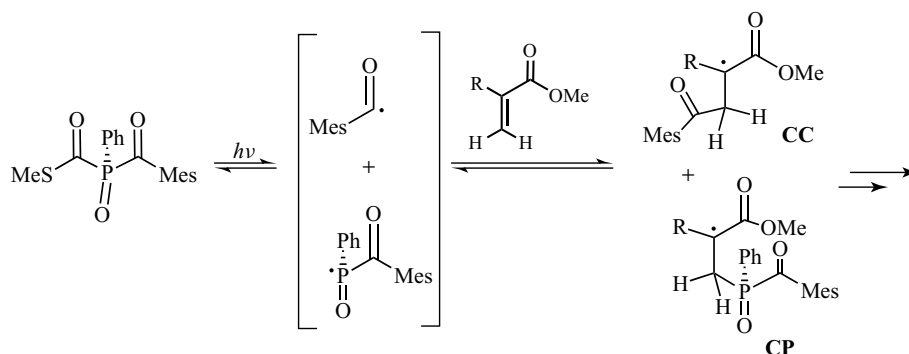


Figure 14 CIDEF spectra of phenylbis(2,4,6-trimethylbenzoyl)phosphine oxide in the presence of butyl acrylate.

much longer lived. The reason for this observation is that only radicals carrying a substantial amount of polarization are detectable by this technique. Thus, when the polarization created by TM and RPM in the initial stage relaxes, subsequently formed radicals become “invisible.”

Often, the central signals in X-band EPR spectra overlap, and an unambiguous analysis of the signals is impaired. A helpful development is the design of high-field (W-band) time-resolved EPR spectrometers,¹²⁴ which (analogous to the extension of the chemical shift resolution corresponding to the g -factor scale in

EPR) enhances the resolution between EPR signals of different radicals. The power of this approach is demonstrated in Figure 15, which shows the photolysis of 1-(4-methylthio)phenyl-2-(4-morpholinyl)-2-phenylpent-4-en-1-one. Here, the 4-methylthiobenzoyl (b in Figure 14) and the corresponding α -amino carbon-centered radical (c in Figure 15) are formed.¹²⁵ While the X-band EPR shows two overlapping signals, they are well separated in the W-band spectrum substantially simplifying analysis (another feature is the different polarization of the signals which



Scheme 8 Radicals observed during the first steps of radical polymerization.

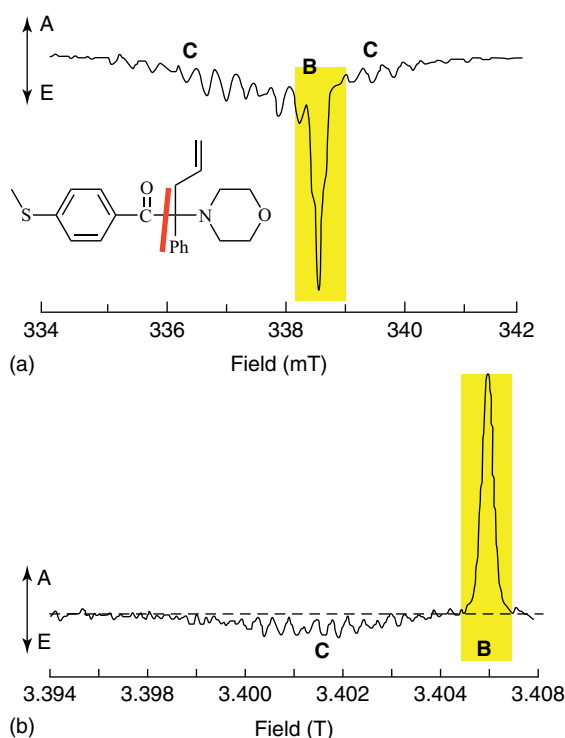


Figure 15 (a) X- and (b) W-band time-resolved EPR spectra of 1-(4-methylthio)phenyl-2-(4-morpholinyl)-2-phenylpent-4-en-1-one.

is due to a substantial contribution of Boltzmann distribution¹²⁴).

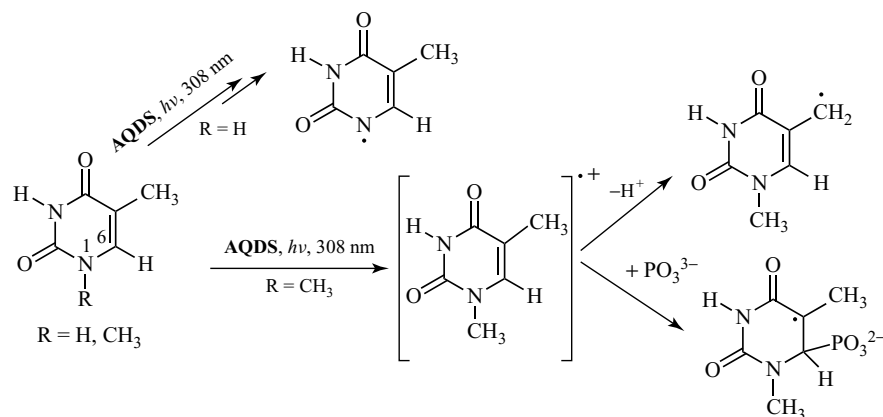
With the structures of short-lived radicals and the observation of growing polymer chains being established, it is tempting to utilize CIDEP for measuring rate constants for radical reactions, in particular, the

addition of a monomer to the initiating radical.¹²⁶ This is more valuable since often the short-lived radicals can unambiguously be identified by CIDEP, but are hardly detectable by optical techniques because either they have very low extinction coefficients as their absorptions are masked by reaction products or the bands are too far in the UV region. As shown above, CIDEP has the shortcoming that the polarization mechanisms cause the situation where the decay curves do not generally represent chemical lifetimes. Bartels *et al.*, have shown how to circumvent this obstacle^{127,128} by using the linewidth of the CIDEP signals (indicating the lifetime of the radical—lifetime broadening). This principle was shown to work well with more complex reactions followed by cw and FT-EPR.^{125, 129–131} With this approach, the addition constants of several monomers to initiating radicals could be determined.

6.2 CIDEP Radical Ions and Follow-Up Products

Conversions of peptides and DNA residues on oxidative stress are of principal interest. Such conditions can be modeled by reacting the substrates with oxidants like 9,10-anthraquinone-2,6-disulfonic acid (AQDS). This oxidant is well soluble in water, but it must be taken into account that its reactivity is pH dependent.

When AQDS is reacted with thymine and the reaction is followed by FT-EPR CIDEP spectra, the formation of the thymine-1-yl radical and an AQDS-based radical (depending on pH) are detected (Scheme 9)¹³²; accordingly under the given



Scheme 9 Reactivity of thymine and 1-methylthymine upon photoinduced reaction with AQDS as established with FT-CIDEP.

experimental conditions, deprotonation of the primary thymine radical cation is very rapid. With 1-methylthymine, however, the analogous reaction leads to the detection of the corresponding radical cation together with deprotonated isomers. In the presence of phosphate buffer and phosphoric acid, a phosphate adds to the 6-position of thymine (Scheme 9).¹³³ In a similar way, the formation of radicals from cyclic dipeptides was followed.¹³⁴ A summary of organic radicals detected via CIDEP can be found in Ref. 135.

7 CONCLUSIONS

The results presented here demonstrate that short-lived paramagnetic species, preferentially (organic) radicals can be very well distinguished by CIDNP and CIDEP. Both techniques take advantage of RP phenomena and transitions between spin-correlated triplet and singlet domains. While CIDNP provides information on reaction products and offers knowledge on the reaction pathways and intermediates, which led to these products, CIDEP characterizes the initially formed radicals. However, care must be taken for the interpretation of these results since the signals depend on several (photo)physical and magnetic phenomena.

The TR-CIDNP technique is very suitable for characterizing short-lived paramagnetic reaction intermediates, whereas it has to be emphasized that only the polarization observed within the first microsecond after the photoexcitation arises solely

from recombination of geminate RPs. Thus, any attempts to get quantitative information about the geminate evolution of radicals from CIDNP spectra detected at continuous irradiation of the sample are fault-prone. Important consequences for CIDNP of protein residues are in particular not only geminate factors, such as surface accessibility that determines the CIDNP amplitude, but also effects of neighboring groups, for example, of N versus C terminal, which have to be taken into account. As it has been demonstrated, aromatic amino acid residues give CIDNP, and at the N-terminus other residues, such as Gly, also become polarized. Moreover, the protonation state of the diamagnetic and paramagnetic species plays a major role. The direct application of the CIDNP method to complex peptides may lead to erroneous conclusions; therefore, systematic studies on peptides of increasing complexity are necessary in the first place.

Time-resolved measurements allow to separate primary and secondary reaction stages and to determine the reaction rates as well as the paramagnetic nuclear relaxation times at the radical stage. Because of the high spectral resolution, site-specific information on the spin density distribution in the radicals was achieved. From these data, information about the structure of the radicals and the way of their formation was obtained. At ambient conditions, in aqueous solutions these species are too short-lived to be registered by EPR. On the other hand, they do not have an absorption band to be detected by optical spectroscopy. However, the time-resolved and field-dependent CIDNP methods at high field

allowed for the identification of the radicals and determination of their structure.

The identification of radicals via CIDEP proceeds in a straightforward way analogous to standard CW-EPR since the hyperfine patterns are constructed in the same way. However the CIDEP signal intensities are substantially controlled by TM and RPM and, accordingly, do not reflect steady-state conditions. Thus, the intensity patterns of time-resolved EPR spectra in the nanosecond–microsecond region present intensities which do not simply reflect radical concentrations. These mechanisms also hamper a direct kinetic analysis. Nevertheless, kinetic analysis is feasible by line-shape analysis (or direct measurement of T_2).

In a nutshell, CIDNP and CIDEP provide an advantageous way for a straightforward and highly sensitive detection of short-lived radicals. Moreover, the photophysical details can be deduced from the spectra. The possibilities of using these techniques to answer questions in the field of chemical reactions involving homolytic bond cleavage, atom abstraction, or electron transfer are immense. Although this methodology has been developing over decades, its scope is, by far, underestimated.

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Matrix Isolation of Radicals

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1 INTRODUCTION

1.1 Matrix Isolation

Since its introduction almost half century ago, matrix isolation spectroscopy has been one of the most important tools for the characterization of free radicals.^{1–4} In 1954, Pimentel *et al.* published their studies of trapping unstable species in frozen inert gases.⁵ Argon, xenon, and nitrogen were used as inert matrices to stabilize molecules that are otherwise not isolable, either because they are highly reactive (dimerize or react with other molecules) or because they have a high tendency for aggregation (e. g., formation of hydrogen bonds). Although frozen organic solvents (organic glasses) had been used before for the stabilization of reactive molecules, the introduction of frozen inert gases as medium was the important step forward that allowed the isolation and spectroscopic characterization of even the most reactive free radicals. Under conditions of matrix isolation, radicals are kinetically stabilized by using cryogenic temperatures (below 20 K) and by immobilization of the radicals (preventing diffusion) in a chemically inert environment. As a matter of fact, immobilization is so complete that even the rotation of molecules is prevented (with the exception of water and other similar very small molecules that show a hindered rotation in matrices). Thus, bimolecular reactions that require the diffusion of the components are completely inhibited and unimolecular reactions are extremely slowed down by the low temperatures.

Rearrangements are only observed if the activation barriers are less than approximately 2 kcal mol^{−1} or if tunneling takes place.

Typical conditions for matrix isolation are high dilution (1:500–1:2000 matrix ratio), very low temperatures (3–10 K), and argon, neon, or nitrogen as inert matrix (Figure 1). Argon and nitrogen can be used between 10 and 30 K, whereas neon matrices require temperatures below 6 K. Matrix isolation is basically a preparative technique, and the goal is to obtain high yields of the reactive intermediate. For the synthesis of radicals, there are two basic techniques available: either a suitable photolabile precursor is matrix-isolated and the radical is formed in a subsequent photolytical step, or the radical is produced in the gas phase via flash vacuum pyrolysis (FVP), and the pyrolysis products are subsequently trapped with a large excess of inert gas on top of a cold spectroscopic window. Other techniques, such as laser ablation^{6,7} or microwave discharge,^{8,9} are less generally used.

The photolysis of matrix-isolated precursors is the technique most frequently used for the synthesis of matrix-isolated radicals; however, this method has some severe drawbacks. In a typical photochemical synthesis, singlet radical pairs are produced by the cleavage of a covalent bond in the photochemically excited precursor. In the gas phase or in solution, these radicals might diffuse apart, form triplet pairs via intersystem crossing (ISC) or isolated radicals. In the solid matrix, however, diffusion is inhibited and the radical pair is trapped in a matrix cage. In many cases, this results in a rapid recombination back to the precursor. Thus, iodobenzene can be

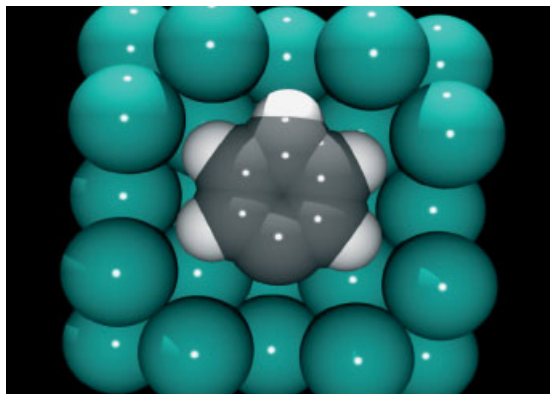


Figure 1 Phenyl radical trapped in argon.

used as photochemical precursor of phenyl radicals in the gas phase, whereas under the conditions of matrix isolation, only traces of radicals are formed owing to the rapid recombination of the phenyl radical and the iodo atom. The yields of radicals formed by matrix photolysis depend on the precursor, the matrix material, and the temperature. Therefore, some precursors give reasonable yields of radicals in argon at 10 K, whereas others require temperatures as low as 3 K or neon matrices.^{10–13} Unfortunately, this is not predictable and a series of experiments is necessary to optimize the photolysis conditions.

To circumvent these problems, diacylperoxides have been used as photochemical precursors of radicals.¹⁴ Cleavage of the O–O bond results in the formation of highly labile acyloxy radicals, which readily split off CO₂ under the formation of a radical pair separated by two molecules of CO₂. Owing to the photolysis, the initially formed radicals are vibrationally excited, which might lead to local heating of the matrix and subsequent diffusion and recombination processes. Again, the yields of radicals are unpredictable and highly dependent on the experimental conditions.

Another disadvantage of the photolytical synthesis of matrix-isolated radicals is that they, if formed at all, are in close proximity to other products of the photolysis. This results in intermolecular interactions that might lead to spectral shifts and line broadening. Annealing of these matrices at higher temperatures (see below) induces diffusion and in most cases results in recombination of the radical pair.

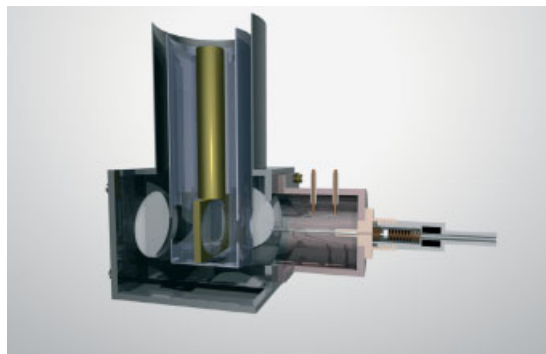


Figure 2 Cryostat combined with a pulsed hyperthermal nozzle. After the expansion into the high vacuum system, the molecular beam is trapped on a cold spectroscopic window.

A different technique to generate free radicals, which avoids these problems, is the FVP, followed by trapping of the pyrolysis products in an inert matrix. Under these conditions, the radicals are formed in the gas phase and trapped in individual matrix cages. Therefore, radical recombination is unlikely as long as the matrix is highly diluted and diffusion is prevented. A problem of this technique is that the energy is transferred to the precursor molecule by collisions with the wall of the hot pyrolysis tube. This frequently leads to unwanted decompositions and side reactions, resulting in low yields of radicals. To overcome this problem, the precursor has to be carefully selected.

Alternatively, a pulsed hyperthermal nozzle can be used to produce the radicals in a supersonic jet.^{2,15,16} In this case, the energy is transferred to the precursor via collisions with a hot inert gas, which is much cleaner than wall collisions. In a supersonic expansion, the radicals are already cooled down and subsequently trapped with the inert gas (most frequently argon) on a cold spectroscopic window to form the matrix. Prerequisite for this method is that the radical precursor has a rather high vacuum pressure to seed the inert gas. For a number of small radicals, very clean spectra could be obtained this way (Figure 2).^{2,17,18}

1.2 Spectroscopy of Matrix-Isolated Radicals

The most important spectroscopic methods used for the characterization of matrix-isolated radicals are electron paramagnetic resonance (EPR) and infrared

(IR) spectroscopy. Other methods frequently used are UV–vis and fluorescence spectroscopies, but by far the most useful method for the characterization of matrix-isolated species is IR spectroscopy. The absence of molecular rotations and the weakly interacting environment results in well-resolved, narrow bands of high intensity. Even in complex mixtures, IR bands of the individual molecules are in most cases well separated and can be directly compared to gas phase spectra or quantum chemical calculations (which in most cases are used to calculate gas phase IR spectra). Neon is the least interacting matrix host, and molecular vibrations of molecules isolated in neon show only small deviations from the gas phase values (in average less than 1 cm^{-1}). Argon is most frequently used as matrix since it requires less sophisticated cryostats (10 K instead of 4 K for neon). The deviation of IR frequencies compared to the gas phase is significantly larger here, but on average still less than 2 cm^{-1} (Figure 3).⁸

To obtain IR spectra, the matrix is deposited either on a cold spectroscopic window such as CsI that is positioned in the IR beam or on a reflecting metallic mirror to measure in reflectance. In the early days of matrix spectroscopy, the most difficult task was to assign the spectra and to identify reactive species such as radicals in the matrix. The synthesis of the same radical from chemically very different precursors is one method to become confident about the identification. Extensive

isotopic labeling is another important tool for the assignment of species. Nevertheless, since many of the reactive species isolated in matrices were completely unprecedented, many early assignments were only tentative and some assignments later had to be corrected. The development of powerful quantum chemical methods (density functional theory (DFT) and *ab initio*) for the calculation of IR spectra was a major step forward for IR matrix spectroscopy and largely improved the assignments of new and unusual species.

An interesting method that has been successfully used in some cases to gain information on the symmetry of IR or UV–vis transitions is based on the complete immobilization, including rotation, of molecules in inert gas matrices at very low temperatures.^{19,20} Since rotations are inhibited in matrices, the distribution of orientations of trapped molecules is random. If these matrices are irradiated with linear polarized light, molecules with their transition moment vectors oriented closely to the direction of the E-vector of the irradiating light will undergo faster photolysis than molecules oriented in other directions. Partial photolysis therefore leads to an orientation of both the remaining precursor and the product formed. This results in IR or UV–vis dichroism if the spectra are recorded using a polarized IR or UV–vis beam, respectively. The analysis of these spectra allows to obtain information on the symmetry and in some cases even on the geometry of the molecules.

EPR spectroscopy is the other important tool to characterize matrix-isolated radicals. The method is very sensitive and specific to paramagnetic species. This allows detection of very low concentrations of radicals. Thus, frequent by-products in pyrolysis reactions are hydrogen atoms or methyl radicals, which are easily detected by EPR spectroscopy. The high sensitivity can also be a disadvantage, since minor paramagnetic side products might result in large signals, whereas major diamagnetic products are not observed at all. In most instances, EPR spectra of radicals were measured in organic glasses at $4\text{--}77\text{ K}$. These are easily prepared by cooling solutions of the precursor in a suitable solvent that forms glasses upon freezing. However, these glasses are strongly interacting with the solute and in many cases react with the radicals and other highly reactive species. Thus, matrix EPR spectroscopy is a better choice, although technically more demanding. For these experiments, the matrix is deposited on

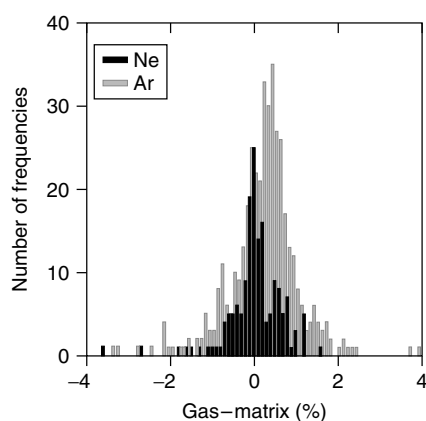


Figure 3 Deviation of IR frequencies measured in neon and argon, respectively, compared to gas phase values. [M. E. Jacox, *Chem. Soc. Rev.*, 2002, **31**, 108. Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/B102907J>.]

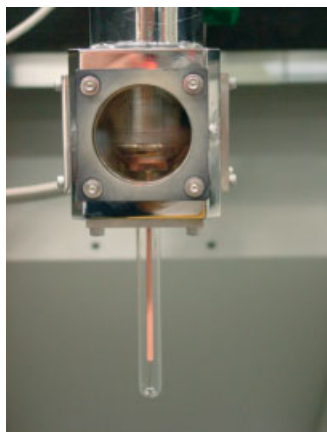


Figure 4 Cryostat with attached copper rod and quartz tube for EPR spectroscopy.

top of a copper or sapphire rod, which is positioned inside a quartz tube in a high vacuum system (Figure 4). This quartz tube is then inserted into the microwave cavity of the EPR spectrometer.

1.3 Reactions of Matrix-Isolated Radicals

Matrices are well suited to isolate and characterize radicals. Irradiation of matrix-isolated radicals with visible or UV light in many cases results in rearrangements or fragmentations. These might be true photochemical reactions or hot ground-state reactions induced by local heating via internal conversion from excited states. In some instances, xenon exciplexes were successfully used to induce thermal reactions in cryogenic matrices.²¹ However, this technique requires that the precursor does not absorb the light required for the formation of the exciplexes, and has not found many applications.

Bimolecular reactions in matrices require the diffusion of the components in the solid state. Small molecules such as O₂, CO, or CO₂ diffuse rapidly if the matrix is annealed at a temperature of about 30–50% of its melting point. For argon, this is at 30–35 K and for neon, this is already at 5–6 K. At these temperatures, bimolecular reactions can be monitored directly by spectroscopy. Prerequisite for a bimolecular reaction to take place at these low temperatures is an extremely low or absent activation barrier, such as for many radical recombinations. This is the reason why bimolecular reactions

other than recombination of the radical pair to form back the precursor molecule are rarely observed if the radical has been produced photochemically. The best conditions to observe bimolecular reactions of matrix-isolated radicals are synthesis of the radicals via FVP and subsequent trapping in argon or nitrogen doped with 0.5–2% of the second reactant at 3–10 K. If the radicals are trapped in matrix cages that contain a reactive molecule (e. g., molecular oxygen), the reaction product is formed directly after deposition. At concentrations between 0.5% and 2%, still enough radicals are trapped that do not directly react with the added reagent. Annealing of these matrices at 25–35 K results in bimolecular reactions induced by diffusion.

In this article, we focus on matrix-isolated radicals of relevance to organic chemistry. Atoms and small diatomic radicals such as HO[•] have been excluded as also mainly inorganic radicals and EPR studies in organic glasses. Some of these systems are covered in a recent, highly recommended review.²² Most of the organic radicals described here are of fundamental importance and have been characterized by both IR and EPR spectroscopy. This provides detailed insight into the electronic structure, spin distribution, and geometry of these radicals. A step further is investigations of uni- and bimolecular reactions in matrices, which give important information about radical reactivity and the primary reaction products. These data are included in the article wherever they are available.

2 ALKYL RADICALS

2.1 Methyl Radical

The methyl radical is a highly reactive intermediate of fundamental importance to chemistry,²³ which plays a key role in atmospheric chemistry²⁴ and combustion processes.²⁵ Therefore, methyl radical has been investigated in a large number of studies using a variety of spectroscopic methods such as EPR,^{26,27} IR,²⁸ or UV–vis spectroscopy in combination with the matrix-isolation technique. A major question that has been addressed by many spectroscopic studies concerned the structure of CH₃[•], in particular whether or not it is a planar species or pyramidal with a low inversion barrier. This question was settled by a gas phase

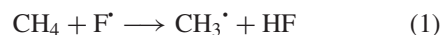
microwave study,²⁹ which, in accordance with quantum chemical calculations,¹⁴ indicates a planar structure with D_{3h} symmetry. Thus, the methyl radical is described best as a π -radical with the unpaired electron in the carbon p orbital perpendicular to the CH bond.

The matrix isolation of $\text{CH}_3^\bullet$ was pioneered by Milligan and Jacox in 1967.³⁰ Vacuum UV photolysis of methane, matrix-isolated in argon or nitrogen at 14 K, results in the formation of the methyl radical with a UV absorption at 150.3 nm, in agreement with the gas phase absorption that had been previously reported by Herzberg and Shoosmith,³¹ and a prominent IR absorption at 611 cm^{-1} . The latter band was assigned to the CH out-of-plane deformation mode, which was confirmed by deuterium and ^{13}C isotopic labeling that resulted in the predicted isotopic shifts.³⁰ As expected, the harsh irradiation conditions do not selectively produce $\text{CH}_3^\bullet$, but rather a complex reaction mixture that also contains CH, C_2 , C_3 , and C_2H_2 . Although not directly observed, the formation of CH_2N_2 in nitrogen matrices indicates that CH_2 is also present. Annealing of matrices containing $\text{CH}_3^\bullet$ results in the disappearance of this species via bimolecular reactions (e. g., with hydrogen atoms to give back CH_4), which is indicative of its reactive nature. To record more complete spectra of $\text{CH}_3^\bullet$ and to investigate its chemistry under the conditions of matrix isolation, more suitable precursors and higher yields of the radical were clearly necessary.

Methyl iodide and dimethyl mercury were used as precursors of $\text{CH}_3^\bullet$ and $\text{CD}_3^\bullet$ using FVP with subsequent trapping of the products in neon at 4 K (Scheme 1). Three IR active bands were observed, and the D_{3h} structure was confirmed by these experiments.³² Another interesting method for the generation of matrix-isolated $\text{CH}_3^\bullet$ is the abstraction of H atoms from CH_4 with fluorine atoms.²⁸ Fluorine

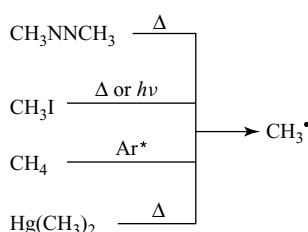
atoms are generated by microwave discharge of an Ar/ CF_4 or Ar/ NF_3 mixture. If the Ar/F mixture is codeposited with CH_4 to form an argon matrix, HF and $\text{CH}_3^\bullet$ are detected by IR spectroscopy (1). Additional sets of vibrational bands were assigned to the $\text{CH}_3\text{F}\cdots\text{HF}$ and $\text{CH}_3^\bullet\cdots\text{HF}$ weakly bound complexes.²⁸ Johnson and Andrews³³ photolyzed the $\text{CH}_4\cdots\text{F}_2$ van der Waals complex in argon to obtain the $\text{CH}_3^\bullet\cdots\text{HF}$ complex with a prominent HF stretching mode at 3764 cm^{-1} .

Therefore, matrix isolation not only allows to generate and characterize the methyl radical but also to obtain weakly bound complexes of the radicals. An interesting question is whether complexation leads to pyramidalization of $\text{CH}_3^\bullet$. Indeed, the hyperfine constant determined from electron spin resonance (EPR) experiments indicates C_{3v} symmetry for the $\text{CH}_3^\bullet\cdots\text{HF}$ complex, in agreement with *ab initio* calculations at the UMP4/6-311(d,p)//UMP2/6-311(d) level of theory.^{34,35}



The D_{3h} symmetry of $\text{CH}_3^\bullet$ implies that the IR active modes with E' , A_1' , and A_2' symmetry are Raman inactive and similarly the Raman modes are IR inactive. In accordance with this, the three IR active frequencies are found at $\nu_4 = 617\text{ cm}^{-1}$ (A_2'), $\nu_1 = 3162\text{ cm}^{-1}$ (E'), and $\nu_2 = 1396\text{ cm}^{-1}$ (E'') (Figure 5).¹⁴

The EPR spectra of the methyl radical trapped in various matrices have been investigated in detail. In solid N_2 , CO, and CO_2 , the EPR spectra show axial anisotropy, which indicates a free rotation about the C_3 axis.²⁶ In Ar, an isotropic EPR spectrum was



Scheme 1 Reaction channels for the synthesis of methyl radical.

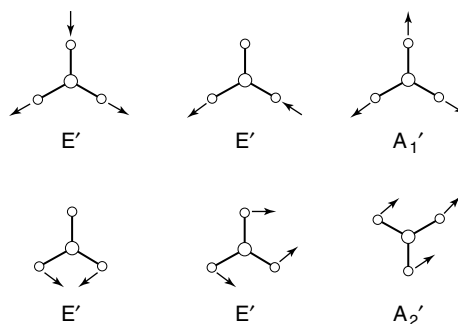


Figure 5 Normal mode displacement diagrams for the methyl radical.

observed above 20 K, whereas in Kr, the spectrum is isotropic throughout the whole temperature range.²⁷ This suggests that below 20 K in argon, CH₃[•] is not rotating. In methanol glass, the EPR spectrum shows forbidden lines as satellites as a result of dipolar coupling of the unpaired electron with protons of neighboring methanol molecules.³⁶

The reaction of CH₃[•] with molecular oxygen produces the methyl peroxy radical (2), an important reactive intermediate in the oxidation of methane³⁷ that plays a major role in the oxidation of NO to NO₂. This process is of large relevance to stratospheric chemistry, since NO₂ is the direct precursor of ozone smog and a major driving force in urban air pollution (3–6).^{38,39}

Of relevance to atmospheric chemistry is also the reaction of the methyl radical with ozone (7), which has been the subject of several direct⁴⁰ and indirect studies.⁴¹ Albaladejo *et al.* determined the rate constant for the reaction (7) to be $9.68 \pm 1 \times 10^{-14} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$. The methoxyl radical (CH₃O[•]) formed in this reaction was detected by laser-induced fluorescence (LIF) spectroscopy.⁴²

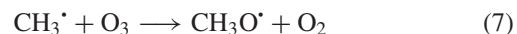
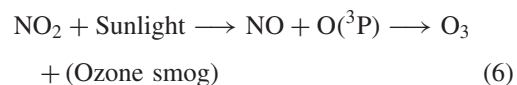
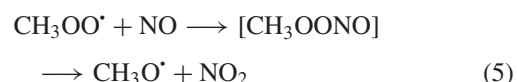
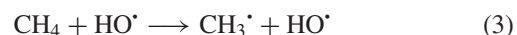
The methyl peroxy radical (CH₃OO[•]) was isolated in cryogenic matrices by co-depositing pulses of methyl radicals produced by pyrolysis of azomethane and pulses of O₂/Ar.⁴³ Ten of the 12 fundamental IR absorptions were observed and the symmetries (a' or a'') were determined via photoorientation of the trapped species. According to these experiments, the methyl peroxy radical is planar with 12 vibrational modes that are all IR active (Table 1).⁴³

Table 1 Vibrational frequencies of matrix-isolated methyl peroxy radical.^a

Mode	Symbol	Ar	Assignment
1	a'	3032	Sym. CH ₃ str.
2		2957	Sym. CH ₃ str.
3		1448	CH ₃ def.
4		1410	CH ₃ def.
5		1180	CH ₃ rock/O–O str.
6		1109	O–O str.
7		1002	C–O str.
8	a''	492	C–O–O bend
9		3024	Asym. CH ₃ str.
10		1434	CH ₃ def.
11		—	CH ₃ rock
12		—	CH ₃ –O–O tor.

Sym., symmetrical; str., stretching; def., deformation; Asym., antisymmetrical; tor., torsion.

^aReference 43.



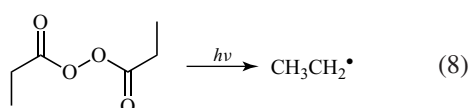
According to electron affinity and gas phase acidity measurements⁴⁴ in combination with *ab initio* calculations,⁴⁵ the heat of formation $\Delta_f H_{298}$ of the methyl peroxy radical (CH₃OO[•]) was determined to be $4.8 \pm 1.2 \text{ kcal mol}^{-1}$. From that follows a heat of reaction $\Delta_{\text{rxn}} H_{298}$ for the direct reaction of the methyl radical with molecular oxygen of $-30.1 \pm 1.2 \text{ kcal mol}^{-1}$.

The electronic structure of CH₃OO[•] in its ground state is X ²A'' with a low-lying A ²A'' excited state in the near-IR.⁴⁶ The electronic spectrum shows a broad transition at 250 nm attributed to the excitation to the B ²A'' state.³⁹

2.2 Ethyl Radical

The ethyl radical has been extensively studied over the past three decades, both experimentally⁴⁷ and theoretically.⁴⁸ The first high-resolution IR spectrum of CH₃CH₂[•] in the gas phase was obtained by Johnson and Sears,^{49,50} showing a band at 528 cm^{-1} attributed to the out-of-plane vibration at the CH₂ radical center. A barrier of about 20 cm^{-1} was determined for the rotation about the CC bond. The almost free internal rotation has been later confirmed by high-level *ab initio* calculations. Davis *et al.*⁵¹ reported the rotationally resolved spectrum of the CH stretching region of the jet-cooled ethyl radical. The strong coupling between the CH₂ and CC torsional modes was attributed to open-shell hyperconjugation between the singly occupied p orbital at the radical center and the β-CH bond in the methyl group. This stabilizing interaction results in a shortening of the CC bond and elongation of the CH bond compared to ethane.¹⁴

The C_s symmetrical ethyl radical possesses 15 vibrational modes, 9 of A' symmetry and 6 of A'' symmetry, which are all Raman and IR active.¹⁴ The IR spectrum of the ethyl radical in an argon matrix was reported by Pacansky *et al.* The radical was generated by irradiation of dipropionyl peroxide in high yield (8).^{52,53} A quantitative assignment of the spectrum was obtained by comparison with calculated spectra at the unrestricted Hartree–Fock (UHF) and UMP2/6-311G(d,p) levels of theory.^{14,54} The matrix IR spectrum of $CH_3CH_2\cdot$ shows a strong CH stretching vibration at 2840 cm^{-1} , which is unusually low in frequency, and assigned to the CH stretching mode of the β -CH bond. The low frequency of the CH stretching vibration was also observed in the partially deuterated ethyl radical. The redshift indicates the weakening of the β -CH bonds in alkyl radicals by hyperconjugation.⁵⁵



The EPR spectrum of the ethyl radical was observed after γ -radiolysis of ethane⁵⁶ or ethyl halides at 77 K,⁵⁷ UV photolysis of ethyl alcohol at 77 K,⁵⁸ or photolysis of ethyliodide in argon at 4 K.⁵⁹ Owing to the broadening of the EPR spectra by dipolar interactions, it was not possible to determine the anisotropic hyperfine couplings. McDowell *et al.*⁶⁰ obtained the EPR spectrum of the ethyl radical in an argon matrix after UV photolysis of a mixture of ethane and HI. The lineshape analysis allowed determination of the anisotropic hyperfine interaction parameters for the α and β protons as well as the g -values ($A^\alpha = 19.4 \pm 0.5$ G, $A^\alpha = 29.6 \pm 0.5$ G, $A^\beta = 25.9 \pm 0.5$ G, $A^\beta = 28.7 \pm 0.5$ G, $g_{\text{av}} = 2.0023 \pm 0.0003$, $\Delta g = g_{||} - g_{\perp} \leq 0.0003$).

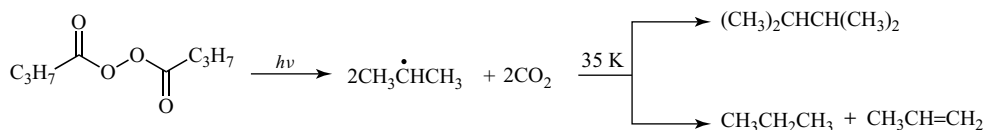
A variety of spectroscopic techniques including UV absorption spectroscopy,⁶¹ flash photolysis/time-resolved UV spectroscopy,^{62,63}

mass spectrometry,⁶⁴ pulse radiolysis,⁶⁵ and recently, near-IR cavity ring-down spectroscopy were used to obtain kinetic and mechanistic data of the reaction of the ethyl radical with molecular oxygen (9).⁶⁶ Snelson's laboratory has reported the matrix IR spectra of several alkylperoxy radicals prepared by $[R^\cdot + O_2]$ recombination reactions. Chettur and Snelson⁶⁷ pyrolyzed azoethane to produce the ethyl radical that was subsequently deposited in a mixture of oxygen and argon at 10 K. Mode assignments were based on the frequency shifts using isotopically labeled $^{18}O_2$. The OO stretching mode at 1112 cm^{-1} shows the expected large redshift of 47 cm^{-1} when $^{18}O_2$ was used.

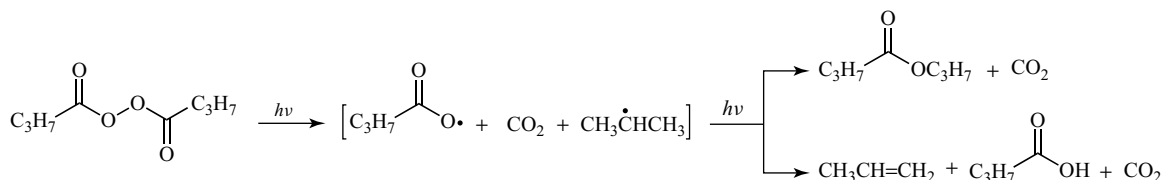


2.3 *n*-Propyl and Isopropyl Radicals

The matrix IR spectrum of the isopropyl radical was reported for the first time by Pacansky and Counfal in 1980 (Scheme 2).⁶⁸ Irradiation of diisobutyl peroxide in an argon matrix with UV light produces the isopropyl radical in good yield. Further irradiation with shorter wavelength UV light leads to isobutyric ester, propylene, and isopropyl isobutyrate (Scheme 3). The formation of the latter product is explained by the reaction of the excited radical with CO_2 . The IR spectrum reveals that more than one conformer of the isopropyl radical is trapped in the matrix. According to quantum chemical calculations, the isopropyl radical is nonplanar at the radical center and shows C_s symmetry with the α -CH bond lying in the plane of symmetry and the two methyl groups being symmetrical to this plane. The nonplanar geometry at the radical center introduces some s character into the carbon p orbital of the unpaired electron, and the geometry acquires a pyramidal structure similar to ammonia.¹⁴ Pacansky *et al.* located seven different conformers of the isopropyl radical of very



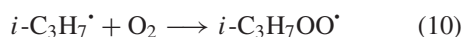
Scheme 2 Generation and thermal reactions of *n*-propyl radical in argon matrix.



Scheme 3 Photochemistry of diisobutyryl peroxide in an argon matrix.

similar energy, which differ mainly by rotation of the methyl groups.^{69,70}

The isopropyl radical $i\text{-C}_3\text{H}_7\cdot$ was synthesized by pyrolysis of bis(1-methylethyl)diazene and subsequently trapped in solid argon.⁷¹ The radical shows a characteristic out-of-plane bending mode at 374 cm^{-1} . Irradiation of the isopropyl radical results in its rearrangement to the n -propyl radical with bands at 523, 1035, 3028, and 3118 cm^{-1} . Upon annealing of the matrix at 40 K, the n -propyl radical dimerizes to n -hexane.



The isopropyl peroxy radical was synthesized by the reaction of the isopropyl radical with molecular oxygen in an argon matrix (10).⁷¹ The nonlinear COO group in this radicals results in a lowering of the symmetry to either C_1 or C_s symmetry with a total of 30 IR active frequencies. The $\nu(\text{OO})$ stretching mode shows the expected pronounced redshift from 1101 to 1059 cm^{-1} when $^{18}\text{O}_2$ is used.

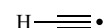
The n -propyl radical was also directly synthesized and characterized in argon matrices.^{72,73} UV photolysis of dibutyryl peroxide produces the n -propyl radical and CO. Annealing of the matrix to allow diffusion of the n -propyl radical results in its dimerization to n -hexane and disproportionation to n -propane and propene.

3 UNSATURATED RADICALS

3.1 Ethynyl Radical

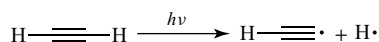
The ethynyl radical, $\text{C}_2\text{H}\cdot$, is an unsaturated aliphatic radical that plays an important role in combustion chemistry,⁷⁴ as a key intermediate in the formation of polyenes in the atmospheres of planets^{75,76} and as a constituent of interstellar clouds.^{77,78} The bond dissociation energy DH_{298}

of the CH bond of acetylene has been determined by negative ion mass spectroscopy and photoelectron spectroscopy to be $133.3 \pm 0.3\text{ kcal mol}^{-1}$, and the heat of formation $\Delta_f H_{298}$ to $135.6 \pm 0.2\text{ kcal mol}^{-1}$.^{44,79}



A high-resolution gas phase spectrum was obtained for the lowest rotational transition in the $X^2\Sigma^+$ electronic ground state of $\text{C}_2\text{H}\cdot$.⁷⁷ The very complex rotational spectrum of $\text{C}_2\text{H}\cdot$ was obtained at millimeter and submillimeter wavelengths in the vibrational ground state^{80–82} and in the lowest bending vibrational level.⁸³ The complexity of the spectrum arises from the vibronic coupling of the bending and CC stretching vibrations in the $X^2\Sigma^+$ ground state with the low-lying $A^2\Pi$ state.^{84–86} The energy between the $A^2\Pi$ and $X^2\Sigma^+$ states was determined to be about 3700 cm^{-1} .⁸⁷ Laser magnetic resonance (LMR) spectroscopy in combination with quantum chemical calculations was used to determine the lowest vibronic state of the $A^2\Pi$ state.^{88–90} Carrick *et al.*⁹¹ used high-resolution color center laser spectroscopy to assign several bands of the $A^2\Pi \leftarrow X^2\Sigma^+$ system in the region $3600\text{--}4200\text{ cm}^{-1}$. Time-resolved absorption spectroscopy allowed to assign a UV absorption at 243 nm to an electronic transition of $\text{C}_2\text{H}\cdot$.⁹²

Milligan *et al.*⁹³ reported the isolation and IR spectroscopic characterization of $\text{C}_2\text{H}\cdot$ in solid argon. The radical was generated by discharge in $\text{C}_2\text{H}_2/\text{Ar}$ mixtures and trapped on a spectroscopic window at 14 K. The complicated spectrum contains more than 50 transitions between 3000 and 8000 cm^{-1} arising from a conical intersection between the Σ^+ and Π states.⁸⁶ A band at 1848 cm^{-1} was assigned to the $\text{C}\equiv\text{C}$ stretching mode ν_3 of $\text{C}_2\text{H}\cdot$, which was confirmed by isotopic substitution studies, and a band at 3611 cm^{-1} was



Scheme 4 Photochemistry of acetylene.

attributed to the CH stretching mode ν_1 .⁹⁴ ^{13}C substitution allowed to assign the band at 3610 cm^{-1} to a combination vibration ($\nu_1 + \nu_2$ or $\nu_1 + 2\nu_2$) and in addition bands at 2104 and 258 cm^{-1} to the $\nu_2 + \nu_3$ and ν_2 bending modes.⁹⁵ Wu and Cheng⁹⁶ generated $\text{C}_2\text{H}\cdot$ by vacuum UV photolysis of acetylene in solid neon using synchrotron irradiation at 185, 171, 130, and 114 nm and found that in particular 171-nm irradiation is efficient to produce the $\text{C}_2\text{H}\cdot$ radical (Scheme 4). Although the major photoproduct formed under these conditions is $\text{C}_2\text{H}\cdot$, other photoproducts observed are C_2H_3 , C_4 , C_4H , C_4H_2 , C_6 , and C_8H_2 . The high yields of $\text{C}_2\text{H}\cdot$ obtained in these experiments allowed to reassign the CH stretching mode ν_1 at 3292.3 cm^{-1} (2536.7 cm^{-1} in $\text{C}_2\text{D}\cdot$).⁹⁶



3.2 Vinyl Radical

The vinyl radical $\text{C}_2\text{H}_3\cdot$ plays a role in combustion and atmospheric chemistry, and therefore has been subject to a number of experimental and theoretical studies.^{74,97} The vinyl radical is typically produced by H-atom abstraction from ethylene. The CH bond dissociation energy DH_{298} of ethylene was determined to be $110.7 \pm 0.6\text{ kcal mol}^{-1}$, and the heat of formation $\Delta_f H_{298}$ of the vinyl radical was determined to be $71.1 \pm 0.6\text{ kcal mol}^{-1}$.^{44,79}



The vinyl radical is a σ -type radical with an X^2A' electronic ground state.^{97,98} Electron spin resonance (EPR) studies indicate that the vinyl radical is essentially planar and the unpaired electron occupies an sp^2 hybrid orbital.^{99,100} The structure and electronic properties of the vinyl radical were investigated at various levels of theory.^{97,98,101,102}

The electronic absorption spectrum of $\text{C}_2\text{H}_3\cdot$ reported by Hunziker *et al.* shows an absorption at

499.5 nm assigned to the $^2A'' \leftarrow ^2A'$ transition.¹⁰³ The UV spectrum was later also observed by cavity ring-down spectroscopy.^{104,105} An absorption at 230 nm was assigned to the $\pi^*(2a'') \leftarrow \pi(1a'')$ transition by comparison with the results of *ab initio* calculations. In addition, two intense vacuum UV absorptions at 164.7 and 168.3 nm were reported by Fahr and Laufer¹⁰⁶.

The matrix isolation of the vinyl radical was reported by Jacox and Olson.¹⁰⁷ The radical was generated by microwave discharge of a gaseous mixture of $\text{C}_2\text{H}_2/\text{Ar}$ and trapped in argon at 12 K. For the C_s symmetrical vinyl radical, nine IR active vibrational modes are expected, seven of A' symmetry and two of A'' symmetry. An IR band near 900 cm^{-1} was assigned to the out-of-plane bending vibration mode (ν_7). Later, a prominent absorption at 900.8 cm^{-1} was assigned to this vibration on the basis of deuterium and ^{13}C -isotopic-substitution experiments.¹⁰⁸ In solid neon, this band is shifted to 895.4 cm^{-1} .⁸³ An alternative route to the vinyl radical is the thermal reaction between hydrogen atoms and acetylene under the conditions of matrix isolation (12).¹⁰⁹ Vacuum UV (120 nm) irradiation of ethylene was used to generate the vinyl radical in solid neon (Table 2).¹¹⁰



The reaction of the vinyl radical with molecular oxygen has been studied using matrix isolation IR spectroscopy.¹¹¹ The vinyl radical was produced by discharge in a $\text{C}_2\text{H}_4/\text{Ar}$ mixture and co-deposition with Ar/O_2 on top of a cold window. Annealing of these matrices produced the vinylperoxy radical $\text{C}_2\text{H}_3\text{OO}\cdot$ (13). According to calculations at the UB3LYP/6-311++G(d,p) level of theory, the reaction of $\text{C}_2\text{H}_3\cdot$ with O_2 to give $\text{C}_2\text{H}_3\text{OO}\cdot$ is exothermic by $40.8\text{ kcal mol}^{-1}$, with the s-trans conformer being 1.3 kcal mol^{-1} more stable than the cis form. Absorptions at 1140.7 and 875.5 cm^{-1} were assigned to the OO stretching and out-of-plane CH_2 bending vibrations, respectively, of the *trans*-vinylperoxy radical.



Irradiation of $\text{C}_2\text{H}_3\text{OO}\cdot$ with visible light produced a weakly bound complex between $\cdot\text{CH}_2\text{OH}$

Table 2 Vibrational frequencies of matrix-isolated vinyl radical.

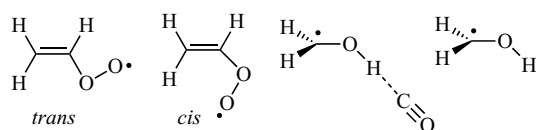
Mode	Symbol	Ar ^a	Ne ^b	Assignment
1	a'		3141.0	α -CH. str.
2			2953.6	Asym. CH ₂ str.
3			2911.5	Sym. CH ₂ str.
4			—	C=C str.
5	a''	1356.7	1357.4	CH ₂ bend
6			—	HCCH <i>trans</i> bend
7		677.0	677.1	HCCH <i>cis</i> bend
8		900.8	895.3	CH ₂ o.o.p. bend
9			857.0	α -CH o.o.p. bend

Sym., symmetrical; str., stretching; Asym., antisymmetrical; o.o.p., out of plane.

^aReference 109.

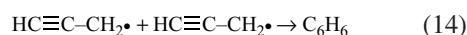
^bReference 110.

and CO, which was characterized by its vibrations at 3604.5, 2155.8, 1188.2, 1063.9, and 494.4 cm⁻¹.¹¹¹



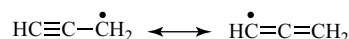
3.3 Propargyl Radical

The propargyl radical C₃H₃• plays a central role as a precursor of benzene in many gas phase processes, including combustion^{112–114} and atmospheric chemistry.¹¹⁵ The most important gas phase reaction of C₃H₃• is the dimerization to produce benzene (14).¹¹⁶

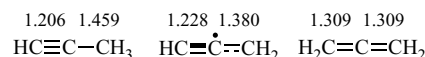


The bond dissociation energy DH_{298} of the methyl CH bond in propyne was determined to be 90 ± 3 kcal mol⁻¹, and the heat of formation $\Delta_f H_{298}$ of C₃H₃• was determined to be 83 ± 3 kcal mol⁻¹.^{44,117} Thus, the radical stabilization energy of the propargyl radical is similar to that of the allyl radical, indicating a similar amount of delocalization of the unpaired electron. This has been confirmed by EPR measurements¹⁰⁰ and by quantum chemical calculations.^{17,118,119} The electronic structure of the propargyl radical is represented best by the propargyl and allenyl resonance structures,

which contribute almost equally to the spin distribution.



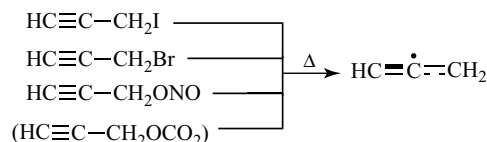
On the basis of the spin density calculations, 35% of the spin is localized at C(3) and 65% at C(1).¹⁷ According to high-level computational studies, the bond lengths of the propargyl radical are between that of methyl acetylene and allene, in agreement with the resonance structures.¹⁷ The propargyl radical is a highly delocalized π -type radical with C_{2v} symmetry and X²B₁ electronic ground state.^{100,120}



The UV spectrum of C₃H₃• has been obtained in the gas phase by flash photolysis of C₃H₃Cl and C₃H₃Br where a broad band at 242 nm was assigned to the B²B₁ ← X²B₁, $\pi^*(b_2) \leftarrow \pi(b_2)$ transition.¹²⁰ Electronic absorptions at 351.9 and 343.0 nm assigned to the A²A'' ← X²B₁ and B²A'' ← X²B₁ transitions, respectively, were observed in neon matrix at 5 K.¹²¹ From a high-resolution rotational spectrum of the propargyl radical, the ground-state rotational constants $A_0 = 288\,055.0$ MHz, $B_0 = 9523.6775 \pm 0.0060$ MHz, and $C_0 = 9206.8805 \pm 0.0060$ MHz were obtained.¹²²

The propargyl radical has 12 normal modes that are all IR active (five of a₁, three of b₁, and four of b₂ symmetry). The first IR spectrum of C₃H₃• was obtained in matrices produced by trapping the products of the vacuum UV photolysis of allene or methylacetylene.¹²³ Four IR bands at 3308, 686, 548, and 484 cm⁻¹ were assigned to the propargyl radical initially by Jacox and Milligan,¹²³ but later the band at 548 cm⁻¹ was reassigned to triplet propargylene.¹²¹ Higher yields of C₃H₃•, which allowed to assign all 12 IR bands, were obtained by FVP of propargyl iodide (HC≡CCH₂I) or dipropargyl oxalate (HC≡CCH₂OCO)₂ with subsequent trapping of the products in inert matrices (Scheme 5).¹²⁴

High yields of the propargyl radical were also obtained by thermolysis of propargyl bromide (HC≡CCH₂Br) or butyne nitrite (HC≡CCH₂ONO) in a hyperthermal nozzle in the presence of high pressure of argon (Scheme 5). Expansion into a

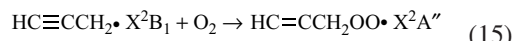


Scheme 5 Synthesis of the propargyl radical.

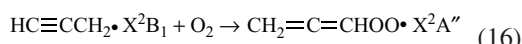
vacuum system formed a supersonic jet, which was trapped on a cold spectroscopic window to form an argon matrix.¹⁷ The high quality of the matrices obtained by this method allowed to observe nine IR transitions. The symmetry of these transitions was determined by measuring the IR dichroism in partially oriented matrices after photolysis with polarized 248-nm light (Table 3). Zhang *et al.*¹²⁵ were able to assign the out-of-plane bending mode ν_8 at $378.0 \pm 1.9 \text{ cm}^{-1}$ and a number of overtones and combination bands (Table 3).

The propargyl radical reacts with oxygen in solid argon to produce the propargyl peroxy radical, which suggests that this reaction occurs with a very

small or no barrier (15).¹²⁶



Two isomeric products are obtained from this reaction, the propargyl peroxy and the allenyl peroxy radical (15 and 16).



On the basis of the QCISD(T,Full)/6-311++G (3df,2pd) calculations, the addition of O_2 to the CH_2 group of $\text{C}_3\text{H}_3\cdot$ is dominating at low temperatures, whereas the addition to the CH group becomes the dominant process at higher temperatures.¹¹⁶ The barrier for the O_2 addition to the CH_2 group was estimated to be $3.4 \text{ kcal mol}^{-1}$ lower than that to the CH group, which suggests that under the conditions of matrix isolation, preferentially $\text{HC}\equiv\text{CCH}_2\text{OO}\cdot$ is formed.¹¹⁶ Jochowitz *et al.*¹²⁶ calculated the bond energies of the peroxy bond at the CBS-QB3 level of theory. From the analysis of the IR spectrum of the reaction product including measuring the IR dichroism in partially oriented matrices, it was concluded that *trans*- $\text{HC}\equiv\text{CCH}_2\text{OO}\cdot$ was

Table 3 Vibrational frequencies of matrix-isolated propargyl and propargyl peroxy radicals.

$\text{HC}\equiv\text{C}-\text{CH}_2\cdot$				$\text{HC}\equiv\text{C}-\text{CH}_2\text{OO}\cdot$			
Mode	Symbol	$\text{Ar}^{a,b}$	Assignment	Mode	Symbol	Ar^c	Assignment
1	a_1	3308 ± 0.5	CH str.	1	a'	3326 ± 3	CH str.
2		3028 ± 0.6	Sym. CH_2 str.	2		2960 ± 3	Sym. CH_2 str
3		1935.4 ± 0.4	$\text{C}\equiv\text{C}$ str.	3		2148 ± 1	$\text{C}=\text{C}$ str.
4	b_1	1440.1 ± 0.8	CH_2 sciss.	4		1440 ± 1	CH_2 sciss.
5		1061.6 ± 0.8	$\text{C}-\text{C}$ str.	5		1338 ± 1	CH_2 wag.
6		686.5 ± 0.7	CH_2CCH umb.	6		1127 ± 1	$\text{O}-\text{OCH}_2\text{CCH}$ str.
7	b_2	483.6 ± 0.7	$\text{C}-\text{H}$ o.o.p. bend	7		982 ± 1	$\text{C}-\text{C}$ str.
8		378.0 ± 1.9	CH_2CCH o.o.p. bend	8		928 ± 3	$\text{O}-\text{C}$ str.
9		—	Asym. CH_2 str.	9		684 ± 1	$\text{C}=\text{C}-\text{H}$ in pl. bend
10		1016.8 ± 0.6	$\text{C}-\text{C}/\text{C}=\text{C}$ in pl. bend	10		499 ± 1	$\text{O}-\text{C}-\text{C}$ bend
11		619.5 ± 1.4	$\text{C}-\text{H}$ in pl. bend	11		—	$\text{O}-\text{O}-\text{C}$ bend
12		333 ± 10	CH_2CCH in pl. bend	12		—	$\text{C}-\text{C}=\text{C}$ in pl. def.
$2\nu_{12}$		667 ± 1.0		13	a''	—	Asym. CH_2 str.
$2\nu_7$		972.5 ± 0.9		14		1218 ± 1	CH_2 twist
$\nu_6 + \nu_8$		1053.9 ± 0.9		15		972 ± 1	CH_2 rock
$\nu_{10} + \nu_{12}$		1339.0 ± 0.8		16		63 ± 1	$\text{C}=\text{C}-\text{H}$ o.o.p. bend
$2\nu_6$		1369.2 ± 0.6		17		—	$\text{C}-\text{C}=\text{C}$ o.o.p. def.
$2\nu_{10}$		2029.7 ± 0.5		18		—	$\text{O}-\text{O}-\text{CH}_2-\text{C}$ tor.
$2\nu_4$		2863.3 ± 0.8					

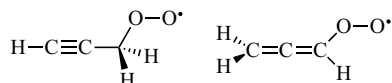
Sym., symmetrical; str., stretching; Asym., antisymmetrical; tor., torsion; o.o.p., out of plane; def., deformation; sciss., scissoring; twist., twisting; wag., wagging; in pl., in plane; in pl. def., in plane deformation.

^aReference 17.

^bReference 125.

^cReference 126.

observed in the matrix and not the isomeric $\text{CH}_2=\text{C}=\text{CH}-\text{OO}^\bullet$ (Table 3).¹²⁶



3.4 Allyl Radical

Ellison *et al.* carefully measured the bond dissociation energy DH_{298} of the methyl group of propene as $88.4 \pm 0.4 \text{ kcal mol}^{-1}$ and the heat of formation $\Delta_f H_{300}$ as $41.4 \pm 0.4 \text{ kcal mol}^{-1}$. This bond dissociation energy is around 12 kcal mol^{-1} lower than that of ethane ($DH_{298}(\text{CH}_3\text{CH}_2-\text{H}) = 101.1 \pm 0.4 \text{ kcal mol}^{-1}$), which results from the resonance stabilization of the unpaired electron in the allyl radical.¹¹⁷ EPR studies^{127,128} and numerous absorption measurements^{129–131} suggest that the allyl radical is planar with C_{2v} symmetry and its electronic configuration in the ground state is X^2A_2 .

The electronic absorption spectrum of the allyl radical was reported by Currie and Ramsay.¹³² Flash photolysis of several precursors produced a band at 408.3 nm that was assigned to a transition ($A^2B_1 \leftarrow X^2A_2$) of the allyl radical. This assignment was later confirmed by cavity ring-down spectroscopy,¹³³ picosecond time-resolved photoelectron spectroscopy,¹³⁴ and photofragment action spectroscopy.¹³⁰ A UV absorption near 224 nm was assigned to a transition into an upper state of 2B_1 symmetry.¹³⁵ Maier *et al.* measured the UV–vis absorption spectrum of the allyl radical in an argon matrix and reported a strong band at 213 nm and a weak band centered at 408.5 nm.¹³⁶ Resonant multiphoton ionization allowed to detect three transitions in the region between 238 and 250 nm, which were assigned by using their symmetry and isotopic shifts.¹³¹ More recently, the vibronic spectra of the 3s and 3p Rydberg states of the jet-cooled allyl radical was identified by resonance-enhanced multiphoton ionization combined with electronic ground-state depletion spectroscopy.¹³⁷

The allyl radical has 18 normal modes (seven of a_1 , two of a_2 , three of b_1 , and six of b_2 symmetry), of which the two a_2 modes are not IR active. Slit discharge supersonic expansion has been used to obtain the high-resolution IR spectra of the jet-cooled allyl radical at low

temperature ($T_{\text{rot}} \approx 20 \text{ K}$) in the CH_2 stretching region.¹³⁸ The in-phase (ν_1) and out-of-phase (ν_{13}) asymmetric CH stretching vibrations were observed at 3113.98 and 3110.60 cm^{-1} , respectively. In the region between 3045 and 3010 cm^{-1} , bands at 3033.87, 3023.46, and 3020.32 cm^{-1} were assigned to the CH stretching vibrations ν_2 , ν_3 , and ν_{14} , respectively.¹³⁹

The first matrix IR spectrum of the allyl radical was reported by Maltsev *et al.*¹⁴⁰ who reported 16 vibrational modes of the allyl radical in argon. Later Maier¹³⁶ and Oth¹⁴¹ were also investigating the allyl radical; however, several assignments of vibrational modes were not consistent with each other. This was solved by measuring the deuterated isotopomers $\text{CH}_2\text{CHCH}_2^\bullet$, $\text{CH}_2\text{CDCH}_2^\bullet$, and $\text{CD}_2\text{CDCD}_2^\bullet$ and the IR dichroism of the IR transitions in partially oriented matrices.¹⁸ UV irradiation at 351 nm with polarized light leads to a partial bleaching of the IR bands of the allyl radical and formation of a new product. By comparison with DFT calculations, all observed vibrations could be assigned according to their symmetry (Table 4).¹⁸

Upon irradiation with 410-nm light (argon matrix), the allyl radical rearranges to the cyclopropyl radical (Scheme 6), which in addition allowed to record the IR spectrum of the cyclopropyl radical. Of the 18 IR active normal modes of the cyclopropyl radical, 16 were observed and assigned.¹⁴¹ From these IR data, it was concluded that the cyclopropyl radical is a σ radical with C_s symmetry (Table 4).

4 ARYL RADICALS

4.1 Phenyl Radical

The phenyl radical ($\text{C}_6\text{H}_5^\bullet$) is the archetypical aromatic σ radical of very high reactivity. It plays a key role in many gas phase and high temperature processes such as combustion and soot formation,¹⁴² formation of polycyclic aromatic hydrocarbons (PAHs),¹⁴³ and the chemistry of the interstellar gas and circumstellar envelopes.¹⁴⁴ It also plays a role as reactive intermediate in many organic reactions.^{145,146} Because of its fundamental importance, the phenyl radical has been extensively studied both experimentally and theoretically. Formally, the phenyl radical is derived from benzene

Table 4 Vibrational frequencies of matrix-isolated allyl and cyclopropyl radicals.

CH ₂ =CH-CH ₂ [*]					Cyclopropyl radical		
Mode	Symbol	Ar ^a	Laser absorption ^{b,c}	Assignment	Symbol	Ar ^d	Assignment
1	a ₁	3109	3113.98488 ^b	Asym.CH ₂ str.	a'	3118	νCH
2		3052	3033.8745 ^c	Sym. CH ₂ str.		3049	ν _{as} CH ₂
3		3027	3023.4605 ^c	CH str.		2980	ν _s CH ₂
4		1478		Sym. CH ₂ sciss.		1440	δCH ₂
5	a ₂	1242		C-C str./CH ₂ sciss.	a''	1237	δ _s CCC
6		—		C-C str./CH ₂ rock		1077	τ _s CH ₂
7		—		CH ₂ CHCH ₂ bend		997	ω _a CH ₂
8		—		CH ₂ CHCH ₂ o.o.p. umb.		827, 824	ν _s CC
9	b ₁	—		CH ₂ CHCH ₂ o.o.p. twist	a''	743	ρCH ₂ + δCH
10		983		CH ₂ C-HCH ₂ o.o.p. bend		—	δCH
11	b ₂	801		CH ₂ CHCH ₂ in. p. unb.	a''	3033	ν _{as} CH ₂
12		510		CH ₂ CHCH ₂ in. p. twist		2965	ν _s CH ₂
13		3107	3110.59857 ^b	Asym.CH ₂ str.		1416	δCH ₂
14		3020	3020.32 ^c	Sym. CH ₂ str.		1229	τ _{as} CH ₂
15		1464		Asym. CH/CH ₂ sciss.		1085	γCH
16		1390		Asym. CH ₂ -CH-CH ₂ str.		1037	ω _{as} CH ₂
17		1182		Asym. CH ₂ -CH-CH ₂ str.		—	ν _{as} CC
18		—		Asym. CH/CH ₂ rock		777	ρCH ₂ + γCH

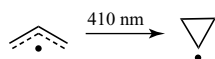
Sym., symmetrical; str., stretching; Asym., antisymmetrical; o.o.p., out of plane; umb., umbrella; twist., twisting; in p. unb., in plane umbrella.

^aReference 18.

^bReference 138.

^cReference 139.

^dReference 141.

**Scheme 6** Photochemical transformation of the allyl radical to the cyclopropyl radical.

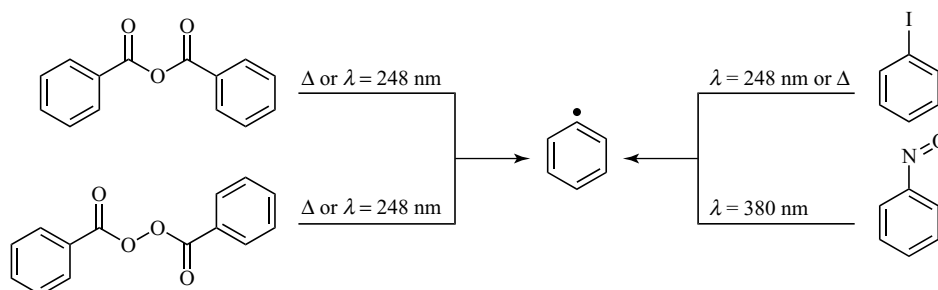
by homolytic cleavage of one of the CH bonds with a bond dissociation energy DH_{298} of 112.9 ± 0.5 kcal mol⁻¹. From that for the phenyl radical, the heat of formation $\Delta_f H_{298}$ of 80.5 ± 0.5 kcal mol⁻¹ was determined.¹⁴⁷

The EPR spectrum of C₆H₅^{*} reported by Bennett *et al.* revealed a C_{2v} structure and an ²A₁ electronic ground state.^{148,149} Later, Kasai *et al.* confirmed that the unpaired electron is localized mainly in a σ -type orbital.¹⁵⁰ In these experiments, C₆H₅^{*} was generated by the photolysis of phenyl iodide in an argon matrix at 4 K. The EPR spectrum of the phenyl radical shows the expected hyperfine coupling of the unpaired electron with two *ortho* ($a_{xx} = 2.19$ mT, $a_{yy} = 1.54$ mT, $a_{zz} = 1.49$ mT), two *meta* ($a_{xx} = 0.66$ mT, $a_{yy} = 0.61$ mT, $a_{zz} = 0.50$ mT), and one *para* ($a_{xx} = 0.20$ mT, $a_{yy} = 0.25$ mT, $a_{zz} = 0.12$ mT) hydrogen atom.

The electronic absorption spectrum of matrix-isolated C₆H₅^{*} in the region of 52 000–4000 cm⁻¹ consists of three band systems corresponding to the A²B₁ ← X²A₁ transition at 510.5 nm, the B²A₁ ← X²A₁ transition at 235.1 nm, and the C²B₂ ← X²A₁ transition at 211.5 nm.¹⁵¹ The symmetry of the electronic transitions was obtained from polarization measurements on photooriented samples.¹⁵¹

The rotational spectrum of C₆H₅^{*} produced by discharge in benzene/argon mixtures was obtained in a supersonic molecular beam.¹⁵² Fourteen rotational transitions between 9 and 40 GHz and over 50 transitions between 150 and 330 GHz were measured for the normal isotopic species. The rotational constants were assigned with the help of CCSD(T)/cc-pVTZ calculations. The high-resolution IR spectrum of the jet-cooled phenyl radical was obtained in a supersonic expansion.¹⁵³

The phenyl radical can be generated by photolysis or pyrolysis of a variety of precursors such as benzoic anhydride, benzoyl peroxide, iodobenzene, or nitrobenzene (Scheme 7). Pacansky *et al.*



Scheme 7 Synthesis of the phenyl radical.

reported the IR spectrum of $C_6H_5^\bullet$ produced by the photolysis of acetyl benzoyl peroxide in an argon matrix^{154,155} Ellison and coworkers were able to record all 24 IR active transitions of $C_6H_5^\bullet$ in matrices produced by matrix photolysis of benzoyl peroxide or benzoyl anhydride.^{156,157} In addition, the symmetry and absolute intensities of the IR modes were reported (Table 5). The Raman active modes were assigned with the help of the isotopic shifts after ^{13}C substitution.¹⁵⁸

Bimolecular reactions of $C_6H_5^\bullet$ with a number of small molecules under the conditions of matrix isolation have been investigated by spectroscopy. Both in the gas phase and in an argon matrix (in the matrix annealing at 30 K is necessary to allow diffusion), the phenyl radical reacts with molecular oxygen to form the phenyl peroxy radical (17).¹⁵⁹



The reaction was calculated to be exothermic by $46.3 \text{ kcal mol}^{-1}$ at the G2M level of theory.¹⁶⁰ In that study, azobenzene was used as a new thermal precursor for the generation of $C_6H_5^\bullet$. The IR spectrum of $C_6H_5OO^\bullet$ exhibits strong bands at 1122.9 , 793.9 , and 607.2 cm^{-1} which are redshifted by 67.2 , 15.6 , and 11.8 cm^{-1} if $^{18}O_2$ is used. These bands were assigned to the $\nu(OO)$, $\nu(CO)$, and $\delta(CCO)$ vibrational modes, respectively, with the aid of DFT calculations (UB3LYP/cc-pVTZ).¹⁵⁹

Matrix-isolated $C_6H_5OO^\bullet$ exhibits a broad visible absorption at 480 nm , in agreement with cavity ring-down experiments.¹⁶¹ Irradiation ($\lambda > 400 \text{ nm}$) of $C_6H_5OO^\bullet$ results in the formation of the 2-oxepinoxy radical with the CO carbonyl stretching vibration at 1726.9 cm^{-1} . This band shows the expected large ^{18}O isotopic redshift (-30.7 cm^{-1}). Prolonged irradiation with visible light ($\lambda > 400 \text{ nm}$)

Table 5 Vibrational frequencies of matrix-isolated phenyl radical.

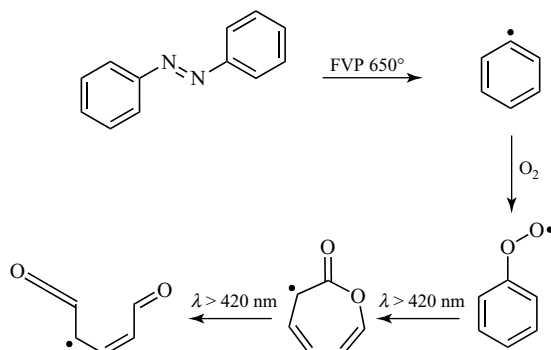
Mode	Symbol	Ar ^a	Assignment
1	a ₁	3086	CH str.
2		3072	CH str.
3		3037	CH str.
4		1581	CH def.
5		1441	CH def.
6		1154	CH def.
7	a ₂	1027	CCC bend
8		997	Ring breath
9		976	Ring def.
10		605	Ring def.
11		—	CH wag.
12		—	CH wag.
13	b ₁	—	Ring def. o.o.p.
14		972	CH wag.
15		874	CH wag.
16		706	CH wag.
17		657	CH wag.
18		416	Ring def. o.o.p.
19	b ₂	3071	CH str.
20		3060	CH str.
21		1624	CC str.
22		1432	CH def.
23		1321	CH def./CC str.
24		1283	CH def.
25		1159	CH def.
26		1063	Ring str.
27		587	Ring def.

Str., stretching; def., deformation; wag., wagging; o.o.p., out of plane.

^aReference 157.

finally leads to the cleavage of the phenyl ring and formation of a mixture of conformers of a ketoketene (Scheme 8).¹⁵⁹

The thermal reaction of $C_6H_5^\bullet$ with CO in argon matrices produces the benzoyl radical with a strong CO carbonyl stretching vibration at 1824.4 cm^{-1} (18).¹⁶² The IR spectrum is in good agreement with



Scheme 8 Reaction of the phenyl radical with molecular oxygen.

DFT calculations (UB3LYP/cc-pVTZ).



This reaction was predicted by B3LYP/6-311G(d,p) calculations to be exothermic by $24.58 \text{ kcal mol}^{-1}$ with an activation barrier of only $0.7 \text{ kcal mol}^{-1}$.^{163,164} From EPR studies at 77 K, it was concluded that the benzoyl radical is a σ -type radical with an sp^2 hybridized radical center.^{165,166} The formation of the benzoyl radical is photochemically reversible. Irradiation of $\text{C}_6\text{H}_5\text{CO}^\bullet$ with UV light ($\lambda > 260 \text{ nm}$) results in the cleavage back to $\text{C}_6\text{H}_5^\bullet$ and CO. In matrices doped with both CO and O_2 , the benzoyl radical reacts further with molecular oxygen to produce the benzoyl peroxy radical (Scheme 9).¹⁶² It is remarkable that in these experiments, the phenyl radical was trapped with CO and O_2 in two subsequent steps, which could be directly monitored by IR spectroscopy. The benzoyl peroxy radical was characterized by IR spectroscopy in combination with DFT calculations.

Another interesting reaction of the phenyl radical is the reaction with water. In argon matrices doped with water, the phenyl radical forms a weakly bound complex via an $\text{OH} \cdots \pi$ interaction. This complex

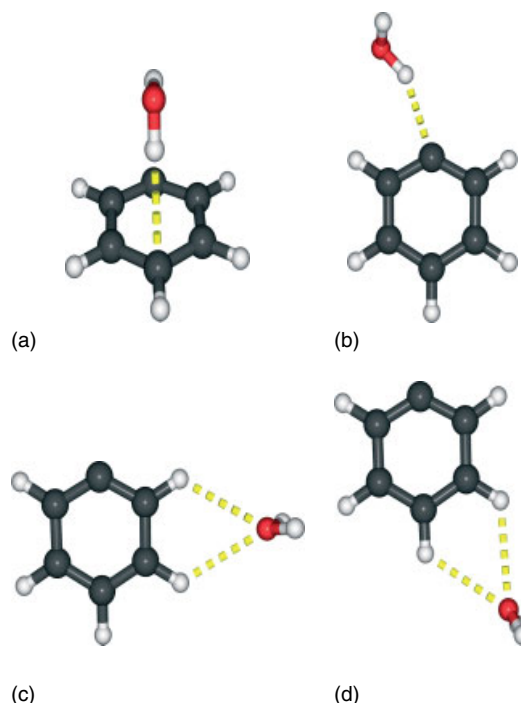
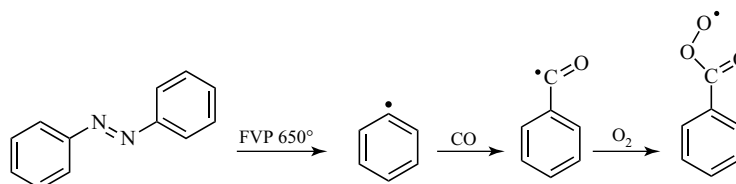


Figure 6 Phenyl radical $\cdots$ water complexes calculated at the UM05-2x/6-311++G(2d,2p) level of theory.^{167,168}

was characterized by IR spectroscopy.^{167,168} In the complex, the most intense bands of $\text{C}_6\text{H}_5^\bullet$ at 705.8 and 657.4 cm^{-1} (CH out-of-plane deformation vibrations) are blueshifted by 5.6 and 2.4 cm^{-1} and the OH stretching vibration of water at 3639.7 cm^{-1} is redshifted by 21.7 cm^{-1} . This suggests that the water molecule is forming a weak $\text{OH} \cdots \pi$ hydrogen bond with the phenyl ring (Figure 6). A comparison of these IR data with calculations at the UM05/6-311++G(2d,2p) level of theory suggests that indeed the energetically most stable complex A is formed. C and D are very weak van der Waals complexes, whereas B is a pre-reactive complex



Scheme 9 Reaction of the phenyl radical with carbon monoxide and oxygen.

with an $\text{OH}\cdots\text{C}$ interaction pointing toward the radical center.

Surprisingly, visible light ($\lambda > 420\text{ nm}$) irradiation results in hydrogen atom transfer from water to the phenyl radical and formation of a second, highly labile complex between benzene and the OH radical with distinct absorptions at 3502.2, 1482.8, 1040.3, and 684.2 cm^{-1} . If H_2^{18}O is used, the OH stretching vibration of the benzene $\cdots\text{HO}^\bullet$ complex shows an isotope shift of -11 cm^{-1} , which proves that indeed a complex of the $\text{HO}^\bullet$ radical is observed. Obviously, there is a small activation barrier that prevents the $\text{HO}^\bullet$ radical from reacting with benzene. This activation barrier can be overcome by prolonged photolysis with $\lambda > 420\text{ nm}$ light, resulting in the complete destruction of the aromatic ring of the benzene $\cdots\text{HO}^\bullet$ complex and formation of a highly unsaturated ketene (Scheme 10). The mechanism of this reaction was investigated in detail by calculations at the UB3LYP/6-311++G(2d,2p) level of theory.

Derivatives of the cyclohexadienyl radical are important intermediates in radical reactions involving aromatic systems. The parent radical $\text{C}_6\text{H}_7^\bullet$ was generated in a xenon matrix by the reaction of benzene with hydrogen atoms at 45 K and characterized by EPR and IR spectroscopy (19).¹⁶⁹

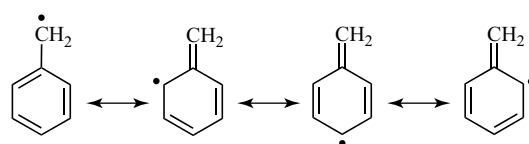


In the IR spectrum, a very strong doublet at 618 and 620 cm^{-1} and several other weak absorptions were assigned to the cyclohexadienyl radical based on DFT calculations. The EPR spectrum shows a triplet of quartets owing to the large hyperfine

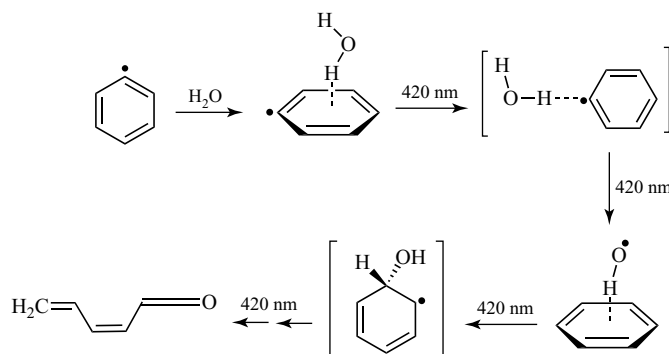
coupling with the two CH_2 protons and a weaker coupling with the three equivalent CH protons.¹⁶⁹

4.2 Benzyl Radical

The benzyl radical, $\text{C}_7\text{H}_7^\bullet$, is another fundamental species that plays a role in combustion processes^{170,171} and in the chemistry of the atmosphere.¹⁷² The bond dissociation energy DH_{298} of a CH bond in the methyl group in toluene was determined to be $89.8 \pm 0.6\text{ kcal mol}^{-1}$ and the heat of formation of the benzyl radical to be $49.7 \pm 0.6\text{ kcal mol}^{-1}$.¹¹⁷ This CH bond dissociation energy is about 12 kcal mol^{-1} lower than that of a saturated system, which indicates the large resonance stabilization of the benzyl radical.^{173,174} Extensive experimental^{175–177} and theoretical studies^{178,179} conclude that the benzyl radical is an aromatic π -type radical with a C_{2v} symmetry and a $^2\text{B}_2$ electronic ground state.



EPR spectra of the benzyl radical could be obtained after FVP of phenacyl iodide followed by matrix isolation of the products with a large excess of argon or neon.¹⁸⁰ The isotropic coupling constants of the matrix-isolated benzyl radical are close to those measured in solution ($A(\text{H}_\alpha) = 16.40$, $A(\text{H}_o) = 5.17$, $A(\text{H}_m) = 1.77$, and $A(\text{H}_p) = 6.19\text{ G}$, respectively).



Scheme 10 Reaction of the phenyl radical with water.

LIF and multiphoton ionization spectroscopy were used to gain insight into the electronic structure of the benzyl radical.¹⁷⁷ The UV spectrum of the benzyl radical, matrix-isolated in neon, exhibits an absorption at 454.4 nm assigned to the $1^2A_2 \leftarrow 1^2B_2$ transition. Another band at 305.5 nm was attributed to the $2^2A_2 \leftarrow 1^2B_2$ transition, and a broad band at 245 nm corresponds to the $3^2B_2 \leftarrow 1^2B_2$ transition.¹⁸¹ The emission spectrum of the benzyl radical was obtained by UV photolysis of toluene and toluene- d_8 in an argon matrix.¹⁷⁵ The emission band at 457.4 nm is in good agreement with that observed in the gas phase at 454.5 nm.¹⁸²

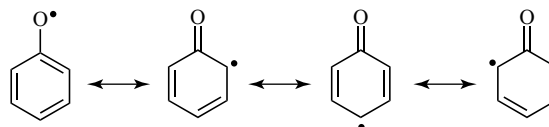
FVP of benzyl bromide ($C_6H_5CH_2Br$) or 1,2-diphenylethane ($C_6H_5CH_2$)₂ with subsequent trapping in argon produced high yields of the matrix-isolated benzyl radical ($C_6H_5CH_2\cdot$) that could be characterized by IR spectroscopy. The CH stretching vibration $\nu_{as}(CH_2)$ at 3111 cm^{-1} is in accordance with the sp^2 hybridization of the methylene carbon atom, as predicted by theory. This is in line with the frequency of the C–CH₂ stretching vibration found at 1264 cm^{-1} , which is considerably higher than the C–CH₃ stretching vibration of toluene at 1215 cm^{-1} , indicating the sp^2 hybridization of the methylene carbon atom and strong resonance stabilization of the radical.^{22,183}

4.3 Phenoxyl Radical

The phenoxyl radical, $C_6H_5O\cdot$, is another aromatic radical of fundamental importance in many reactions, such as combustion of organic compounds.¹⁸⁴ Derivatives of the phenoxyl radical, such as the tyrosyl radical, are important biological intermediates,¹⁸⁵ which has triggered a large number of experimental and theoretical studies on these systems.^{186,187}

The phenoxyl radical is formally obtained by homolytic cleavage of the OH bond of phenol. The bond dissociation enthalpy DH_{298} of this bond was determined to be $90 \pm 3\text{ kcal mol}^{-1}$, and subsequently the heat of formation $\Delta_f H_{298}$ of phenoxyl to be $-58 \pm 3\text{ kcal mol}^{-1}$.¹⁸⁸ The phenoxyl radical is a π radical that is stabilized by delocalization of the unpaired electron into the π system of phenyl ring. This results in a partial double bond character of the CO bond, which

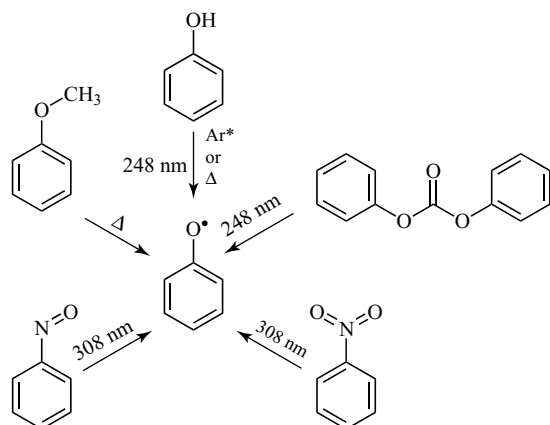
is in accordance with EPR^{189–193} and theoretical studies.^{186,187}



The phenoxyl radical shows C_{2v} symmetry and a $2B_1$ electronic ground state. There has been some debate in literature concerning the CO bond length, which varies depending on the level of calculations used, between 1.22 and 1.38 Å. High-level *ab initio* calculations (CAS-SCF/6-311G(2d,2p)) predict a CO distance of 1.228 Å, in the range of typical CO double bonds, and CC bond distances similar to that expected for a quinoid structure.¹⁹⁴ This stresses the importance of quinoid resonance structures for the description of the electronic structure of the phenoxyl radical.

The resonance Raman spectra of phenoxyl, phenoxyl- d_5 , and phenoxyl-2,4,6- d_3 were obtained in water after photoexcitation of phenol at 400 nm.^{195–197} The strongest band at 1505 cm^{-1} was assigned to the CO stretching mode.¹⁹⁸ In phenoxyl- d_5 , and phenoxyl-2,4,6- d_3 , this band is shifted to 1489 and 1487 cm^{-1} , respectively. The band at 1505 cm^{-1} observed in a UV resonance Raman study was shifted by 13 cm^{-1} on ^{17}O substitution, indicating a large contribution of the CO stretching mode.¹⁹⁹ The low frequency of this mode (compared to “normal” CO double bonds) reflects the only partial double bond character in phenoxyl.

The first electronic spectrum of the phenoxyl radical was reported by Porter and coworkers.²⁰⁰ There was some debate concerning the assignment of the symmetry of the ground state.²⁰¹ Vacuum UV photolysis of matrix-isolated phenol or anisole produced phenoxyl with several UV absorptions between 397.2 and 367.5 nm.²⁰² In a comprehensive study, the phenoxyl radical was obtained in solid argon by laser photolysis of phenol, diphenyl carbonate, nitrosobenzene, or nitrobenzene (Scheme 11).²⁰¹ In the UV–vis region, the spectrum exhibits four electronic transitions with origins at 626, 398, 295, and 239 nm, assigned to transitions to $2A_2$, $2B_1$, $2A_2$, and $2B_1$ states, respectively, by measuring the linear dichroism in partially photooriented matrices.²⁰¹



Scheme 11 Reaction channels for the synthesis of the phenoxy radical.

The phenoxy radical shows 30 normal vibrational modes, of which 27 are IR active. In an extensive study, 26 vibrational modes of $C_6H_5O^\bullet$ were measured in an argon matrix and assigned by isotopic labeling ($C_6D_5O^\bullet$ and $^{13}C^{12}C_5H_5O^\bullet$ were investigated) and measuring the IR dichroism in photoselection experiments.²⁰³

An intense band at 1481 cm^{-1} was assigned to the CO stretching vibration (ν_7), which differs slightly from the band at 1505 cm^{-1} observed by Raman spectroscopy in aqueous solution.^{196,199} The discrepancy results from specific interactions (hydrogen bonding) between the CO group and water. The shifts observed after isotopic labeling is in agreement with the results from the Raman experiments and confirms the assignment of the CO stretching vibration (Table 6).²⁰³ The complete set of experimental frequencies of $C_6H_5O^\bullet$ observed in argon matrix is listed in Table 6.

An interesting derivative of phenoxy that was also investigated in argon matrices is the 2-hydroxyphenoxy radical.²⁰⁴ UV photolysis ($\lambda > 220\text{ nm}$) of 2-nitrophenol results in the rearrangement to 2-hydroxyphenyl nitrite into its *s-trans* conformation. Prolonged irradiation produces 2-hydroxyphenoxy radical and NO, which on annealing of the matrices react thermally to a mixture of *s-trans* and *s-cis* 2-hydroxyphenyl nitrite. The 2-hydroxyphenoxy radical has a strong absorption at 3336 cm^{-1} , which is assigned to the OH stretching mode. The redshift compared to the OH stretching mode in phenol (3638.5 cm^{-1})²⁰⁵

Table 6 Vibrational frequencies of the phenoxy radical.

Mode	Symbol	Ar ^a	RR	Assignment
1	a ₁	3090		CH str.
2		3065		CH str.
3		3018		CH str.
4		1550	1552 ^b	CC str.
5		1481	1502 ^b	CO str.
6		1397	1398 ^{c,d}	CH bend/CH str.
7		1167	1157 ^c	CH bend
8		1038	1050 ^e	CH bend/ring breath
9		997	990 ^{b,c}	CCC bend
10		813	801 ^b	Ring breath/CCC bend
11		520	528 ^c	CCC bend
12	a ₂	—		HCCH tor.
13		—		CH wag
14		—		Ring def.
15		1016		HCCH tor.
16	b ₁	898		CH wag./boat def.
17		784		Chair def./CO CH wag.
18		635		Chair def./CH wag.
19		472		Boat def./CO wag.
20	b ₂	—		Boat def./CO wag.
21		3074		CH str.
22		3054		CH str.
23		1515		CC str./CH bend
24		1441		CH bend/CC str.
25		1318	1331 ^c	CC str./CH bend
26		1266		CC str./CH bend
27		1140		CH bend/CC str.
28		1072		CH bend/CC str.
29		616		CCC bend
30		446		CO bend

Str., stretching; def., deformation; wag., wagging; tor., torsion.

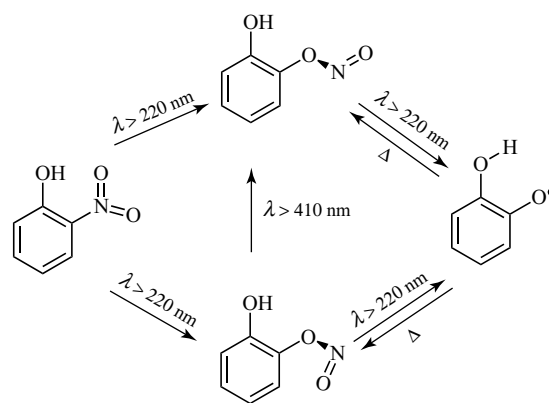
^aReference 203.

^bReference 198.

^cReference 196.

^dReference 199.

^eReference 195.



Scheme 12 Photochemistry of 2-nitrophenol.

reveals a strong intramolecular OH $\cdots$ O hydrogen bond (Scheme 12). This assignment was supported by DFT calculations (B3LYP/6-31++G(d,p)).

5 CONCLUSION

The isolation and spectroscopic characterization of highly reactive free radicals was one of the driving forces for the development of the matrix isolation technique five decades ago. Since that time, the field has become mature and the development of easy to use, powerful cryostats, highly sensitive spectrometers (in particular FTIR), and advanced computational methods that allow to simulate the spectra of elusive species made matrix isolation the method of choice for the investigation of free radicals. In particular, the simulation of spectra by using DFT methods has dramatically reduced the risk of incorrect assignments of spectra, which was common in the early days of matrix isolation. One has to keep in mind that many species isolated in matrices are unprecedented with no reference compounds to compare with. IR and EPR spectroscopy proved to be the most important spectroscopic methods for the characterization of radicals, and in combination with quantum chemical calculations, detailed insights into the geometry, electronic structure, and many other properties of radicals are now available. The most severe limitation for the matrix isolation of radicals is the availability of suitable precursors. A more recently developing application of the matrix isolation technique is the investigation of bimolecular reactions by carefully controlling the diffusion of trapped species. In particular, reactions with molecular oxygen, CO, CO₂, and other small molecules have been studied. This leads to highly labile peroxy radicals, acyl radicals, and other species that previously could not be isolated. These studies are important since they link matrix isolation to the more traditional solution and gas phase chemistry.

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Radical Chemistry in the Gas Phase

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1 INTRODUCTION

In solution, radicals are viewed as reactive intermediates that have a significant impact on the outcome of chemical reactions, but are usually short-lived. A thorough analysis shows on the other hand that many radicals are only kinetically unstable, that is, the barriers to chemical reactions are low and collisions almost always lead to a reaction. The most important reaction for the depletion of radicals often is their recombination. Once this process is sufficiently hindered, the fate of free radicals can even be followed in the bulk, as, for example, the time-honored triphenylmethyl radicals discovered by Gomberg (see **The History of Free Radical Chemistry**).¹ Thermochemically, however, many radicals are quite stable.² Under isolated conditions such radicals are then long-lived and can be studied in detail. This permits to gain insight into the structure and dynamics that is not available from solution-phase experiments. There are two major reasons to study chemical reactions of isolated radicals. First, owing to their open-shell electronic structure and high reactivity, radicals are employed as model compounds for chemical reaction dynamics. In this respect, the existence of low-lying electronically excited states renders radicals a particular challenge for theoretical chemistry. Therefore, detailed studies which allow for a direct comparison of

experimental data with *ab initio* computations serve as important benchmarks for the evaluation of contemporary theoretical methods. This in turn can help to improve the insight into the chemistry occurring in solution. Second, isolated radicals are in fact of considerable chemical importance. Specifically, they are key species in the chemistry of numerous environments and processes, such as

1. Combustion processes.^{3–6}
2. Atmospheric chemistry.⁷
3. Low-temperature plasmas.^{8,9}
4. Interstellar chemistry.¹⁰
5. Biochemical processes¹¹ including prebiotic chemistry.¹² Owing to the importance of the subject, the whole Volume 3 of this encyclopedia is dedicated to radicals in biochemical processes.

A large part of the basic research on free radicals is driven by the desire to understand the chemistry of these systems. Thermochemical data, structural information, rate constants, and information on the reaction dynamics are required and can be obtained from investigations of radicals in the gas phase. In this contribution, we summarize the contemporary means to achieve specific and detailed information about the intrinsic properties and the elementary reactions of free radicals in the gas phase.

Owing to the richness of information available in the whole field of isolated radicals in the gas phase, we focus on certain aspects, while omitting others. Specifically, the following criteria were applied to limit the topics discussed in detail. (i) Stable species that are formally radicals or biradicals, but can be filled in bottles, are excluded, examples being $\text{NO}^\bullet$, $\text{NO}_2^\bullet$, or the triplet ground state of O_2 . (ii) Despite being worth considerable interest on their own, we do not include the reactions of single atoms, even if these are open-shell species, reactive, and of considerable chemical importance (e.g., in the radical halogenation of alkanes). (iii) Since the focus of this article is on *reactions* of isolated radicals, to a large extent we ignore the extensive work on the *spectroscopy* of isolated radicals, unless it is relevant for the discussion of chemical reactions. We refer the reader, for example, to the articles **Analysis of Radicals by EPR** and **Matrix Isolation of Radicals**. Owing to the research interest of the authors, the focus is mostly on organic radicals, but the concepts and experimental strategies applied as well as the general conclusions derived also apply for radicals of other main-group elements. On the other hand the term “radical” loses most of its conceptual meaning in the chemistry of transition metals, lanthanides and actinides. In lanthanide compounds, for example, the unpaired electrons in the f-shell can almost be regarded as “core-like” electrons and do often not participate in the chemistry, while the compounds as such have, of course, open-shell character.¹³

2 CHEMICAL SYSTEMS DOMINATED BY RADICALS

Above we have summarized the environments in which radicals are crucial for the chemistry taking place. In the next subsections, we outline their role in more detail.

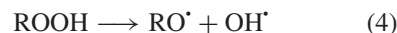
2.1 Combustion Research

Combustion ranging from smoldering via engines to open fire is the culturally, technologically, and economically most important process dominated by radicals. The urge to understand the elementary chemical processes in combustion engines is a

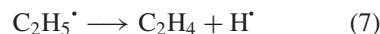
major driving force for a large part of free radical research. A particular challenge in this respect is the introduction of biofuels, which are chemically much more complex than the conventional fuels on the basis of crude oil. The foundations of combustion research are described in textbooks¹⁴ and only some selected key aspects are summarized here. Many reactions occur in a flame or a combustion engine, among them the cleavage of C–C bonds at high temperature, which leads to two radicals, one of them often a methyl radical (reaction 1).



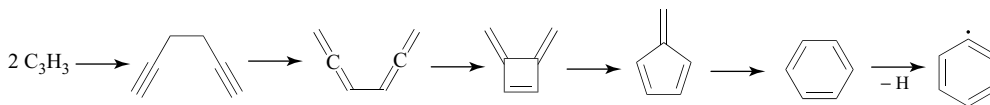
Central in combustion is the interaction of initially formed hydrocarbon radicals $\text{R}^\bullet$ with molecular oxygen (reactions 2–4), which *inter alia* lead to oxy- and peroxyradicals that undergo further reactions.



Particularly important with regard to combustion is the generation of two new radicals in the cleavage of the hydroperoxide in reaction (4), which leads to the exponential increase of the rate of combustion, once radical processes are initiated sufficiently fast. Other important reactions shown are the dimerization of radicals (reaction 5), hydrogen abstractions, and hydrogen additions (reactions 6 and 7) as well as the fragmentation of radicals into others (reaction 7). The latter two processes can be bimolecular or unimolecular in nature.



These few examples illustrate the wide range of radical reactions that are important in combustion. Whether a certain reaction occurs and to what extent it is important, depends on numerous factors, such as the composition of the fuel, the temperature, and the pressure. In modern technology, the optimization of combustion engines is therefore accompanied by an explicit kinetic modeling of the combustion reactions.^{15,16} Such kinetic models contain



Scheme 1 The dimerization of two propargyl radicals yields an aromatic unit in a single bimolecular step followed by several unimolecular isomerizations.

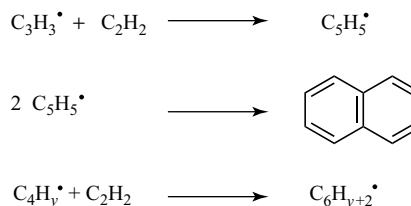
a large manifold of species that are interconnected by numerous chemical reactions. A large number of rate constants and thermochemical data are therefore required for a satisfactory description. However, accurate rate constants are difficult to obtain experimentally, in particular, for the reactions of radicals. Notwithstanding these difficulties, radicals frequently serve as the key species in the respective kinetic schemes. They often constitute branching points in chain reactions and in many cases there exist several reaction channels with comparable energetics. Alkyl radicals, for example, can lose a hydrogen atom in a unimolecular dissociation or they can abstract a H-atom from another molecule (or radical) in a bimolecular reaction, for example, reactions (6) and (7). The relative importance of the two pathways depends on various parameters, such as the pressure, the temperature, and the concentration of the various species.

Ideally, *in situ* monitoring of the reactions occurring in engines is carried out by following the concentration of characteristic species using laser spectroscopic methods, in particular laser-induced fluorescence (LIF) or coherent anti-Stokes Raman spectroscopy.¹⁷ In most cases, NO[•] and OH[•] are monitored, because of their high concentrations and cross-sections. The methods are quite sophisticated and have been described in several reviews and textbooks.⁶ Monitoring hydrocarbon radicals *in situ* would be helpful, but concentrations are generally too small. In this respect, recent photoionization experiments with tunable synchrotron radiation (SR) are quite promising for the rapid on-line monitoring of open-shell species formed in combustion.⁴ One of the most important challenges in combustion research is to understand the formation of polycyclic aromatic hydrocarbons (PAHs) and soot, because of both the carcinogenic potential and the engine damage associated with them. Experiments in flames suggest that formation of the first aromatic units is central.³ Subsequent reactions building up larger aromatic structures are then comparably fast. Hydrocarbon radicals are known to be important intermediates in the early stages of

soot formation, even though they only appear in small concentrations.^{3,18–21} Radicals with C₃ units are particularly relevant,²² because an aromatic C₆ unit can be formed in one bimolecular reaction step only,²³ as shown for the dimerization of two propargyl radicals in Scheme 1. All further reactions after the initial dimerization are unimolecular in nature.

Other important reaction pathways to the first aromatic ring include acetylene and C₄ or C₅ units^{3,23} as shown in Scheme 2. The accuracy of kinetic models describing combustion systems and in particular the formation of PAH and soot depends on the rates of many different elementary reactions, forming a considerable task for laboratory chemists interested in gas-phase radical reactions. The large amount of compounds formed in a combustion process and of possible reaction pathways makes this a formidable challenge.

In recent years, the so-called “alternative” or “biofuels,” derived from agricultural products (such as palm oil, corn, sugarcane, and soy beans) or even from agricultural waste, have received growing interest. In addition to few pure hydrocarbons, biomass includes many oxygen- or nitrogen-containing species. Upon combustion of these novel fuels, a number of radical species will appear that are not present with conventional fuels and have thus only poorly or even not at all been characterized.⁴ Modeling the combustion of biofuels requires additional data on such radicals. This serves as a strong motivation for scientists to investigate the largely unexplored chemistry of N-containing radicals in more detail.



Scheme 2 Important C–C coupling reactions of C_n-radicals (*n* = 3–5).

Hydrocarbon cracking is related to combustion. Long-chain hydrocarbons are broken down to saturated or unsaturated species containing less carbon atoms. This requires the breaking of carbon–carbon bonds and leads to hydrocarbon radicals, in particular alkyl radicals. Many reactions are similar to those that appear in combustion chemistry. Modeling cracking, such as modeling combustion, thus requires considerable knowledge about the kinetics of radical reactions.²⁴

2.2 Atmospheric Chemistry

Radicals are ubiquitous in the earth's atmosphere. In particular, oxygen-containing radicals, such as OH[•] and OOH[•], dominate its chemistry; note that O₂ itself also is an open-shell species. Owing to the importance of radical chemistry in the earth's atmosphere, a whole article of this handbook is devoted to the subject of "Atmospheric Radical Chemistry" (see **Atmospheric Radical Chemistry**). Thus, we will not discuss the chemistry of the earth's atmosphere in any further detail. However, other planets and their moons also bear atmospheres. Their chemistry came into focus recently because of the NASA/ESA Cassini–Huygens mission, which aimed at exploring the planets Jupiter and Saturn as well as their moons. In particular Titan,

a moon of Saturn, is of interest here.^{25,26} The main constituents of its atmosphere are nitrogen, methane, and argon. In Figure 1 the Titan atmosphere is compared with that of earth. While earth has an oxidizing atmosphere (containing O₂ instead of CH₄) dominated by oxygen-containing radicals, Titan has a reducing atmosphere dominated by hydrocarbon radicals (including nitrogen-containing species). A surprisingly large number of radicals and ions has been observed in the fly-by of Huygens.^{27,28} A large part of the interest in the Titan atmosphere stems from the fact that this particular atmosphere is believed to resemble that of the early earth. Studying its chemistry might thus provide hints on how complex organic and bioorganic molecules were formed on the earth, a field termed "astrobiology" or "exobiology."²⁹

2.3 Plasma Chemistry

A plasma can be described as a collection of (charged and neutral) particles that appears neutral but is a conductor of electrical current. In the so-called low-temperature plasmas, chemistry is initiated by hot electrons (temperatures on the order of some 10⁴ K), whereas ions and molecules can be comparably cold, that is, around room temperature. Low-T plasmas are of considerable technical importance and are used for surface modification and functionalization,^{30,31} for lighting (an example being the so-called energy saving lamp), displays (plasma TV), or the cleaning of archeological artifacts.^{32,33} The electron–molecule interactions generate ions and radicals that dominate an often complex and poorly understood chemistry. Numerous reactive species have been identified in plasmas and are monitored in plasma diagnostics,⁹ among them CF_n or SiX_n (X = Cl, F) that occur in CF₄, SF₆, or Cl₂ plasmas used for etching of Si and SiO₂ surfaces. The chemistry of reactive species determines to a large extent the selectivity and the rate of the etching process. For example, fluorocarbon plasmas are reported to selectively etch Si over SiO₂.⁹ Some of the relevant questions in plasma chemistry are, therefore, (i) which species are deposited on surfaces, (ii) which species lead to surface etching, and (iii) what effect do transient species have on the chemistry going on at the surface? To answer these questions, a profound

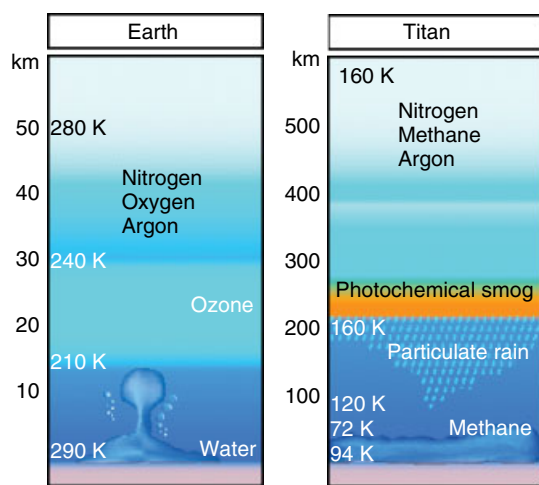


Figure 1 Comparison between the atmospheres of earth and Titan, taken from 26. [Reprinted by permission from Macmillan Publishers Ltd: Nature, 438, 756–757, Copyright 2005.]

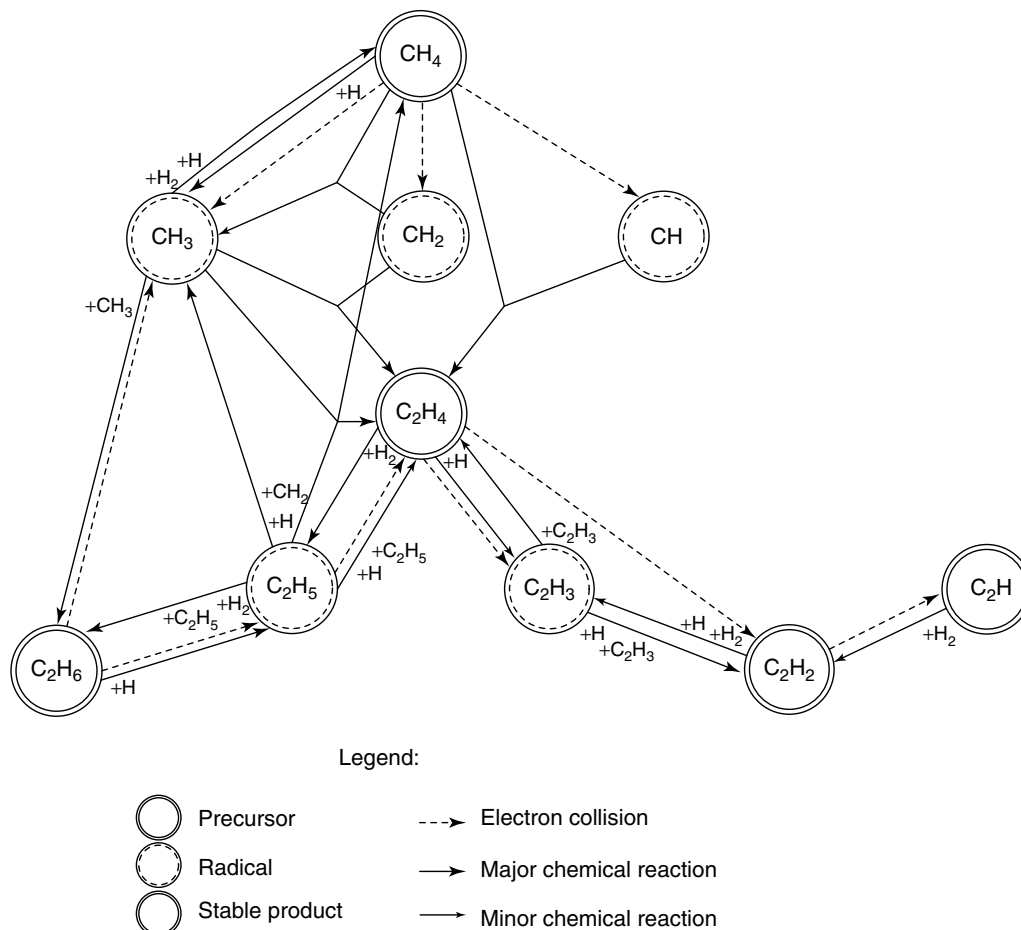


Figure 2 Important chemical reactions in a CH_4/H_2 plasma, taken from Ref. 35. [Reproduced with permission from J. Röpcke, L. Mechold, X. Duten, A. Rousseau, A time resolved laser study of hydrocarbon chemistry in H_2 - CH_4 surface wave plasmas, *J. Phys. D: Appl. Phys.*, **34**, 15, 2336–2345, 7th August 2011, IOP Publishing. DOI: 10.1088/0022-3727/34/15/313.]

knowledge on the chemistry of ions, radicals, and carbenes is required. For the modeling of hydrocarbon plasmas that are used for the deposition of diamond films on surfaces, a large number of radical reactions has to be included.³⁴ Figure 2 shows the species detected in a CH_4/H_2 discharge and the reactions that connect them.³⁵ As visible in the figure, several small hydrocarbon radicals and carbenes are in the center of this reaction network. The relative rates of the various reactions determine the concentrations of intermediates and products. Modeling plasma processes³⁶ requires accurate kinetic data on the reaction of isolated radicals, similar to the modeling of a combustion engine. However, the inclusion of surface reactions provides an additional challenge.

2.4 Interstellar Chemistry

Interstellar space is a hostile environment for chemistry, because high-energy radiation is abundant. Thus even chemists are sometimes surprised to hear that radicals play a crucial role in the formation of complex molecules in interstellar space. As mentioned in the introduction, radicals are kinetically unstable, but can be thermochemically stable. In a low-temperature environment with low collision rates, radicals and ions can therefore exhibit long lifetimes. Regions of space consisting of neutral matter, termed *molecular clouds*³⁷ can be formed in-between stars and within planetary systems. Atomic and molecular densities range

from 10^2 cm^{-3} (diffuse clouds) to 10^6 cm^{-3} (dense clouds). A density of 10^4 cm^{-3} corresponds to a pressure on the order of 10^{-14} mbar. Since such low pressures are hard to achieve in a laboratory, the name “dense” sounds somewhat euphemistic. A back-of-the envelope estimate for H_2 (the by far most abundant species in molecular clouds), using simple gas kinetics shows that hydrogen at a temperature of 10 K experiences a mean free path of more than 10^9 m (assuming a collision cross section of roughly 10^{-18} m^2 , note that cross sections are strongly energy dependent) and a time between collisions on the order of 10^7 seconds, which corresponds to roughly three months. This estimate for hydrogen shows that reactions between molecules will be rare; note, however, that time is not a real limitation in astronomical context. Moreover, the average temperatures in interstellar clouds are on the order of only a few Kelvin, such that only reactions with low barriers and high cross sections will significantly contribute to the chemistry. So one might wonder how complex molecules can be formed in molecular clouds that are thought to be the cradle of star formation. Notwithstanding these obstacles, several types of reactions can occur in interstellar environments. One class are ion–molecule reactions because the long-range attractive potential of ions increases the collision cross-section with neutral molecules and because ion–molecule reactions often occur without a barrier. Furthermore, some reactions are supposed to proceed on the surface of small grains.³⁸ Nevertheless both pathways cannot explain all of the chemistry observed. In recent years, it was proposed that radical–radical and radical–molecule reactions do also contribute to the formation of complex molecules. Despite the rather low number densities of open-shell species in the interstellar space, they can in fact play a significant role for the growth of larger molecules because the activation barriers associated with the reactions of radicals often are low, such that the reactive events can occur close to collision rate.³⁹ Among the unsaturated species observed in space^{40–42} are molecules as exotic as polyynes of the type $\text{C}_m\text{H}^\bullet$ with $m \leq 8$ and $\text{HC}_m\text{CN}^\bullet$ with m ranging up to 10. Another important species is cyclopropenylidene, $c\text{-C}_3\text{H}_2$, a carbene with a free electron pair. Their number densities relative to H_2 are on the order of 10^{-8} . Despite the small concentrations, the formation of complex molecules in the universe cannot be explained without taking reactions of radicals and carbenes into

account. However, for modeling purposes the rate constants for such reactions have to be known accurately at temperatures as low as 10 K, which poses a considerable challenge to the laboratory scientists. A method that overcomes this obstacle, Cinétique de Réaction en Ecoulement Supersonique Uniforme, abbreviated as CRESU, is introduced in Section 6.

3 EXPERIMENTAL CONSIDERATIONS

3.1 How to Study Isolated Radicals

Due their kinetic instability, the structure, thermochemistry, and unimolecular reactions of radicals are preferentially studied under collision-free conditions. A suitable approach is free jet spectroscopy.^{43–45} In this technique, the molecule of interest is diluted in 1–2 bar of a rare gas (typically He or Ar) and this mixture is expanded through a small nozzle (diameter 0.1–1 mm) into the vacuum. Pulsed operation allows to maintain a low pressure and matches the duty cycles of the typical laser systems. In the subsequent adiabatic expansion, energy is transferred to translational energy of the rare gas and the molecules cool vibrationally and rotationally. After a couple of centimeters the process is completed and a cold beam is formed, in which the molecules travel with almost equal speed into the same direction and no further collisions occur. Such beams are not limited to applications in spectroscopy but permit to study the structure, dynamics, and thermochemistry of reactive species in general. While stable molecules can be cooled to a few K, radical beams are in general warmer, as discussed in the next section.

3.2 The Generation of Isolated Radicals

It is still a challenge to generate radicals cleanly and in a number density sufficient to perform gas-phase experiments. In addition, it is often unavoidable to generate, beside the species of interest, a second fragment from the precursor that can in principle interfere in the experiment. Typically a chemical bond in a suitable precursor is cleaved by means of pyrolysis, photolysis, electric discharges, or a chemical reaction. Examples for all four sources are depicted in Figure 3. With the exception of

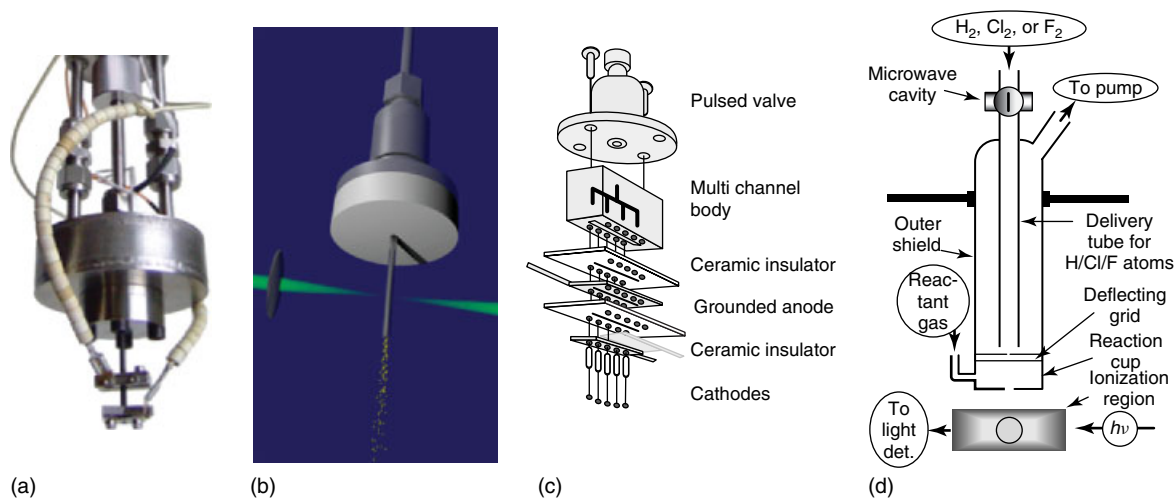


Figure 3 A selection of sources used to generate radicals. (a) Pyrolysis. (b) Photolysis using a quartz tube. (c) Slit discharge.⁴⁶ [Reproduced from Ref. 46, Copyright (2002), with permission from Elsevier.] (d) Chemical reactor.⁴⁷ [Reproduced with permission from Ref. 47. © Transworld Research Network, 2000.]

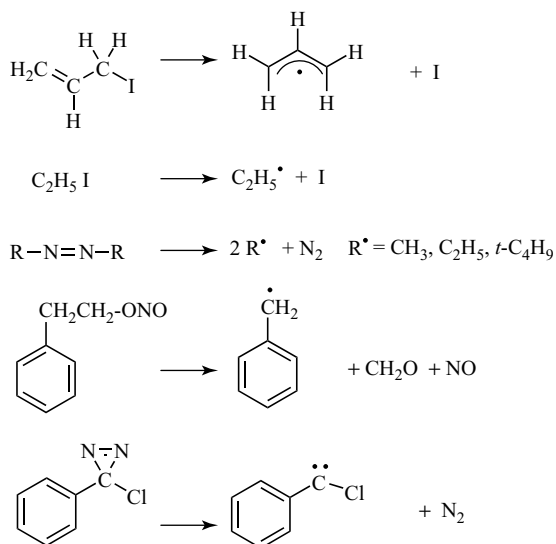
the chemical reactor, which constitutes an effusive source, they are coupled to pulsed valves and produce free jets of radicals.

3.2.1 Pyrolysis

In pyrolysis sources radicals are generated thermally from suitable precursors. In earlier experiments, vapor at low pressure was passed under effusive flow conditions through a heated tube into the apparatus.^{48,49} Secondary reactions, such as radical/radical recombination or the formation of unwanted side products were unavoidable. In the mid-1980s, a high-pressure flash pyrolysis source coupled with a supersonic expansion was introduced and largely solved these problems.⁵⁰ The design is depicted in Figure 3a. An electrically heated silicon carbide tube with a length of 10–20 mm and a diameter of 1 mm is mounted onto a molecular beam source with an orifice of 0.6–0.8 mm. A suitable precursor, diluted in 1–2 bar of a rare gas is expanded through this nozzle into the vacuum. In recent modifications of this design, water cooling was added for a more stable valve operation. Under these conditions a fast gas flow is achieved, which leads to short contact times with the heated wall on the order of some 10 μ s and reduces secondary reactions.⁵¹ In engineering terms, a pyrolysis source can be considered to be a

tubular flow reactor.⁵² A variety of radicals and carbenes have been generated by this method cleanly and in high number densities, hydrocarbon radicals in particular. Examples are alkyl radicals, $C_nH_{2n+1}^{\cdot}$,^{53–57} and unsaturated radicals with a conjugated π -system, such as $C_3H_3^{\cdot}$,⁵⁸ $C_3H_5^{\cdot}$,⁵⁹ benzyl ($C_7H_7^{\cdot}$),⁶⁰ and $C_9H_7^{\cdot}$ isomers.⁶¹ Also more exotic species such as the vinyl radical ($C_2H_3^{\cdot}$),⁶² benzyne,^{63,64} diazirine,⁶⁵ carbenes, that is, the various isomers of C_3H_2 ,^{66,67} the chlorophenyl carbene,⁶⁸ CF_2 ,⁶⁹ and other compounds have been successfully generated. Precursors often contain a carbon–halogen bond such as C–Br and C–I, but azo-compounds, diazirines, nitrites, and esters have also been employed. Precursors that yield N_2 as the side product are advantageous, because nitrogen does not interfere with most experimental schemes. A selection of pyrolytic routes to radicals and carbenes is depicted in Scheme 3. Often the precursors are themselves not very stable and have to be synthesized shortly before the experiments.

Flash pyrolysis has been successfully combined with a variety of spectroscopic techniques in all regions of the electromagnetic spectrum over the last couple of years, ranging from the microwave region⁷⁰ via infrared spectroscopy in both rare-gas matrices⁷¹ and free jets,⁷² electronic spectroscopy in the visible and in the UV^{53,73} to photoelectron spectroscopy with vacuum ultraviolet (VUV) radiation.⁷⁴ As described further below, it has



Scheme 3 Possible routes to the pyrolytic generation of radicals and carbenes.

also been employed in time-domain spectroscopy, photofragment and translational energy spectroscopy. Alternative designs,^{69,75} some of them relying on a longer contact time (≈ 1 ms),⁷⁶ are also used. Water cooling increases the stability of the pulsed valve at high pyrolysis temperatures,^{57,77} as depicted in Figure 3. Successful application in studies on small inorganic radicals has also been reported.⁷⁶

The selectivity of the method is demonstrated in Figure 4, using the generation of the indenyl radical, $\text{C}_9\text{H}_7\cdot$, by flash pyrolysis of 1-bromoindene as an example.⁶¹ Photoionization mass spectra utilizing VUV light at 8.5 eV were obtained with the pyrolysis source off (lower trace) and on (upper trace). As visible, the precursor is almost quantitatively converted and no side products (beside the Br atoms that cannot be ionized at this energy) are detected. In favorable cases radical densities of more than 10^{14} cm^{-3} can be achieved at the exit of the pyrolysis source.

3.2.2 Photolysis

The most common method for the generation of radicals is photolysis. It relies on the laser excitation of a precursor molecule to an electronic state that dissociates directly into the radical of interest plus a second fragment. For the generation of organic radicals, the corresponding iodides R-I are frequently used precursors because they are known to have dissociative states in the UV. These states can be populated by excitation with the fourth harmonic of a Nd:YAG laser at 266-nm or a 248-nm excimer laser. Photolysis can easily be coupled to supersonic beams by focusing the laser a few mm behind the pulsed valve orifice. The radicals will then be internally cooled in the subsequent expansion. An early example was the generation of CH_2 from ketene

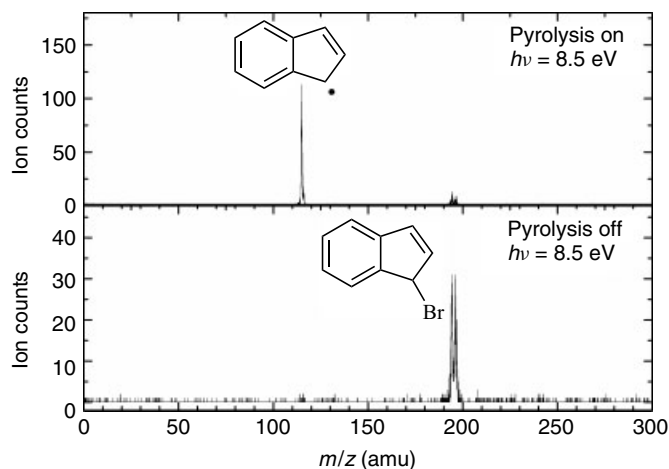


Figure 4 Photoionization mass spectra of 1-bromoindene with pyrolysis off (lower trace) and on (upper trace), demonstrating the potential of a pyrolysis source. [Reproduced with permission from Ref. 61. Copyright 2010 American Chemical Society.]

using 337-nm radiation.⁷⁸ In a recent improvement, a quartz tube was attached to a pulsed valve to carry out the photolysis.⁷⁹ This setup is schematically depicted in Figure 3b. Reactive species such as $\text{NH}_2^\bullet$,⁸⁰ $\text{CH}_2^\bullet$,⁸¹ and even the elusive $\text{NH}_4^\bullet$ ⁸² have been generated photolytically in supersonically cooled jets. Allyl radicals with rotational temperatures of a few K have been obtained,^{83,84} a temperature that is lower than the one achieved in a pyrolysis source. Several peroxy radicals have been spectroscopically studied that are not accessible by other methods.⁸⁵ Sometimes the photolysis is carried out in the ionization region of a mass spectrometer and can then be coupled with an effusive source.^{86,87} In this case, hot radicals with a significant amount of internal energy can be investigated.

To obtain a sufficient photon flux for radical generation, a laser is required as the light source. This makes the technique more expensive than pyrolysis, but also more difficult because of the need for accurate synchronization. In addition, a single fixed-frequency photolysis laser is not enough to set up a general radical source. Although for many radicals good precursors exist (e.g., iodides) that dissociate upon 266-nm excitation, other radicals are not accessible at this wavelength. Thus a tunable system is required for a general photolysis source. On the other hand many radicals, in particular oxygen-containing species, have been successfully generated by photolysis that have not yet been produced by pyrolysis. Photolysis is commonly applied also in experiments studying bimolecular reactions (see Section 6).

3.2.3 Discharges

Electrical discharges are also frequently utilized for the generation of radicals. They can be coupled to supersonic jet sources, and radical yields are often quite good.⁸⁸ A common setup for a pulsed electric discharge, the so-called slit-jet discharge, is depicted in Figure 3c. Two electrodes, separated by a ceramics insulator, are mounted onto the pulsed valve.^{46,89} When the valve opens, and the molecules pass through the channel, the circuit is closed, a discharge occurs and the bonds in the precursor are cleaved. The slit jet is advantageous for use in absorption experiments because of the increased path lengths. Similar designs using

a circular channel with a diameter on the order of a millimeter have also been reported.^{90,91} Several halogen-containing species were successfully generated,^{90,92–94} but also allyl and ethyl radicals⁹⁵ as well as polyynes relevant to astrochemistry^{96–98} have been produced in this manner. A disadvantage of discharge sources is their lack of selectivity, typically with many side products being formed. On the other hand, they are a suitable source to generate thermochemically unfavorable radicals that are not available by other techniques. Since a pulsed discharge constitutes a low-temperature plasma, the source is well suited to study species relevant in plasma chemistry.

3.2.4 Chemical Methods

There is a large range of approaches to generate a desired radical by chemical reactions. Often abstraction of H-atoms by atomic fluorine, chlorine, or hydrogen is used. The reactive atoms are formed in discharges of the molecular dimer. A typical setup used in photoionization experiments⁴⁷ is depicted in Figure 3d. Dyke and coworkers utilized the abstraction of hydrogen from closed-shell molecules by fluorine atoms to produce radicals for photoelectron spectroscopy.^{99–102} This source works particularly well when all hydrogen atoms in the precursor are equivalent, for example, for alkyl radicals generated from alkanes. The technique has also been applied to produce Si-, Ge-, and N-containing radicals.^{103–105} Two interesting examples of H-atom abstraction by fluorine atoms pertain to species relevant in tropospheric chemistry: The $\text{O}_2\text{H}^\bullet$ radical was generated from H_2O_2 ¹⁰⁶ and $\text{NO}_3^\bullet$ from HNO_3 .¹⁰⁷ The latter is a night-time oxidant in the troposphere, where it is formed from $\text{NO}_2^\bullet + \text{O}_3$. An alternative way to produce $\text{NO}_3^\bullet$ in the laboratory is the reaction of HNO_3 with $\text{OH}^\bullet$, leading to $\text{NO}_3^\bullet + \text{H}_2\text{O}$.¹⁰⁸ Other atoms, such as $\text{Cl}^\bullet$ and $\text{H}^\bullet$, have been applied less often in such abstraction schemes: Cyclopentoxo radical was produced from cyclopentanol and photolytically generated chlorine atoms in a study of its unimolecular and bimolecular reactions.¹⁰⁹ A possible advantage of chlorine might be the better selectivity in H-atom abstractions. $\text{PH}_2^\bullet$ was generated in the reaction $\text{PH}_3 + \text{H}^\bullet$, that is, using hydrogen atoms in the abstraction step.¹¹⁰ A summary of the radicals that have been generated by chemical

reactions is given by Ruscic.⁴⁷ Although chemical methods are versatile, there are some disadvantages. For example, coupling to a supersonic expansion has not been achieved. However, there exist combinations of photolysis and chemical methods that allow a coupling with supersonic jets: The $\text{O}_3\text{H}^\bullet$ radical has been prepared by the reaction $\text{O}_2 + \text{OH}^\bullet$, the latter being formed in the photolysis of nitric acid in a jet.⁷

Metal-containing species can be obtained from laser vaporization.^{111,112} Originally, the method was applied to form metal clusters in a jet of rare gas. When organic compounds are admixed to the carrier gas, metal-containing radicals can be formed in the chemical reaction. Miller *et al.* showed that species such as $\text{CH}_3\text{M}^\bullet$ ($\text{M} = \text{Zn}, \text{Mg}$) could be studied.¹¹³ Species of the type MCH ($\text{M} = \text{Na}, \text{K}$) have been obtained from hot metal vapors^{114,115} and $\text{Na}_2\text{CN}^\bullet$ has been prepared in a sodium/NaCN metal/molecule mixture.¹¹⁶

There are more approaches to generate radicals. Shock tubes (see Section 6) are often used in bimolecular kinetics and can be considered to be in-between pyrolysis and a chemical reactor.

3.2.5 Neutralization–Reionization Mass Spectrometry

A rather specific, but widely applicable approach for the generation of radicals is based on mass

spectrometry. In this method, referred to as neutralization–reionization mass spectrometry (NRMS),¹¹⁷ an ionic precursor species is produced by any of the various mass-spectrometric ionization methods available, accelerated to a kiloelectronvolt kinetic energy, mass-selected, such that only the ion of interest enters the next step, and then neutralized in a collision with a stationary target gas (typically O_2 for the neutralization of anions and Xe for that of cations). The neutral species formed still has the incident kinetic energy in the kiloelectronvolt range and then enters a second collision cell in which it can be re-ionized to either anions or cations which are then detected by conventional mass-spectrometric means. The setup of such an NRMS experiment is shown in Figure 5.

NRMS is not restricted to radicals, but applicable to all ions which can be generated in yields sufficient for this kind of experiment; the neutralization–reionization (NR) yield is typically about 10^{-6} of the incident precursor ions. *Inter alia*, NRMS has also been used to generate and characterize several neutral biradicals.^{118–120} While the high-energy collisions involved pose several obstacles to the analysis of the data obtained, the main advantages of NRMS are that (i) ionic precursors can be used which can be prepared by selective ion/molecule reactions, (ii) the mass-selection steps avoids all possible problems arising from mixtures of species, and (iii) the existence of the neutral species can directly be probed experimentally. As an example, Figure 6 shows the NR mass spectrum of the allyloxide anion $\text{CH}_2 = \text{CH}-\text{CH}_2\text{O}^-$ with

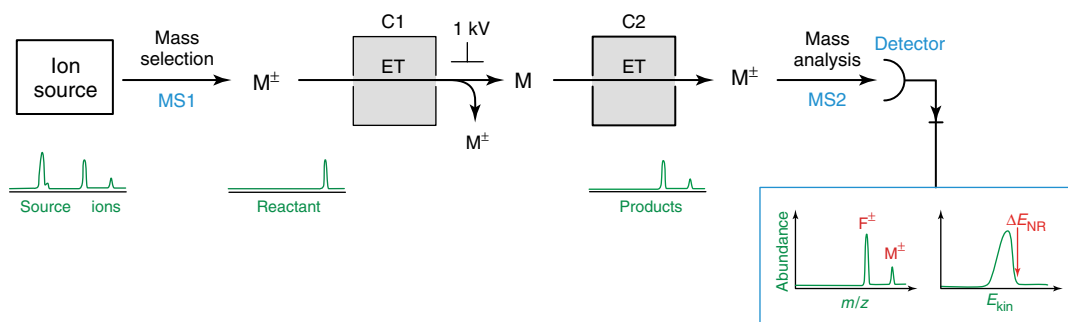


Figure 5 Schematic illustration of a neutralization–reionization (NR) experiment: A mass-selected precursor ion $\text{M}^\pm$ is neutralized by electron transfer in a first collision cell C1, all remaining ionic species are deflected away, the fast beam of neutral species is reionized in a second collision cell C2, and the ions formed are mass-analyzed and detected. The resulting NR mass spectrum provides information about the existence of the neutral species M and about its dissociation into fragment ions $\text{F}^\pm$. The electron-transfer processes are driven by the kinetic energy of the incident beam and the resulting kinetic energy deficit (ΔE_{NR}) of the re-ionized species $\text{M}^\pm$ provides insight into the energetics of the redox reactions involved.

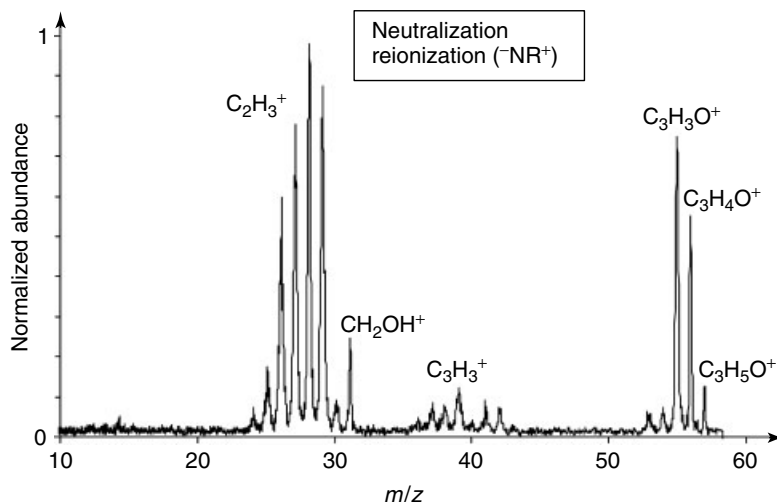


Figure 6 NR mass spectrum of mass-selected $\text{CH}_2=\text{CH}-\text{CH}_2\text{O}^-$ with reionization to cationic species. The “survivor signal” for intact $\text{C}_3\text{H}_5\text{O}^+$ demonstrates the intrinsic stability of the neutral radical. The various fragments signify the preferred dissociation channels via loss of hydrogen atom(s) as well as C–C bond cleavage to afford $\text{C}_2\text{H}_3^+ + \text{CH}_2\text{O}$ with subsequent fragmentations.

reionization to cations.¹²¹ The mere observation of a $\text{C}_3\text{H}_5\text{O}^+$ ion having the mass-to-charge (m/z) ratio of the anionic precursor demonstrates that the neutral allyloxy radical can survive for the time of flight between collision cells C1 and C2 (about 1 μs). The fragment ions observed provide insight into the dissociation of the neutral as well as the ionic species involved. It is interesting to note that NRMS has also been combined with pyrolytic radical generation.¹²²

As an extension to the NR method, a scheme referred to as NIDD (neutral-and-ion decomposition difference) has been introduced.¹²³ It allows to deconvolute the dissociation occurring at the neutral and ionic stages in cases in which the NR process is associated with a charge inversion (i.e., from cations to anions, $^+\text{NR}^-$, or from anions to cations, $^-\text{NR}^+$). In the case of methylamine, for example, the stepwise losses of either H-atoms or molecular H_2 toward the generation of HCN have been probed using the NIDD approach.¹²⁴ While the NR and NIDD approaches share the common drawback that the internal energies of the neutral species are not well defined, a compensation is provided by the mass-spectrometric steps before and after the NR sequence, which allows selection of certain target species from complex mixtures and likewise to study larger, more complicated radicals also including stereochemical features (see below).

4 PHOTOIONIZATION OF RADICALS

Photoionization techniques, associating mass spectrometry with well-defined and tunable sources of energy, are powerful tools to provide structural, energetic, and spectroscopic information on radicals $\text{R}^\bullet$ and their corresponding cations R^+ in the gas phase. This knowledge can be used in turn to probe the neutral radical dynamics by allowing the monitoring of either the reactant decay or the product appearance. Finally, photoionization is also a dedicated tool to produce R^+ cations with well-defined internal energy contents to study their unimolecular or bimolecular reactivity. In this section, we concentrate only on selected points related to the chemistry of $\text{R}^\bullet$ and R^+ on which this article is centered.

4.1 Photoionization: A Signature of the Radical

With the development of intense laser or SR sources, which are complementary in terms of resolution and tunability, studies of radical photoionization made large progress. Photoionization can be used to selectively probe radicals which are difficult to produce in large quantities and the yields of mass-selected ions as a function of photon energy provide detailed information specific for a certain

compound. The shape of the resulting curves, the onset above the radical ionization energy (IE), and possible structures in the spectrum revealing excitation between excited rovibronic states of the radical and the cations are a signature of a given radical. This can be used to identify products of unimolecular and bimolecular reactions as described in Sections 5 and 6, even in the case of isomers which appear at the same mass-to-charge ratio but can be distinguished by their photon energy dependence. Section 6, for example, describes how photoionization with tunable SR can serve as a multiplex detection method in setups that explore the kinetics of bimolecular reactions in chemical reactors and flames.

4.1.1 Ionization Energy and Franck–Condon Effects

The first aspect to be mentioned in the context of ionization of the radicals to the corresponding cations is that most radicals have relatively low IEs. It is a direct consequence of the underlying electronic structures that a radical (usually with doublet spin) upon ionization can *inter alia* yield a singlet species, which typically are quite stable. Hence the neutral state is a relatively energetic radical, whereas the ion state is some favorable closed-shell species, resulting in lower IE than, for example, an ionization of a neutral closed-shell molecule to the radical cation. For illustration, consider the ethyl radical for which the $\text{IE}(\text{C}_2\text{H}_5^\bullet) = 8.12 \text{ eV}$ ¹²⁵ is by more than 2 eV lower than those of its closed-shell congeners with $\text{IE}(\text{C}_2\text{H}_4) = 10.51 \text{ eV}$ ¹²⁵ and $\text{IE}(\text{C}_2\text{H}_6) = 11.52 \text{ eV}$.¹²⁵

The consequence of the low IE of radicals is that moderately energetic photons can induce their ionization. In laboratory experiments, only two or three UV photons in REMPI (resonance enhanced multi-photon ionization) schemes, and 7–12 eV VUV photons in a one-photon excitation scheme are sufficient to ionize most of the radicals. In some natural environments, such as interstellar medium or planetary ionospheres, the Lyman- α solar radiation ($\approx 10.2 \text{ eV}$) dominates the photon spectrum, and thus is sufficient to photoionize a large number of radical species.

Determinations of radical IEs have been conducted using standard methods¹²⁶ such as

photoionization (PI) yield analysis, photoelectron spectroscopy (PES), or threshold photoelectron spectroscopy (TPES) or pulsed field ionization technique (PFI) like zero kinetic energy spectroscopy (ZEKE)¹²⁷ with precision ranging from several tens of millielectronvolt down to a fraction of an inverse centimeter. Their description is outside the scope of this article.

Another important aspect to be discussed is that the ionization cross-sections of radicals often rise relatively slowly from the apparent threshold or even have an ill-defined shape. Upon first sight, this might appear quite surprising considering the low IE and one would hence expect a facile oxidation to the corresponding cation. However, the very same argument raised to explain the modest IEs of many organic radicals also accounts for the slowly rising ionization cross-sections in that the transitions between the neutral and the ionic states are not very efficient. As a measure for this efficiency, the related Franck–Condon factors (FCF) can be used, which describe the overlap of the wavefunctions of the initial state (neutral) and terminal state (cation). From a chemical point of view, FCFs can be correlated to the geometry differences between the initial and the terminal states. For similar equilibrium geometries (bond distances and angles), the FCF is good for the $(v_i, v_i^+) = (0, 0)$ transitions (v_i = vibrational quantum number for the v_i mode) and the ionization cross-section is large already at the ionization threshold. This behavior is found in the indenyl radical.⁶¹ Moreover, if the neutral radical and the cation have similar potential surfaces beyond the equilibrium geometries, the sequence bands associated with the diagonal transitions (1,1), (2,2), and so on will also show up nicely. On the other hand, if the geometries are similar, but the potential surfaces are not parallel, diagonal transitions (v_i, v_i) gradually decrease as a function of n and nondiagonal transitions $(0, v_i^+)$ will appear. This is the case for the methyl radical along the out-of-plane (umbrella) bending angle (v_2 mode). The radical $\text{CH}_3^\bullet$ and the cation CH_3^+ have similar planar structures at equilibrium, but the potential surface of $\text{CH}_3^\bullet$ is much more anharmonic along this coordinate than that of the cation. This results in a strong $(v_2, v_2^+) = (0, 0)$ band, lower (1,1) and (2,2) bands and a visible (0,2) band.^{128–130} Finally, if the geometries significantly differ, the FCF are poor for the lower states and only vibrationally excited states of the final state

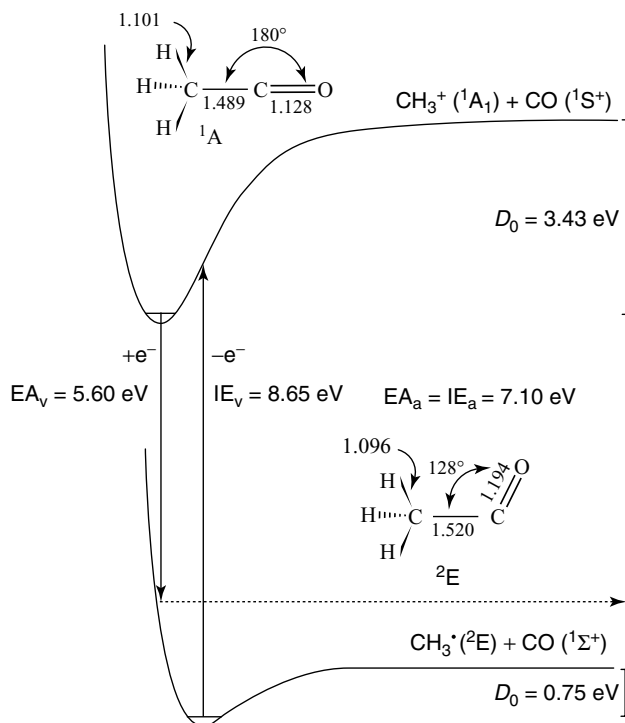


Figure 7 Vertical and adiabatic redox transitions between the acetyl radical $\text{CH}_3\text{CO}^\bullet$ and the acetylium cation CH_3CO^+ .

can be produced efficiently. In the extreme case, the (0,0) transition may even not be detected at all and the ionization cross-section would instead start from some ill-defined point above $\text{IE}(\text{R}^\bullet)$. This is what happens for the $\text{CF}_3^\bullet$ radical and CF_3^+ cation,^{131–133} which have pyramidal C_{3v} and planar D_{3h} geometries, respectively. For the out-of-plane (umbrella) bending mode, the calculated FCF for the $(0, \nu^+)$ transitions is very low for small values of ν^+ and peaks at a much higher value of ν^+ around 20.¹³¹ Hence, the ion yield rises very slowly and the exact value of the adiabatic IE has been debated for a long time as reported by Botschwina *et al.*^{132,133}

To clarify this important aspect in the chemistry of radicals, let us consider the acetyl radical $\text{CH}_3\text{CO}^\bullet$ and the related acetylium ion CH_3CO^+ as an extreme and likewise illustrating case.¹³⁴ The acetyl radical is a carbon-centered σ -radical with the unpaired electron located in the CCO-plane. Repulsion of this electron with a doubly occupied $2p_\sigma$ orbital on oxygen leads to a bent situation of the CCO unit. Ionization via removal of the unpaired σ -electron leads to an acylium ion, having a linear CCO unit with pronounced resonance

stabilization and a formal sp-hybridization of the central carbon atom. While already the acetyl radical can in fact be considered as a reasonably stable species, the acetylium ion is even more stabilized and the associated *adiabatic* IE accordingly amounts to only $\text{IE}_a(\text{CH}_3\text{CO}^\bullet) = 7.10 \text{ eV}$ (Figure 7). Here, adiabatic means the transition from the optimal geometry of the neutral acetyl radical to the optimal structure of the cation, thus including a transition from a bent to a linear CCO unit. As removal of an electron in a typical ionization event is much faster than the movement of nuclei, the geometries often do not or only partially relax. FCFs can be used to express the corresponding transition moments for each rovibrational level. The extreme consideration is the neglect of any structural relaxation, hence a vertical transition. In this respect, the acetyl system is quite instructive. Thus, vertical ionization of the bent neutral radical leads to a situation in the cation state which cannot fully profit from resonance stabilization and the corresponding $\text{IE}_v = 8.65 \text{ eV}$ is significantly larger than $\text{IE}_a = 7.10 \text{ eV}$. Likewise, the vertical electron

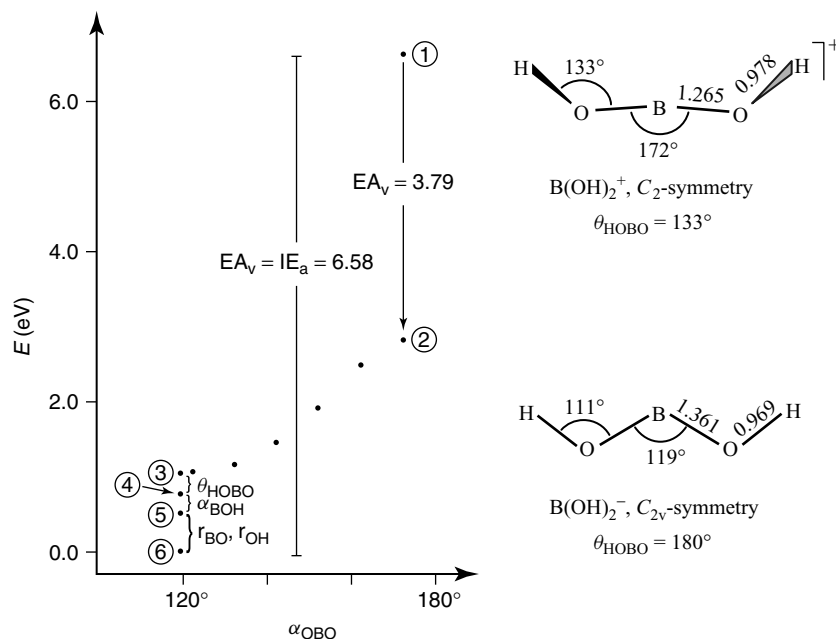


Figure 8 Components in the vertical neutralization of the borinium cation B(OH)_2^+ to the neutral boryl radical $\text{B(OH)}_2^\bullet$ (energies in electronvolts). The transition from ① to ② is just the vertical recombination of the cation with an electron, from ② to ③ the angle α_{OBO} is relaxed for the neutral, while the points from ③ to the final minimum ⑥ include relaxation of the other degrees of freedom.

affinity of the acetylium ion, $EA_v = 5.60$ eV is more than 1 eV lower than $EA_a = IE_a = 7.10$ eV.

An even more extreme case in this respect is the neutralization of the closed-shell, main-group cation B(OH)_2^+ to the corresponding neutral radical.¹³⁵ In this particular example, the vertical electron affinity of the cation is almost 3 eV lower than the adiabatic value. Conventionally, once they think about the differences between vertical and adiabatic processes and the related Franck–Condon effects, chemists are trained to consider bond lengths as decisive properties while triangular or dihedral angles are given less importance. The deconvolution of the various contributions in the case of B(OH)_2^+ impressively demonstrates that this pragmatic simplification not always holds true (Figure 8). Thus, the most influential property in the vertical versus adiabatic electron affinity of B(OH)_2^+ is in fact the angle α_{OBO} whose change from 172° in the cation to 119° in the neutral species affects the cation's EA by almost 2 eV.

Advanced computational methods can also quantify the FCFs involved in ionization processes.^{51, 136–138} For a number of comparably small radicals or cases with a geometry change

limited to a few coordinates detailed simulations were carried out and can be performed with high accuracy as shown, for example, recently for the propargyl radical.¹³⁹ With some simplifications,¹⁴⁰ also more complicated photoionization processes such as in phenyl radical,¹⁴¹ metal-containing species,¹⁴² and toluene¹⁴³ can be simulated efficiently. But despite some approximations,¹⁴⁴ these methods are far from routine applications in the analysis of ionization thresholds. These limitations are to be kept in mind when evaluating the ionization thresholds of radicals in that the experimental uncertainties of data associated with low FCFs strictly speaking only lead to upper limits of the IEs, while the true adiabatic value could still be lower than the extracted value owing to particularly unfavorable FCFs.

4.1.2 Dissociative Photoionization

When the photon energy is higher than the dissociative photoionization thresholds, the radical photoionization contributes not only to the parent ion

yield but also to its fragment ion yield at lower masses by the processes $R^* + h\nu \rightarrow (R^+)^* + e^-$ and $(R^+)^* \rightarrow A^+ + B$. The parent and fragment yields have to be considered together to constitute the signature of a radical photoionization. The thermochemistry of the cation, and often in turn of the neutral radical itself, can also be derived from the measurements of appearance energies (AE) of the ionic fragments. The basic method described up to now, that is, ion yield measurements versus photon energy, is in principle the easiest way to proceed, but not the most precise, in particular because the photoelectron energy is not controlled. Much more reliable threshold energies can be derived from a careful analysis of the fragmentation diagram in experiments where the photoelectron energy is controlled, such as in threshold photoelectron-photoion coincidences (TPEPICO).¹⁴⁵ This technique not only provides valuable information on the radical or cation energetics, but is also used to study their unimolecular reactions and specifically the effect of the parent ion internal energy on its reactivity.

4.1.3 Absolute Photoionization Cross-Section

We have seen that relative photoionization cross-sections are useful signatures to identify radicals produced in reactions. It can also be helpful to know the absolute values of these photoionization cross-sections, in particular to derive branching ratio between reaction products or to quantify the concentration of a given species. Let us illustrate this aspect by reference to the photolysis of methane (CH_4) by VUV photons, which leads to various radicals in competitive channels: $CH_3^* + H^*$, $CH_2^* + H_2$, $CH_2 + 2 H^*$, or $CH^* + H_2 + H^*$. A precise knowledge of the branching ratio between these channels is very important for various environments, in particular for the Titan atmosphere, as methane photolysis is one of the starting steps for the radical chemistry. Surprisingly though, the branching ratio are not yet well determined and published values scatter over a large range as described by Gauyacq *et al.*^{146,147} Even if H-atom detection is very efficient, its exclusive use as a detection technique is not sufficient to extract the branching ratio because of overlaps between different channels. More precise data about the branching ratio are expected from the direct detection of CH_3^* , CH_2^* , and CH^* by photoionization. However, for the derivation of the branching

ratio, absolute photoionization cross-sections have to be determined first. Absolute photoionization cross-sections measurements for radical have been reported for methyl,^{146,148} ethyl,¹⁴⁹ vinyl, propargyl,¹⁵⁰ allyl, 2-propenyl,¹⁵¹ and phenyl.¹⁵² Usually, the methods used are based on the knowledge of a reference absolute photoionization cross-section (molecule A) and on the simultaneous measurements of two ion yields, A^+ and R^+ , where A and R^* are consumed or produced by the same process such as $A \rightarrow R^* + B$ or $B \rightarrow A + R^*$, B being a second molecule (or atom, respectively). In the case of the methyl radical for instance, pyrolysis of CH_3I leading to $CH_3^* + I^*$ has been used together with the reference absolute photoionization cross-section of CH_3I .¹⁴⁶ In this kind of experiment, great care has to be taken on the control of the relative detection efficiency of A^+ and R^+ . As absolute photoionization cross-section measurements are quite difficult and usually done with laser sources, they are often limited to selected photon energies. However, absolute values can be derived over a much larger range of photon energies by an additional and more simple experiment where only photoionization cross-sections relative to an absolute value obtained at a specific photon energy are measured with easily tunable radiation such as provided by a synchrotron source.^{146,148}

4.2 Photoionization of R^* Radicals as a Source of State-Selected Cations R^+

If one wants to study the reactivity of ground-state cations, there are several ways to produce cations by electron ionization or photoionization from various precursors and relax them to their vibrational ground state. However, if one wants to study the reactivity of polyatomic cations as a function of their internal energy (i.e., the vibrational quantum number), the only method at present is to produce the neutral radical R^* first, and use state-selection techniques such as TPEPICO described above to form the cation with a well-defined internal energy content. It has been demonstrated recently for the methyl case,¹²⁸ that the TPEPICO technique can be used to prepare the cation CH_3^+ from the neutral radical CH_3^* in a series of excited vibrational states corresponding to the symmetric out-of-plane (umbrella) bending mode, ν_2 . Experiments to study

the reactivity of the methyl cation as a function of its vibrational energy in an ion–molecule reaction setup are currently planned at Orsay.¹⁵³

5 UNIMOLECULAR REACTIONS

Unimolecular reactions of radicals, such as dissociation or isomerization reactions, are mostly studied using photoexcitation by a laser. This has the advantage that a well-defined amount of energy is deposited in the radical. The reaction products and rates of formation are then monitored at different excitation energies. Thermal rate constants necessary for combustion studies can easily be obtained from such data by convoluting them with the appropriate distribution functions. Studies of unimolecular reactions are focused on four central questions: (i) What are the reaction products? (ii) What is the reaction mechanism leading to those products? (iii) What are the time scales for the different steps involved in the reaction, that is, how long does each step take? (iv) How is the excess energy distributed among the product degrees of freedom?

The primary photophysical processes after excitation are best investigated by ultrafast spectroscopy.¹⁵⁴ It turns out that the lifetimes of excited electronic states in polyatomic radicals are generally

rather short. Since radicals often possess several low-lying excited electronic states, the spacings between them are small and the electronic couplings are large, so the excited states generally deactivate fast. The most suitable method is time-resolved photoionization, because charged particle detection is very sensitive and mass information is available. This is critical in experiments on species that are difficult to generate cleanly and at high number density. In the corresponding experiments, a first laser pulse (pump) excites the radical to the electronic state of interest, while a second pulse (probe) ionizes the radical. The delay between the two pulses is varied and either the ion- or photoelectron signal is monitored as a function of the delay time.¹⁵⁵

As an example, the time-resolved photoelectron spectrum of the *tert*-butyl radical recorded at pump-wavelengths of 324 nm is given in Figure 9.¹⁵⁶ This wavelength corresponds to excitation into the $A\ ^2A_1\ (3s)$ state. Two bands at different photoelectron kinetic energy are visible that grow in around the zero in time and decay quickly. The two bands correspond to different ionization processes: Although absorption of two photons at 810 nm is sufficient for ionization, most of the *tert*-butyl radicals absorb three photons. The maximum possible electron kinetic energy is depicted in Figure 9 as a dashed line. The

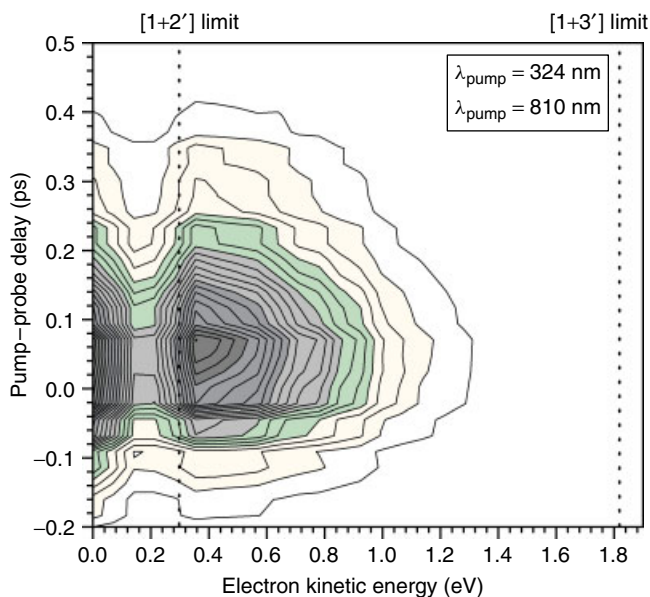


Figure 9 Femtosecond-time-resolved photoelectron spectrum of the *tert*-butyl radical.

Table 1 Lifetimes of excited electronic states for a number of reactive intermediates, as determined by ultrafast spectroscopy.

Intermediate	State	λ_{exc} (nm)	Lifetime	References
Ethyl, C_2H_5	$2^2\text{A}'$ (3s)	250	20 fs	157
Propargyl, C_3H_3	3^2B_1	255	50 fs	157
Allyl, C_3H_5	$\text{B } 2^2\text{A}_1$, $\text{C } 2^2\text{B}_1$	250–230	20–9 ps	158
<i>tert</i> -Butyl, $t\text{-C}_4\text{H}_9$	$\text{A } 2^2\text{A}_1$ (3s)	347–307	175–75 fs	156
	2^2E (3p)	268	2 ps	156
Hexyl, C_6H_{13} (2,3-dimethylbut-2-yl)	3p	265	25 fs/400 fs	159
Propadienylidene, $\text{l-C}_3\text{H}_2$	$\text{C } 1^1\text{A}_1$	250	70 fs	160
Benzyl, C_7H_7	4^2B_2	255	150 fs	157
	$\text{C } 2^2\text{A}_2$	305–298	400 fs/4.5 ps–180 fs/2.1 ps	60
Ph–C–Cl	$3^1\text{A}'$	267	40 fs/350 fs/1 ps	68

time-dependence is obtained from a cut through the two-dimensional plot at a given electron kinetic energy.

Table 1 summarizes results obtained for a number of radicals and two carbenes, chlorophenyl carbene, and propadienylidene. While some radicals have been investigated at a single wavelength only, others have been studied over a large range of excitation energies. For most radicals the excited-state lifetimes are on the order of a few picoseconds or less. An exception is allyl, which has a structured UV-spectrum that exhibits lifetimes of up to 20 ps for the origin of the B-state. In this context, it should be noted that several of the vibronic bands in allyl have been reassigned recently.⁸³ The lifetimes given in Table 1 correspond to the time for internal conversion (IC) to a lower electronic state. IC is the most important mechanism for excited-state deactivation in radicals. Intersystem crossing (ISC) does usually not occur, because quartet states are generally high in energy. For some species, more than one time constant is given, indicating a more complex dynamics. In these cases, we refer the reader to the original articles for more detailed discussions.

After IC, the radical ends up in the electronic ground state and electronic energy is converted to internal energy. The radicals may now possess enough energy to overcome the barrier to dissociation. In most radicals, this process takes place on the ground-state surface and occurs on a timescale between hundreds of picoseconds and several nanoseconds. It is the major task of the experimentalists to distinguish between the various possible reaction channels and to identify the most important reaction products. Since the reactions do not occur on an ultrafast time scale, ns-lasers are often sufficient. A common reaction pathway of

hydrocarbon radicals is the loss of a hydrogen atom, because a closed-shell molecule is formed. An excellent means to study this process is photofragment spectroscopy, as schematically depicted in Figure 10. A first laser promotes the radical into an excited electronic state that deactivates by IC to the electronic ground state. The energy is redistributed in the radical, and electronic excitation is converted to internal energy. In many radicals the amount of internal energy after IC is sufficiently high for a dissociation to occur. The H-atom product is then ionized by a second laser via the $1s\text{-}2p$

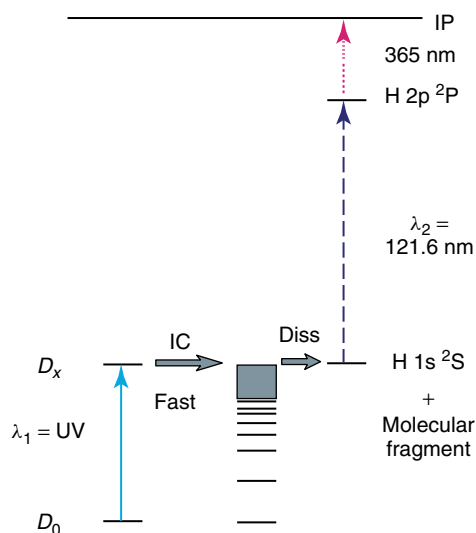


Figure 10 Description of photofragment spectroscopy. The radical is photoexcited in the UV by a first laser. After deactivation to the electronic ground state, the radical has enough internal energy to overcome the barrier to dissociation. One of the fragments is then detected by a second laser.

(Lyman- α) transition. Note that the ultrafast studies mentioned above monitor the first step (IC) indicated in Figure 10. Detection of the molecular fragment is also possible, but since it is formed in a range of rovibrational states, the signal from each individual transition is small and distributed over a large energy range. In contrast all H-atoms are formed in the 1s state and the oscillator strengths of the 1s $\rightarrow$ 2p transition is large, which makes H-atom detection extremely sensitive.

Three types of experiment are possible: (i) the delay between the lasers is varied to obtain reaction rates, (ii) the detection laser is scanned over the Doppler profile of the H-atom (accordingly, the method is also referred to as Doppler-spectroscopy) to get information on the H-atom reaction product, and (iii) the excitation energy is varied to get insight into the energy dependence of the processes. Figure 11 illustrates a type (ii) experiment, carried out on partially deuterated allyl radicals, excited at 248.15 nm (B 120¹). Only very few D-atoms are visible, thus the central C–H bond is preferentially broken. Therefore, the dominant reaction channel is the formation of allene¹⁶¹ and not propyne. An analysis of the profile of the H-atom signal reveals further details of the dissociation process.¹⁶²

The dissociation of numerous radicals has been studied by this method, including alkyl radicals such as ethyl,⁵⁴ 1- and 2-propyl,⁵⁷ *tert*-butyl,⁵⁶ and propargyl⁵⁸ as well as the carbenes 1-C₃H₂¹⁶³

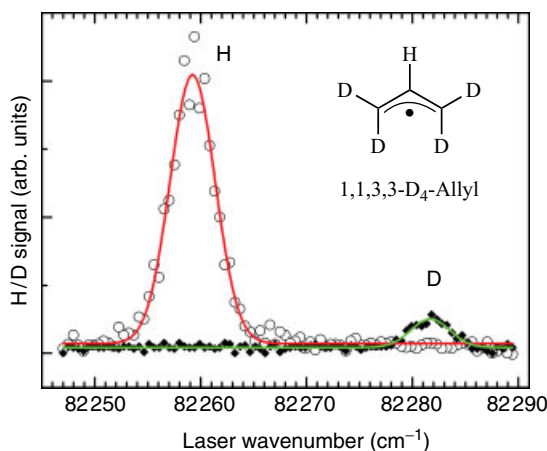


Figure 11 The H/D-atom Doppler spectrum of partially deuterated allyl radicals shows that cleavage of the central C–H bond and formation of allene is the most important reaction channel.⁵⁹

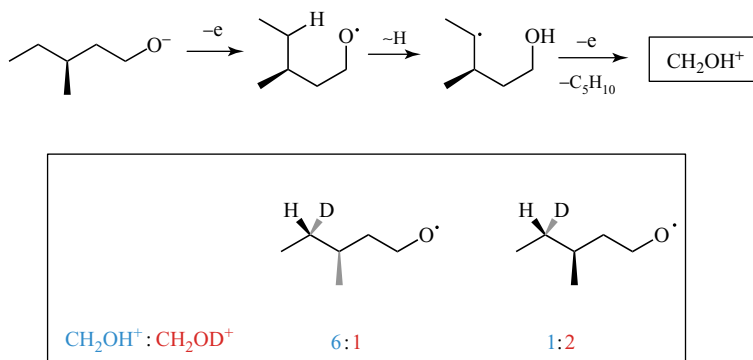
and c-C₃H₂.⁶⁷ The method is well suited for light fragments being formed, for example, H[•] and D[•], but not well adapted to study C–C bond cleavage processes. An alternative technique is translational energy spectroscopy. Here fragmentation is also induced by a photon and the translational energy of the neutral reaction product is examined.¹⁶⁴ This method is well suited for investigating the products of a C–C bond cleavage. For example, the minor pathway in allyl photodissociation to CH₃[•] + C₂H₂ was examined using the technique,¹⁶⁵ but also the dissociation dynamics of the C₃H₅[•] isomers 1- and 2-propenyl.^{166–168} Some radical dissociations were investigated by both methods, among them the H-atom loss from propargyl at 248-nm excitation.^{58,169} Both methods yielded the same results.

For more complex radicals, the mass-spectrometric NR method (see Section 3.2.5) can provide valuable insight into the unimolecular rearrangement of transient radicals. In the case of alkoxy radicals, for example, electron detachment from the corresponding alkoxide ions provides a facile way for the generation of the neutral open-shell species. Using NRMS techniques, the fragmentation of a number of alkoxy radicals has been elucidated in quite some details and even stereochemical preferences in the dissociation of alkoxy radicals were derived from the mass-spectrometric studies (see Scheme 4 for an example).^{170,171}

Likewise, several carboxy radicals were probed using NRMS and similar hydrogen rearrangements involving the activation of C–H bonds remote from the functional group were observed in the case of aliphatic carboxylates.^{172–175} Further, these NR experiments could establish the existence of transient carboxy radicals beyond any doubt, even though decarboxylation according to reaction (8) is generally by about 0.5 eV exothermic.



In addition to these typical organic radicals, also several hypo- or hypervalent radicals involving main-group elements have been studied using NR methods, such as B(OH)₂[•],¹³⁵ CH₃BOH[•],¹⁷⁶ hypervalent ammonium radicals R₄N[•],^{177,178} and their oxygen analogs R₃O[•].^{179,180}



Scheme 4 Diastereoselective C–H(D) bond activation in the unimolecular rearrangement of neutral 3-methylpentoxy radicals formed via neutralization of the corresponding anions and probed via dissociative reionization of the rearranged species.

6 BIMOLECULAR REACTIONS

As discussed in a Section 2.1, modeling of combustion and plasma processes requires considerable knowledge on reaction rate constants¹⁹ under various conditions. Therefore, bimolecular reactions of many small molecules including radicals have been studied over a large range of pressures and temperatures using basically all of the radical generation techniques discussed in Section 3. Within the scope of this survey, only a selection of experiments can be discussed. High temperature data relevant for combustion kinetics have often been studied using shock tubes.^{181,182} Such devices consist of two compartments filled with gas, one at low pressure and one at high pressure, that are separated by a diaphragm. Once this diaphragm breaks, a shock wave travels through the low pressure gas and heats it up quickly. Reaction products are monitored by absorption or emission spectroscopy. A common light source for detecting atomic products is a microwave discharge lamp, but laser-based methods are also applied. According to Tsang and Lifshitz¹⁸¹ “a shock tube can be considered to be a millisecond high temperature furnace.” Typical temperatures that are studied range from 1000 to over 3000 K. Rate constants, activation energies, and Arrhenius parameters have been determined for the reactions of many hydrocarbons in particular with molecular oxygen. Different ways of radical generation are applied: Cyanonitrene, NCN was, for example, produced thermally from NCN₃ behind the shock wave,¹⁸³ but alternatively shock tubes have been combined with photolysis sources.¹⁸²

In many kinetics experiments, a radical is generated photolytically and reacts with a stable molecule in a suitable reactor. Either the decay of one of the reactants or the formation of a product is monitored by laser spectroscopic methods. Deriving rate constants from the data is straightforward because the time delay between two light sources can be easily varied. This approach works well when only a few species are involved that have a well-characterized electronic spectrum. However, in a complex reaction (a combustion process, for example) a wide variety of species is formed. Hence, there exists a need for the parallel detection of all products or at least most of them (multiplexing). In addition, a chemically selective detection is often required because in many cases several structural isomers of a given composition are conceivable. Simple mass-spectrometric detection is therefore not sufficient. Optical detection on the other hand suffers from the fact that the electronic spectra of larger radicals are often not known. The task to develop a method that permits to detect diluted species in an isomer-selective fashion has recently been accomplished using tunable synchrotron radiation (SR) as a light source for photoionization. SR has been combined with several setups for radical formation, a chemical reactor,¹⁸⁴ a flat flame burner^{5,21} and a plasma discharge.¹⁸⁵ In the chemical reactor,¹⁸⁴ a reaction mixture flows through a tube and a radical is generated photolytically. The reaction mixture (including the products) effuses through a small hole in the reactor and a subsequent sampling cone into the ionization region of a mass spectrometer. All components of the mixture are then continuously photoionized and detected in parallel. The zero in time is given by the photolysis

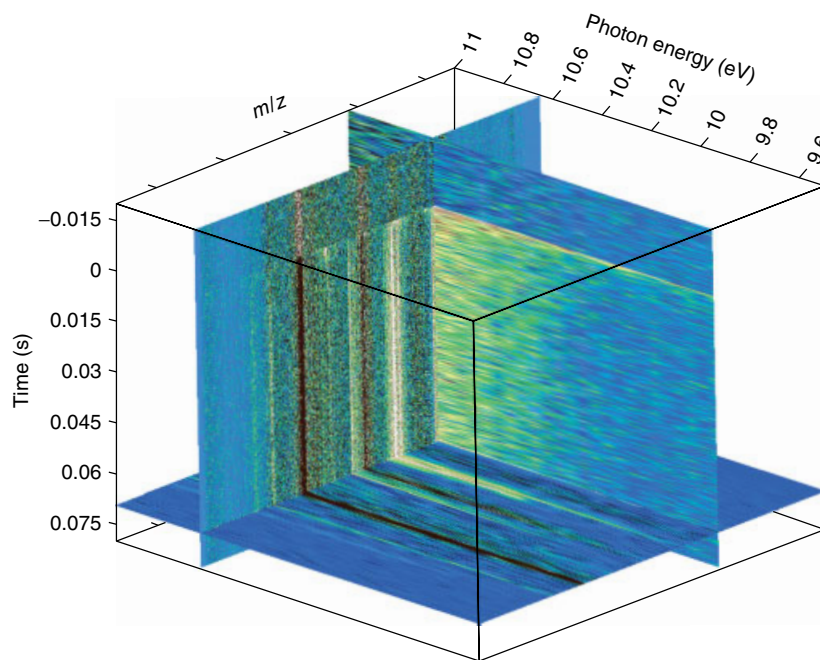
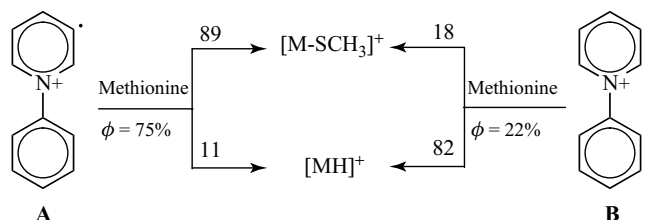


Figure 12 Example of a three-dimensional dataset, obtained in the SR-based product analysis of a flow reactor. It displays the reaction of ethyl radicals, produced by 193-nm photolysis of 3-pentanone, with O_2 . The three slices through the three-dimensional-plot show the photoionization efficiency as a function of reaction time for a given mass (right-hand vertical slice), the mass spectrum as a function of reaction time at a given photon energy (left-hand vertical slice), and the mass spectrum as a function of photon energy at a given time (horizontal slice).

laser. A key advantage of SR in this respect is its wide tuning range. By recording time delay traces over a large range of photon energies, the ionization onset of each component is observed, that is, the IE. Since the IE is characteristic for a given isomer, isomer selectivity is achieved. The experiment yields three-dimensional plots with the ion mass, the photon energy, and the reaction time delay plotted on the various axes. An example for the $C_2H_5 + O_2$ reaction²⁰ is given in Figure 12. Such a plot permits to assign reaction rates to a given isomer. Instead of a flow tube reactor, a flat flame burner can be used, permitting to identify the various intermediates formed during combustion as a function of the burner conditions.^{5,20,21} Several fuels have already been investigated. The plasma discharge experiments work in a similar manner, but radicals are generated in a discharge.¹⁸⁵ For experiments of this kind, it is helpful to know ionization and fragment AEs beforehand. Such data are sometimes available from the experiments described in Section 4, but when this is not the case, computed IEs can nowadays be relied upon quite well.^{186–189}

Bimolecular reaction rates are also important for astrochemistry,¹⁹⁰ as described in Section 2.4. However, here reliable rate constants are required at very low temperature, which is not possible with the approaches described above. In recent years, the so-called Cinétique de Réaction en Ecoulement Supersonique Uniforme (CRESU) technique¹⁹¹ proved to be successful in yielding low-temperature rate constants for bimolecular reactions of small radicals.^{190,192,193} In this technique, a mixture of reactant gases with a buffer gas (rare gas) is continuously expanded from a reservoir held at several 10 mbar through a Laval nozzle into the vacuum, adiabatically cooling the gas mixture to a few Kelvin. A Laval nozzle has an hour-glass shape and an opening diameter of 0.3–5 cm; therefore enormous pumping speeds are required in the experiments. The advantage of such an expansion lies in the well-defined temperature, which is constant over most parts of the beam. Different temperatures can be selected using different nozzles with varying geometries. Photolysis and detection laser are sent down axially with the expanding



Scheme 5 Reaction of the isomeric charged tagged phenyl radicals **A** and **B** with neutral methionine; branching ratios ($\Sigma = 100$) and overall reaction efficiencies (ϕ) are given on top of the respective arrows.

gas. Reactants or products are monitored by LIF. Rate constants have been obtained for a number of reactions of $\text{OH}^\bullet$, $\text{CN}^\bullet$, $\text{CH}^\bullet$, and other radicals with a variety of stable molecules such as H_2 , CO , O_2 , NO , as well as CH_4 and larger hydrocarbons. Rates have been determined for temperatures down to approximately 10 K. Recently, the technique was extended to reactions relevant to atmospheric chemistry,¹⁹⁴ in particular with regard to reactions of $\text{OH}^\bullet$ with volatile organic compounds (VOCs) that impact the chemistry of the troposphere.

Crossed beam techniques yield probably the most detailed insight into bimolecular reactions.^{195,196} In this technique, two reactants are expanded in separate molecular beams that cross in an ultrahigh vacuum and the products are analyzed in a mass spectrometer. Either the molecular beam sources or the mass spectrometer is rotatable so that the reaction products can be analyzed as a function of the scattering angle. Such experiments provide detailed insight into the reaction mechanism that is unmatched by any other method, but are very difficult to carry out. Nevertheless some groups reported studies on the reactions of small- and medium-sized radicals with stable molecules in crossed beams. Information on reactions in combustion,¹⁹⁷ planetary atmospheres,¹⁹⁸ and interstellar space¹⁹⁹ has been gained, and even reactions of hydrocarbon radicals with oxygen atoms (i.e., radical/radical reactions) have been studied.^{200,201}

Techniques based on mass spectrometry also have considerable potential for studying bimolecular reactions, in particular when larger molecules are involved. An interesting variant to investigate the bimolecular reactivity of radicals has been introduced by Kenttämä and coworkers, who applied charge tagging of neutral radicals. Charge tagging of the radical, that is introduction of an auxiliary

charge, ideally not interacting with the radical site, allows handling the so-formed ion radical by the rich repertoire of techniques in gas-phase ion chemistry. The concept is illustrated for the reactions of two aryl radicals with the amino acid methionine ($\text{CH}_3\text{SCH}_2\text{CH}_2\text{CH}(\text{NH}_2)\text{COOH}$).²⁰² The charged tagged radicals are generated from the corresponding iodides via collision-induced cleavage of the C–I bond, then mass-selected and allowed to interact with neutral amino acids. For the isomeric radical cations **A** and **B** in Scheme 5, a pronounced difference in reactivity has been found. Thus, radical **A** with the radical center in the same ring as the charge center predominantly reacts via abstraction of the thiomethoxy group and with a reaction efficiency (ϕ) of 75%; ϕ is the ratio of the overall reaction rate constant k_r and the gas-kinetic collision rate k_c and expresses the percentage of reactive collisions. In marked contrast, radical **B** reacts about three times slower and largely prefers H-atom abstraction.

The presence of a real Coulomb charge in this mass-spectrometric method makes it difficult to directly transfer the results to the respective reactions of the corresponding neutral radicals. However, it is obvious that with the other techniques presently available for the generation of neutral radicals and for the detection and analysis of the reaction products, complex open-shell systems such as **A** and **B** are rather difficult to tackle. Despite the perturbation introduced by the charge, the charge-tagging method is therefore a useful extension to the scope of methods for the investigation of radical reactivity and it has been applied to a number of different systems,^{203–205} including bi-²⁰⁶ and even triradicals.^{207,208} Also an example of a radical–radical reaction has been studied using this approach.²⁰⁹

7 CONCLUSIONS

Fundamental studies of isolated radicals in the gas-phase form an important basis for the understanding of radical reactions in general and for the evaluation of energetical aspects in particular. Furthermore isolated radicals dominate the chemistry of high-energy environments such as combustion engines, hydrocarbon crackers, plasmas, planetary atmospheres, and interstellar space. Especially photoionization studies of jet-cooled radicals can provide accurate benchmark data for the stability of radicals, which are important input parameters for the construction of more general reactivity models. It is to be recognized though that sometimes unfavorable Franck–Condon overlaps may prevent adiabatic ionization of neutral radicals into the corresponding ground-state cations. In addition to their value as such, accurate gas-phase experiments also provide benchmarks for the evaluation of contemporary theoretical methods for the description of open-shell compounds, which are of outmost importance in various areas of chemistry.

The high reactivity of most small radicals poses considerable challenges to the experimentalists. Not only are these species “unbottable” and tend to dimerize and/or dissociate, but often the conversion from the precursor compound to the desired radical(s) is incomplete such that interferences with the precursors can disturb the experiments. A pertinent task remains the selective generation of radicals in a controlled manner which is still a nontrivial task when it comes to more complex molecules. A number of methods exist to generate radicals efficiently that all have their particular strengths. However, there is no general method available for radical production. As far as unimolecular reactions of radicals are concerned, a large body of techniques has been developed which provide detailed insight into the decomposition mechanism of isolated open-shell compounds. Electronically excited states generally deactivate quickly, as shown by time-resolved photoionization using picosecond- and femtosecond-laser pulses. Further reactions often occur from the internally hot electronic ground state. Insight into the dissociation is obtained from techniques such as photofragment spectroscopy that yield information on the energetics of the reaction products. When combined with the mass-spectrometric techniques for the generation

and mass selection of suitable ionic precursors followed by neutralization, also rather complex molecular structures can be investigated in detail.

With regard to investigations of bimolecular reactions of radicals, several challenges emerge which are closely related to the difficulties in the production of free radicals: number densities are low, the high reactivity may lead to reactions with impurities and interferences with precursor molecules may critically disturb the quantitative analysis of the data. In this respect, photoionization with synchrotron ionization is a promising technique that permits to study numerous reaction components in parallel and thus offers the multiplex advantage. In mass spectrometry-based techniques, the charge-tagging method developed by Kentämaa is a useful step forward, although the perturbation introduced by the presence of a real Coulomb charge in ionic species is not negligible.

Considering the significant progress in both radical preparation and detection techniques, further advances are expected in the future. An increased knowledge into radical chemistry will in turn improve our understanding of technologically relevant reactions systems, such as combustion engines or low-temperature plasmas.

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Radical Stability—Thermochemical Aspects

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1 INTRODUCTION

The terms “transient” and “persistent” are used frequently in the scientific literature to describe the kinetic properties of open shell systems in homogeneous solution.^{1–5} The hydroxyl radical (HO•, **1**), for example, is a *transient* species of central importance in atmospheric chemistry (see **Atmospheric Radical Chemistry**), as well as one of the most important reactive oxygen species (ROS) in aqueous solution, whereas the nitroxide 2,2,6,6-tetramethylpiperidine-1-oxyl, TEMPO (**2**) is a persistent radical stable enough to be bottled and sold in bulk (Figure 1) (see **Nitroxides in Synthetic Radical Chemistry**).

However, despite their widespread use, these terms are not too helpful for a quantitative approach to radical chemistry as they do not reflect the influence of thermochemical driving force and intrinsic reaction barrier on the observed lifetime. In this account, we assemble a large amount of thermodynamic data for (mostly neutral) open shell systems to provide a foundation for a quantitative discussion of reactivity. This type of data will, for example, show that reactions of radical **1** are typically much more exothermic than those of radical **2**. Thermodynamic data for open shell systems can be computed with comparable ease for stable as well as for unstable systems, while the experimental determination of quantities such as the heat of formation of a particular radical

is quite challenging. Kinetic data, in contrast, are much more difficult to predict by theory, while the determination of reaction rates can be approached experimentally with a variety of direct or indirect methods, at least for sufficiently fast reactions (see **Radical Kinetics and Clocks**). Theory and experiment pair up nicely in this respect, as a combination of these approaches is able to provide a comprehensive picture of thermodynamic and kinetic data.

2 DEFINITIONS OF RADICAL STABILITY

The thermodynamic stability of C-centered radicals can be defined in various ways and several options are discussed in the following.^{6–10} One of the most often used definitions is based on hydrogen transfer reactions as shown in Scheme 1 for reaction of methyl radical (•CH₃, **3**) with hydrocarbon R¹R²R³C–H.^{6,9,11,12}

$$\begin{aligned} \text{RSE}(\text{R}^1\text{R}^2\text{R}^3\text{C}^\bullet) &= \Delta H_{298}(\text{R}^1\text{R}^2\text{R}^3\text{C}^\bullet) \\ &+ \Delta H_{298}(\text{CH}_4) \\ &- \Delta H_{298}(\text{R}^1\text{R}^2\text{R}^3\text{C}-\text{H}) \\ &- \Delta H_{298}(\text{CH}_3^\bullet) \end{aligned} \quad (1a)$$

$$\begin{aligned} \text{RSE}(\text{R}^1\text{R}^2\text{R}^3\text{C}^\bullet) &= \text{BDE}(\text{R}^1\text{R}^2\text{R}^3\text{C}-\text{H}) \\ &- \text{BDE}(\text{CH}_3-\text{H}) \end{aligned} \quad (1b)$$

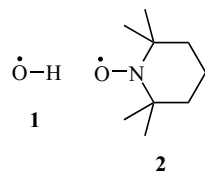
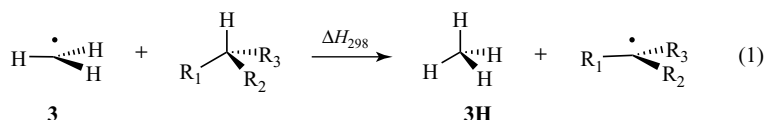


Figure 1 Hydroxyl radical **1** and 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) **2**.

The reaction energy of the reaction in Scheme 1 is often referred to as the radical stabilization energy (RSE) of radical $R^\bullet$ and is, of course, identical to the difference in homolytic C–H bond energies in the two closed shell systems $\text{CH}_3\text{--H}$ (**3H**) and $R\text{--H}$. The RSE value of $R^\bullet$ can thus equally well be expressed by (1a) or by (1b) and is negative for systems more stable than the methyl radical $^\bullet\text{CH}_3$ (**3**). Expression (1b) makes it also clear that theoretically calculated and experimentally measured bond dissociation energy (BDE) data can conveniently be combined to express the stability of radicals in a quantitative way. Using the above definition, the stability of *tert*-butyl radical ($((\text{CH}_3)_3\text{C}^\bullet$, **4**) amounts to $-38.9 \pm 2.9 \text{ kJ mol}^{-1}$ when using experimentally measured heats of formation¹³ or to $-29.1 \pm 0.7 \text{ kJ mol}^{-1}$ using energies derived from G3-level calculations (Table 1). Whether these values are due

to stabilizing interactions between the unpaired spin and the three methyl substituents in radical (**4**) or whether this also reflects other components such as steric strain in the closed shell reference system isobutane (**4H**) cannot be seen from the results in Table 1. For further discussion of alternative approaches to defining radical stability, we also include here data for hydroxymethyl radical (**5**) and fluoromethyl radical (**6**). The C–H bond energies in methanol (**5H**) and fluoromethane (**6H**) are smaller than that in methane (**3H**), implying a stabilizing influence of HO- and F-substituents on the radical center according to (1).

From a conceptional point of view, it is also important to note that (1) is an isodesmic reaction, which is defined as a reaction with retention of the number of bonds of a given formal type.^{15,16} This implies that RSE values can be computed quite accurately even with moderately accurate quantum mechanical methods (Table 1). Alternative definitions to characterize the stability of carbon-centered radicals in a quantitative way have been proposed, which circumvent the cleavage of C–H bonds.^{14,17–19} This involves the cleavage of a fully apolar C–C bond in the formal dimer of the respective radicals. Using again the methyl radical as a (nonstabilized) reference system and accounting for



Scheme 1 Isodesmic hydrogen transfer reaction defining the RSE of C-centered radicals.

Table 1 RSE values for *tert*-butyl radical ($((\text{CH}_3)_3\text{C}^\bullet$, **4**), hydroxymethyl radical ($^\bullet\text{CH}_2\text{OH}$, **5**), and fluoromethyl radical ($^\bullet\text{CH}_2\text{F}$, **6**) calculated according to (1).

	Method	RSE (kJ mol ⁻¹)
$^\bullet\text{C}(\text{CH}_3)_3$ (4)	Exp. ^a	-38.9 ± 2.9^{13}
	G3	-28.4
	G3B3	-29.8
	G3(MP2)-RAD	-28.5
$^\bullet\text{CH}_2\text{OH}$ (5)	Exp. ^a	-37.4 ± 0.6^{13}
	G3B3	-33.5
	G3(MP2)-RAD	-32.3
	Exp. ^a	-15.5 ± 4.2^{13}
$^\bullet\text{CH}_2\text{F}$ (6)	G3B3	-13.4
	G3(MP2)-RAD	-12.8

^aThe following experimentally measured BDE values (see Ref. 13) have been used to calculate RSE values: $\text{BDE}(\text{CH}_3\text{--H}) = +439.3 \pm 0.4 \text{ kJ mol}^{-1}$; $\text{BDE}((\text{CH}_3)_3\text{C--H}) = +400.4 \pm 2.9 \text{ kJ mol}^{-1}$; $\text{BDE}(\text{FCH}_2\text{--H}) = +423.8 \pm 4.2 \text{ kJ mol}^{-1}$; $\text{BDE}(\text{HOCH}_2\text{--H}) = +401.9 \pm 0.6 \text{ kJ mol}^{-1}$.

the fact that two radicals are generated simultaneously in this process leads to (2) as the defining equation (Table 2).

$$\text{RSE}(\text{R}^1\text{R}^2\text{R}^3\text{C}^\bullet) = 0.5[\text{BDE}(\text{R}^1\text{R}^2\text{R}^3\text{C}-\text{CR}^1\text{R}^2\text{R}^3) - \text{BDE}(\text{CH}_3-\text{CH}_3)] \quad (2)$$

While this definition avoids most of the pitfalls of using the C–H BDE process presented first, it also does have its own problems. These are mainly connected to cases, in which the two halves of the symmetric dimer reference system interact through more than just the central covalent bond. For the dimer of *tert*-butyl radical (**4**) we may, for example, assume the presence of steric interactions, whose relief on C–C bond dissociation will artificially stabilize radical **4**. Two additional cases worthy of consideration are ethylene glycol ($\text{HOCH}_2\text{CH}_2\text{OH}$), whose cleavage leads to hydroxymethyl radical ($\text{CH}_2\text{OH}^\bullet$, **5**), and 1,2-difluoromethane ($\text{FCH}_2\text{CH}_2\text{F}$), whose cleavage generates the fluoromethyl radical ($\text{CH}_2\text{F}^\bullet$, **6**). In the first of these systems, the two halves communicate through an internal hydrogen bond and additional stereoelectronic effects, while in the second example only the latter aspect remains. This leads in both of these systems to a preference for gauche conformations. The magnitude of the gauche effect in 1,2-difluoroethane can be quantified through the gauche/anti enthalpy difference as -1.8 kJ mol^{-1} at G3(MP2)-RAD level, in

close proximity to previous estimates.^{20–22} RSE values calculated according to (2) therefore, need to be corrected for these additional interactions to extract the true substituent effect on radical stability.^{14, 17–19} Following the approach pioneered by Zavitsas *et al.*, this leads to corrected RSE values of $\text{RSE}_Z((\text{CH}_3)_3\text{C}^\bullet, \text{4}) = -5.1 \text{ kJ mol}^{-1}$, $\text{RSE}_Z(\text{CH}_2\text{OH}^\bullet, \text{5}) = -8.5 \text{ kJ mol}^{-1}$, and $\text{RSE}_Z(\text{CH}_2\text{F}^\bullet, \text{6}) = +13.7 \text{ kJ mol}^{-1}$ (Table 2). In contrast to the results obtained from (1), this implies that fluorine substituents directly attached to the radical center are destabilizing. A third way of quantifying radical stability involves the cleavage of a C–C bond in a nonsymmetric reference compound^{14, 17–19}:

$$\text{RSE}(\text{R}^1\text{R}^2\text{R}^3\text{C}^\bullet) = \text{BDE}(\text{R}^1\text{R}^2\text{R}^3\text{C}-\text{CH}_3) - \text{BDE}(\text{CH}_3-\text{CH}_3) \quad (3)$$

This definition solves a number of problems arising from steric or stereoelectronic interactions in the symmetric reference compounds discussed above. Without addition of any correction terms, this leads to the results shown in Table 3. For all three systems considered here, the RSE values obtained from (3) are very close to the RSE_Z values resulting from the combination of (2) with the correction terms proposed by Zavitsas.¹⁴

The defining equation (1) for measuring stabilities of carbon-centered radicals can be adapted

Table 2 RSE values for *tert*-butyl radical ($(\text{CH}_3)_3\text{C}^\bullet$, **4**), hydroxymethyl radical ($\text{CH}_2\text{OH}^\bullet$, **5**), and fluoromethyl radical ($\text{CH}_2\text{F}^\bullet$, **6**) according to (2).

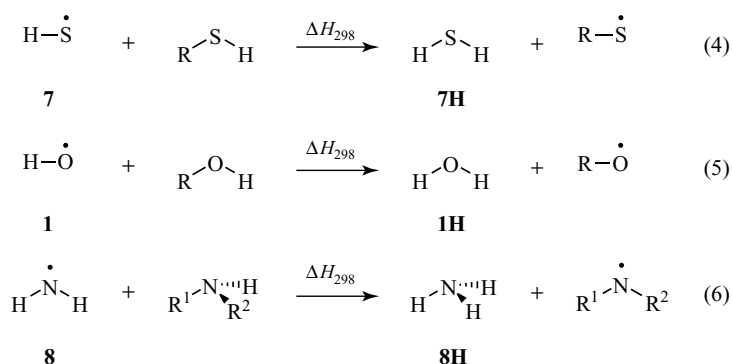
	Conformation	Method	RSE (kJ mol ^{−1})
$\text{C}(\text{CH}_3)_3$ (4)		Exp. ^a	-27.4 ± 2.1^{13}
		G3B3	−16.1
		G3(MP2)-RAD	−15.0
		G3(MP2)-RAD	−5.1(RSE_Z) ¹⁴
		Exp. ^a	-9.6 ± 3.2^{13}
CH_2OH (5)	gauche	G3B3	7.5
	gauche	G3(MP2)-RAD	−6.8
	anti	G3(MP2)-RAD	−10.8
	anti	G3(MP2)-RAD	−8.5(RSE_Z) ¹⁴
		Exp. ^a	-4.6 ± 4.2^{13}
CH_2F (6)	gauche	G3B3	+7.9
	gauche	G3(MP2)-RAD	+8.1
	anti	G3(MP2)-RAD	+6.3
	anti	G3(MP2)-RAD	+13.7(RSE_Z) ¹⁴

^aThe following experimentally measured BDE values (see Ref. 13) have been used to calculate RSE values: $\text{BDE}(\text{CH}_3-\text{CH}_3) = +377.4 \pm 0.8 \text{ kJ mol}^{-1}$; $\text{BDE}((\text{CH}_3)_3\text{C}-\text{C}(\text{CH}_3)_3) = +322.6 \pm 4.2 \text{ kJ mol}^{-1}$; $\text{BDE}(\text{HOCH}_2-\text{CH}_2\text{OH}) = +358.2 \pm 6.3 \text{ kJ mol}^{-1}$; $\text{BDE}(\text{FCH}_2-\text{CH}_2\text{F}) = +368.2 \pm 8.4 \text{ kJ mol}^{-1}$.

Table 3 RSE values for *tert*-butyl radical ((CH₃)₃C[•], **4**), hydroxymethyl radical ([•]CH₂OH, **5**), and fluoromethyl radical ([•]CH₂F, **6**) according to (3).

	Method	RSE (kJ mol ⁻¹)
[•] C(CH ₃) ₃ (4)	Exp. ^a	-13.8 ± 2.9 ¹³
	G3B3	-5.3
	G3(MP2)-RAD	-4.2
[•] CH ₂ OH (5)	Exp. ^a	-12.6 ± 4.2 ¹³
	G3B3	-10.7
	G3(MP2)-RAD	-8.7
[•] CH ₂ F (6)	Exp. ^a	+10.9 ± 8.4 ¹³
	G3B3	+13.7
	G3(MP2)-RAD	+13.9

^a The following experimentally measured BDE values (see Ref. 13) have been used to calculate RSE values: BDE(CH₃-CH₃) = +377.4 ± 0.8 kJ mol⁻¹; BDE((CH₃)₃C-CH₃) = +363.6 ± 2.9 kJ mol⁻¹; BDE(HOCH₂-CH₃) = +364.8 ± 4.2 kJ mol⁻¹; BDE(FCH₂-CH₃) = +388.3 ± 8.4 kJ mol⁻¹.

**Scheme 2** Isodesmic H-atom transfer reactions defining the RSE of S-, O-, and N-centered radicals.

to determine the stability of sulfur-, oxygen-, and nitrogen-centered radicals in a straightforward fashion by adjusting the reference systems to the corresponding radical type (Scheme 2).

How radicals respond to the presence of a particular substituent depends largely on the electronegativity of the atom holding the unpaired spin. This can be exemplified with the effects of the methyl substituent on the stability of C-, S-, O-, and N-centered radicals (Table 4). The RSE values calculated for ethyl radical ([•]CH₂CH₃, **9**) and for methylthiyl radical ([•]SCH₃, **10**) are moderately large with -18.8 and -15.5 kJ mol⁻¹, respectively, and thus illustrate the stabilizing effect of this substitution on the respective reference systems. A larger effect of RSE(**11**) = -25.0 kJ mol⁻¹ is obtained for the methylaminy radical ([•]NHCH₃, **11**), and a much larger stabilizing effect of -56.9 kJ mol⁻¹ is obtained for methyloxy radical ([•]OCH₃, **12**).

The rather different substituent effects calculated for O- and C-centered radicals raise the question of how to characterize the stability of resonance-delocalized radicals involving heteroatoms in the π -system. This is discussed using the enoxy radical **13** as an example, which can either be viewed as a C-centered or as an O-centered radical. Attempting to formulate the corresponding isodesmic equation for the stability of such a resonance-delocalized system, it becomes apparent that there is only one (fully delocalized) radical, but that there are two different closed shell reference systems (Scheme 3). Formal hydrogen transfer between acetaldehyde (**13H(C)**) and methyl radical (**3**) generates enoxy radical **13** and methane (**3H**). The Lewis structure **13a** is shown to reflect the fact that hydrogen abstraction occurred from the C2 atom. This reaction is exothermic by -36.7 kJ mol⁻¹ at G3(MP2)-RAD

at DFT level with subsequent single point calculations using a wavefunction-based method. The most economical of these approaches uses RMP2 single point calculations in combination with the 6-311+G(3df,2p) basis set.³¹ Results obtained with this approach are typically as good as with the best DFT methods, but show some systematic weaknesses in the description of strongly spin-delocalized systems.²⁹ These can, in part, be overcome through combination of correlation energies calculated with density functional and perturbation theory methods as is, for example, employed in the B2-PLYP approach.^{32–34} A notable and systematic improvement in accuracy is obtained when combining large basis set RMP2 calculations with small basis set RCCSD(T) calculations as is done in the G3(MP2)-RAD scheme developed by Radom *et al.*^{35–37} This compound scheme is largely similar to the G3(MP2)B3 method proposed by Curtiss *et al.*,^{24–26} but uses restricted open shell reference wavefunctions for MP2 and CCSD(T) calculations. Owing to a good price/performance ratio, this model has developed into one of the most frequently used methods for accurate predictions of radical thermochemistry in recent years.^{6–9,14,27–29,38} Benchmark studies using a test set of smaller radicals indicate that heats of formation can be predicted with an accuracy of around 5 kJ mol^{−1} with this model. Even better predictions (albeit at a significantly higher price) with an accuracy of around 3 kJ mol^{−1} can be obtained with the G3B3 compound scheme

or its radical-optimized variant G3-RAD.^{35–37} Even more accurate predictions can be obtained using one of the members of the Weizman-n family of methods such as “W1” or selected variations of *Gaussian-4* (G4) theory.^{32,39–43} But the applicability of these methods even to medium-sized systems provides a formidable technical challenge and these approaches will thus be mainly employed for benchmark purposes.³⁸ All RSE values cited in the following text have been calculated at G3(MP2)-RAD level, if not mentioned otherwise.

4 THE STABILITY OF CARBON-CENTERED RADICALS

4.1 The Stability of Monosubstituted C-Centered Radicals

Substituent effects on the stability of alkyl radicals can be classified in three categories: (A) stabilization through resonance effects; (B) stabilization through lone-pair donation; and (C) stabilization through hyperconjugative effects. The resonance-stabilized radicals in group A are among the most stable C-centered radicals, and allyl radical **14** and benzyl radical **15** can be considered to be typical examples. As shown in Figure 2, the unpaired spin is delocalized in these systems over large parts of

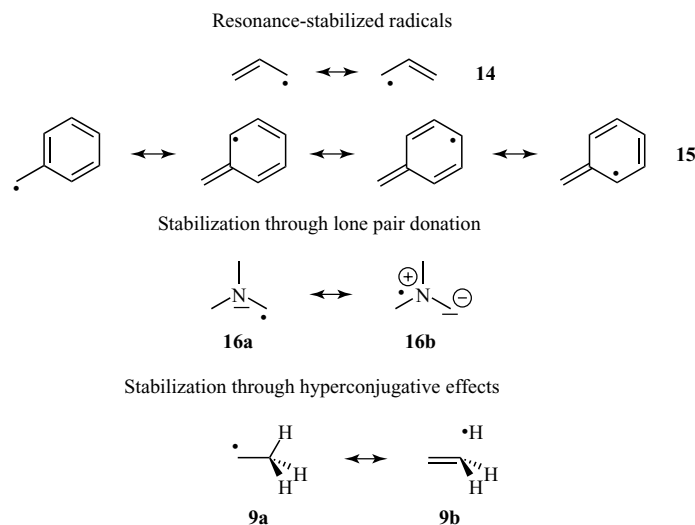


Figure 2 Radicals stabilized through resonance effects (**14**, **15**), through lone-pair donation (**16**), and through hyperconjugation (**9**).

the attached π -system, leading not only to large stabilization energies of $\text{RSE}(\mathbf{14}) = -72.0 \text{ kJ mol}^{-1}$ and $\text{RSE}(\mathbf{15}) = -61.0 \text{ kJ mol}^{-1}$ (Table 5), but also to some challenges in accurate quantum mechanical calculations (see Ref. 7 for a detailed discussion).

Experimentally measured $\text{BDE}(\text{C-H})$ values for methane (**3H**), propene (**14H**), and toluene (**15H**) imply a similarly small difference between radicals **14** and **15** with $\text{RSE}(\mathbf{14})_{\text{exp}} = -67.7 \pm 1.7 \text{ kJ mol}^{-1}$ and $\text{RSE}(\mathbf{15})_{\text{exp}} = -63.6 \pm 2.9 \text{ kJ mol}^{-1}$.⁴⁴

Table 5 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of monosubstituted radicals and C-H bond dissociation energies of the respective closed shell compounds calculated according to equation (1).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C-H) exp. ^a
$\cdot\text{CH}_2\text{CF}_3$ (28)	+8.0	+8.0(G3) +6.4(W1)	+7.1	+446.4 $\pm$ 4.5
$\cdot\text{CH}_2\text{CF}_2\text{CF}_3$	+6.2	+5.2(G3(MP2)-RAD)		
$\cdot\text{CH}_2\text{CF}_2\text{H}$	+3.1	—	−6.3	+433.0 $\pm$ 14.6
$\cdot\text{CH}_2\text{SO}_2\text{CH}_3$	+2.4	—	−25.1	+414.2
$\cdot\text{CH}_3$ (3)	0.0	0.0	0.0	+439.3 $\pm$ 0.4
$\cdot\text{CH}_2\text{CCl}_3$	−0.4	—		
$\cdot\text{CH}_2\text{CCl}_2\text{H}$	−4.6	—		
$\cdot\text{CH}_2\text{CH}_2\text{F}$ (27)	−5.8	−12.4(G3)	−5.8	+433.5 $\pm$ 8.4
$\cdot\text{Ado}$ (29)	−6.8	—		
$\cdot\text{CH}_2\text{C}(\text{CH}_3)_3$ (25)	−7.1	−6.8(G3)	−20.5	+418.8 $\pm$ 8
$\cdot\text{CH}_2\text{S}(\text{O})\text{CH}_3$	−8.4	—	−46.0	+393.3
$\cdot\text{CH}_2\text{CH}_2\text{Cl}$	−10.2	−10.8(G3)	−16.2	+423.1 $\pm$ 2.4
$\cdot\text{CH}_2\text{CH}_2\text{OH}$ (30)	−10.3	−11.6(CBS-QB3)	−15.5	+423.8
$\cdot\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	−10.4	—		
$\cdot\text{CH}_2\text{CH}(\text{CH}_3)_2$ (24)	−10.6	−10.1(G3)	−20.1	+419.2 $\pm$ 4.2
$\cdot\text{CH}_2\text{CH}_2\text{CHCH}_2$	−11.1	—	−28.4	+410.9
$\cdot\text{CH}_2\text{SiH}_3$	−11.8	—		
$\cdot\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	−12.2	−10.5(G3) −12.6(G3B3)	−18.0	+421.3
$\cdot\text{CH}_2\text{Si}(\text{CH}_3)_3$	−12.2	−12.6(G3)	−21.3	+418 $\pm$ 6.3
$\cdot\text{CH}_2\text{CH}_2\text{CH}_3$ (23)	−12.2	−11.5(G3) −11.9(G3(MP2)-RAD) −12.1(W1)	−17.1	+422.2 $\pm$ 2.1
$\cdot\text{CH}_2\text{NO}_2$ (19)	−12.4	−14.4(W1)	−23.9	+415.4
$\cdot\text{CH}_2\text{OCF}_3$	−12.7	—	−12.5	+426.8 $\pm$ 4.2
$\cdot\text{CH}_2\text{F}$ (6)	−12.8	−13.4(G3B3) −15.1(W1)	−15.5	+423.8 $\pm$ 4.2
$\cdot\text{CH}_2\text{CH}_3$ (9)	−13.5	−12.8(G3) −13.8(G3B3) −15.1(W1)	−18.8	+420.5 $\pm$ 1.3
$\cdot\text{CH}_2\text{OPO}_3\text{H}_2$		−15.1(G3B3)		
$\cdot\text{CH}_2\text{Br}$	−15.3	—	−14.2	+425.1 $\pm$ 4.2
$\cdot\text{CH}_2\text{OCHO}$	−17.2	—		
$\cdot\text{CH}_2\text{OC}(\text{O})\text{CH}_3$	−18.4	−17.9(W1)	−34.7	+404.6
$\cdot\text{CH}_2\text{Cl}$	−20.2	−20.5(G3) −22.2(W1)	−20.3	+419 $\pm$ 2.3
$\cdot\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_3)_2$	−21.0	—		
$\cdot\text{CH}_2\text{C}(\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$	−22.6	—		
$\cdot\text{CH}_2\text{COOH}$	−22.7	−25.2(W1)	−40.6	+398.7 $\pm$ 12.1
$\cdot\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$ (37)	−23.1	−23.0(G3X(MP2)-RAD)		
$\cdot\text{CH}_2\text{C}(\text{O})\text{OCH}_3$ (18)	−23.2	−25.0(W1)	−30.3	+406.3 $\pm$ 10.5
$\cdot\text{CH}_2\text{C}(\text{O})\text{NH}_2$	−23.4	−23.4(G3X(MP2)-RAD)		
$\cdot\text{CH}_2\text{CH}(\text{CH}_2)_2$ (26)	−23.4	—	−31.8	+407.5 $\pm$ 6.7
$\cdot\text{CH}_2\text{COOCH}_2\text{CH}_3$	−23.4	−23.4(G3(MP2)-RAD(+))	−37.6	+401.7
		—	−39.8	+399.5
$\cdot\text{CH}_2\text{COOC}(\text{CH}_3)_3$	−23.5	—		
$\cdot\text{CH}_2\text{PH}_2$	−23.5	−27.1(W1)		

(continued overleaf)

Table 5 (continued)

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
*CH ₂ P(CH ₃) ₂	–24.9	—		
*CH ₂ COC ₆ H ₅	–30.4	—	–34.3	+405.0
		—	–36.5	+402.8 ± 3.6
		—	–48.9	+390.4
		—	–50.2	+389.1
*CH ₂ OCH ₃ (21)	–31.5	–32.8(G3) –35.6(W1)	–37.2	+402.1
*CH ₂ OCH ₂ CH ₃	–31.6	—	–50.2	+389.1
*CH ₂ OH (5)	–32.3	–33.2(G3) –33.5(G3B3) –36.0(W1)	–37.4	+401.9 ± 0.6
*CH ₂ COCH ₃	–32.4	–33.3(G3)	–38.1	+401.2 ± 2.9
*CH ₂ CN	–32.5	–32.5(G3(MP2)-RAD(+)) –33.7(W1) –36.2(G3)	–37.6	+401.7
*CH ₂ SC(CH ₃) ₂ CN	–35.6	—		
*CH ₂ SH	–36.2	–37.7(G3) –41.5(W1)	–46.4	+392.9 ± 8.4
*CH ₂ CHO (13a)	–36.7	–36.9(G3) –38.2(W1)	–44.7	+394.6 ± 9.2
*CH ₂ SCH ₂ COOCH ₃	–37.0	—		
*CH ₂ SCH ₂ C ₆ H ₅	–38.5	—		
*CH ₂ BH ₂	–40.9	–41.7(W1)		
*CH ₂ SCH ₃ (22)	–41.0	–43.0(G3)	–47.3	+392.0 ± 5.9
*CH ₂ NHCHO	–42.5	–42.5(G3X(MP2)-RAD)		
*CH ₂ NHC(O)CH ₃ (36)	–43.0	–43.0(G3X(MP2)-RAD)		
*CH ₂ C(NCH ₃)H (17)	–43.5	—		
*CH ₂ NH ₂	–44.9	–44.9(G3X(MP2)-RAD) –46.7(G3) –50.0(W1)	–46.4	+492.9 ± 8.4
*CH ₂ N(CH ₃) ₂ (16)	–46.1	–48.0(G3) –52.2(CBS-QB3) ^{c,d}	–49.5	+389.8
*CH ₂ NHCH ₃	–46.6	–48.6(G3) –52.2(CBS-QB3) ^{c,d}	–45.2	+394.1
*CH ₂ CCH (20)	–52.8	–53.8(G3) –54.2(W1)	–67.3	+372.0 ± 4.2
*CH ₂ C ₆ H ₄ - <i>p</i> NO ₂	–61.0	—	–65.9	+383.4
*CH ₂ C ₆ H ₅ (15)	–61.0	–54.9(G3) –55.1(G3B3) –61.2(W1)	–69.0 –63.6	+370.3 ± 6.3 +375.7 ± 2.5 ^b
*CH ₂ C ₆ H ₄ - <i>p</i> CN	–62.1	—	–71.3	+368.0
*CH ₂ C ₆ H ₄ - <i>p</i> OH	–63.0	—		
*CH ₂ C ₆ H ₄ - <i>p</i> OCH ₃	–63.3	—	–76.8	+362.5
*CH ₂ C(CH ₃)CH ₂		–68.4(G3)		
*CH ₂ CHCH ₂ (14)	–72.0	–70.5(G3B3) –71.6(W1) –72.4(G3)	–70.7 –67.7	+368.6 ± 2.9 +371.5 ± 1.7 ^b
*CH ₂ CHCHCH ₃ (E)	–73.9	–73.0(G3)	–82.5	+356.8
*CH ₂ CHC(CH ₃) ₂	–77.3	—		
*CH ₂ C(CH ₃)C(CH ₃) ₂		–75.9(G3) –83.9(CBS-QB3) ^{c,d}	–86.5	+352.8
*CH ₂ CHCHCHCH ₂	–93.7	–91.3(G3) –95.1(G3)	–92.0	+347.3 ± 12.6

^a Taken from Ref. 13 if not specified otherwise.^b Taken from Ref. 44.^c Taken from Ref. 45.^d Taken from Ref. 46.

The stability of heteroallylic radicals depends systematically on the number and electronegativity of the heteroatoms in the π -system. As a consequence, the allyl radical **14** is much more stable than iminylmethyl radical $\cdot\text{CH}_2\text{C}(\text{NCH}_3)\text{H}$ (**17**) with $\text{RSE}(\mathbf{17}) = -43.5 \text{ kJ mol}^{-1}$, enoxy radical $\cdot\text{CH}_2\text{CHO}$ (**13a**) with $\text{RSE}(\mathbf{13a}) = -36.7 \text{ kJ mol}^{-1}$, methyl acetate radical $\cdot\text{CH}_2\text{C}(\text{O})\text{OCH}_3$ (**18**) with $\text{RSE}(\mathbf{18}) = -23.2 \text{ kJ mol}^{-1}$, and nitromethyl radical $\cdot\text{CH}_2\text{NO}_2$ (**19**) with $\text{RSE}(\mathbf{19}) = -12.4 \text{ kJ mol}^{-1}$. Inspection of the RSE values for monosubstituted alkyl radicals in Table 5 also shows that resonance-stabilized radicals of propargyl type such as radical $\cdot\text{CH}_2\text{CCH}$ (**20**) with $\text{RSE}(\mathbf{20}) = -52.8 \text{ kJ mol}^{-1}$ are less stable than allyl radicals with otherwise comparable substitution pattern. The dimethylaminomethyl radical **16** is a typical representative of group **B**, in which lone-pair donor atoms are directly attached to the radical center. The stabilizing effects of these types of substituents can most easily be described through admixture of Lewis structure **16b**, which derives from the canonical structure **16a** through effective one electron transfer from the heteroatom lone pair to the radical center (Figure 2). Considering the nature of this type of stabilization, it is not surprising to see again a clear effect of the electronegativity of the heteroatom on the size of the stabilization energy. Radical **16** with $\text{RSE}(\mathbf{16}) = -46.1 \text{ kJ mol}^{-1}$ is thus significantly more stable than methoxymethyl radical $\cdot\text{CH}_2\text{OCH}_3$ (**21**) with $\text{RSE}(\mathbf{21}) = -31.5 \text{ kJ mol}^{-1}$ and the fluoromethyl radical $\cdot\text{CH}_2\text{F}$ (**6**) with $\text{RSE}(\mathbf{6}) = -12.8 \text{ kJ mol}^{-1}$. Moving from first to second row elements as substituents also increases radical stability in many cases as is, for example, seen in the larger stability of radical $\cdot\text{CH}_2\text{SCH}_3$ (**22**) with $\text{RSE}(\mathbf{22}) = -41.0 \text{ kJ mol}^{-1}$ as compared to methoxymethyl radical $\cdot\text{CH}_2\text{OCH}_3$ (**21**). Ethyl radical $\cdot\text{CH}_2\text{CH}_3$ (**9**) is a representative of group **C**, in which radical stabilization occurs through interaction of the unpaired spin with adjacent C–H and C–C bonds. This is traditionally portrayed through mixing the canonical Lewis structure **9a** with the “no bond” Lewis structure **9b** (Figure 2). These effects are rather moderate and stabilize ethyl radical **9** by $\text{RSE}(\mathbf{9}) = -13.5 \text{ kJ mol}^{-1}$. Replacing the β -C–H bonds in radical **9** by C–C bonds leads to a small, but notable reduction in radical stability as is readily seen when comparing radical **9** to *n*-propyl radical $\cdot\text{CH}_2\text{CH}_2\text{CH}_3$ (**23**) with

$\text{RSE}(\mathbf{23}) = -12.2 \text{ kJ mol}^{-1}$, 2-methylprop-1-yl radical $\cdot\text{CH}_2\text{CH}(\text{CH}_3)_2$ (**24**) with $\text{RSE}(\mathbf{24}) = -10.6 \text{ kJ mol}^{-1}$ and 2,2-dimethylprop-1-yl radical $\cdot\text{CH}_2\text{C}(\text{CH}_3)_3$ (**25**) with $\text{RSE}(\mathbf{25}) = -7.1 \text{ kJ mol}^{-1}$. Strained C–C bonds as are, for example, present in cyclopropylmethyl radical $\cdot\text{CH}_2\text{CH}(\text{CH}_2)_2$ (**26**) are much stronger interaction partners in hyperconjugative interactions and thus lead to larger stabilization energies of $\text{RSE}(\mathbf{26}) = -23.4 \text{ kJ mol}^{-1}$. The introduction of electron-withdrawing substituents in β -position to the radical center is always destabilizing as is readily seen in the low stability values for 2-fluoroethyl radical (**27**) with $\text{RSE}(\mathbf{27}) = -5.8 \text{ kJ mol}^{-1}$ and 2,2,2-trifluoroethyl radical (**28**) with $\text{RSE}(\mathbf{28}) = +8.0 \text{ kJ mol}^{-1}$. This subgroup also includes C5'-desoxyadenosyl radical ($\cdot\text{Ado}$, **29**) with $\text{RSE}(\mathbf{29}) = -6.8 \text{ kJ mol}^{-1}$, whose stability parallels that of other primary alkyl radicals carrying a β -hydroxy substituent such as ethanol-2-yl radical **30** with $\text{RSE}(\mathbf{30}) = -10.3 \text{ kJ mol}^{-1}$ (Figure 3).^{6,8} This value implies that the adenosine π -system present in radical **29** has only little influence on its thermodynamic stability. Generated through either a thermal process from cofactor B_{12} or through a redox process from *S*-adenosylmethionine (SAM), radical **29** plays a central role in many enzymatic processes employing radical chemistry for substrate turnover (see **Radical Enzymes**).^{47–51}

4.2 The Stability of Di- and Trisubstituted Alkyl Radicals

In more highly substituted alkyl radicals, the interplay of substituents attached to the radical center usually leads to more strongly stabilized radicals (that is, weaker C–H bonds in the respective closed shell parent systems). The actual stability obtained in a highly substituted system is, however, rarely a simple function of the individual substituents (Tables 6 and 7).⁵² This can be exemplified with the textbook examples of methyl radical $\cdot\text{CH}_3$ (**3**), ethyl radical $\cdot\text{CH}_2\text{CH}_3$ (**9**), isopropyl radical $\cdot\text{CH}(\text{CH}_3)_2$ (**31**), and *t*-butyl radical $\cdot\text{C}(\text{CH}_3)_3$ (**4**). The stabilities of these four systems are not equally spaced in the sense that the stabilizing effect of the first methyl group equals that of the second and third addition. Instead of being additive, each further addition of a methyl group leads to a smaller

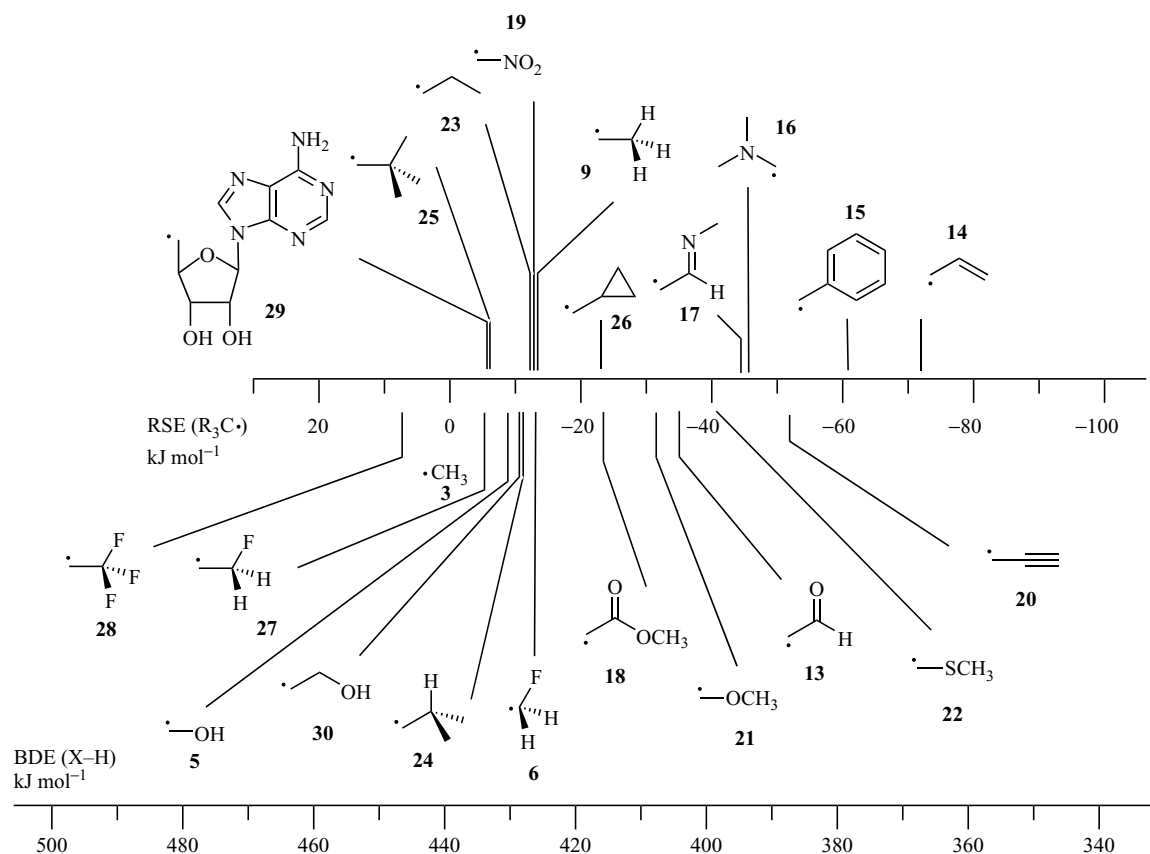


Figure 3 Graphical representation of RSE values for monosubstituted radicals together with the C–H BDE values of the corresponding closed shell parent systems.

change in radical stabilization as can easily be seen from the actual stability values of $\text{RSE}(\mathbf{9}) = -13.5 \text{ kJ mol}^{-1}$, $\text{RSE}(\mathbf{31}) = -23.0 \text{ kJ mol}^{-1}$, and $\text{RSE}(\mathbf{4}) = -28.5 \text{ kJ mol}^{-1}$. This type of saturation behavior⁵³ on repeated addition of the same substituent is also observed for more strongly interacting substituents. Addition of a second phenyl substituent to the already quite stable benzyl radical $\cdot\text{CH}_2\text{Ph}$ (**15**) with $\text{RSE}(\mathbf{15}) = -61.0 \text{ kJ mol}^{-1}$ yields benzhydryl radical $\cdot\text{CH}(\text{Ph})_2$ (**32**), whose stability value of $\text{RSE}(\mathbf{32}) = -85.5 \text{ kJ mol}^{-1}$ is far smaller than expected from a simplistic additivity assumption. The multiple addition of electronegative substituents carrying lone-pair electrons leads to yet another behavior that can be best illustrated with the three fluorinated methyl radicals $\cdot\text{CH}_2\text{F}$ (**6**), $\cdot\text{CHF}_2$ (**33**), and $\cdot\text{CF}_3$ (**34**). The stability of these systems is heavily influenced by stereoelectronic effects among the C–F bonds in both the

open shell systems and in the respective closed shell parents.⁵⁴ This is not yet apparent in fluoromethyl radical ($\cdot\text{CH}_2\text{F}$, **6**), whose RSE value of $-12.8 \text{ kJ mol}^{-1}$ can be taken to reflect mainly the effect of the fluorine substituent on the radical center and on the C–H bonds in the closed shell parent. In the radicals with more than one fluorine atom per carbon, however, the donor–acceptor interactions between lone-pair (lp) electrons on fluorine and the adjacent $\sigma^*(\text{C–F})$ bonds now alter the apparent RSE values in a significant manner. This can be exemplified by inspection of the isodesmic equation (9) used for defining the stability of $\cdot\text{CF}_3$ (**34**), whose evaluation at G3(MP2)-RAD level yields $\text{RSE}(\mathbf{34}) = +13.1 \text{ kJ mol}^{-1}$ (Table 7, Scheme 4).

Radical **34** as well as its closed shell parent **34H** are characterized by several simultaneously acting donor/acceptor interactions (Scheme 4). The size

Table 6 Radical stabilization enthalpies (RSE, in kJ mol⁻¹) at 298.15 K of disubstituted methyl radicals and C–H bond dissociation energies of the respective closed shell compounds calculated according to (1).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
•CH(CH ₂) ₂ (38)	+20.0	+13.1(G3) ^b	+5.5	+444.8 ± 1.0
•CH ₃ (3)	0.0	0.0	0.0	+439.3 ± 0.4
•CH(CH ₃)CF ₃	–7.7	—	—	—
•CHF ₂ (33)	–8.9	–10.0(G3) ^b	–7.5	+431.8 ± 4.2
•CH(CH ₃)CHF ₂	–10.3	—	—	—
•CH(CH ₃)CF ₂ CF ₃	–11.5	—	—	—
•CH(CH ₃)SO ₂ CH ₃	–14.2	—	—	—
•CH(CH ₂) ₃ (39)	—	–15.1(G3) ^b	–30.1	+409.2 ± 1.3
•CH(CH ₃)CCl ₃	–15.5	—	—	—
•CH(CH ₃)CFH ₂	–16.5	—	—	—
•CH(CH ₃)CH ₂ OH	–17.4	—	–44.7	+394.6 ± 8.4
•CH(CF ₃)Cl	—	–18.1(G3) ^b	–13.4	+425.9 ± 6.3
•CH(CH ₃)CCl ₂ H	–19.3	—	—	—
•CH(CH ₃)CH ₂ CH ₃	–19.5	–21.2(G3) ^b	–28.2	+411.1 ± 2.2
•CH(CH ₃)F	–19.7	—	–28.4	+410.9 ± 8.4
•CH(CH ₂) ₅ (41)	—	–20.0(G3) ^b	–23.0	+416.3
•CH(CH ₃)CH ₂ C ₆ H ₅	–20.1	—	—	—
•CH(CH ₃)C(CH ₃) ₃	–20.1	—	—	—
•CH(CH ₃)OCF ₃	–20.6	—	—	—
•CH(CH ₃)CH ₂ CHCH ₂	–20.9	—	—	—
•CHFCI	—	–21.0(G3) ^b	–17.6	+421.7 ± 10.0
•CH(CH ₃)CH ₂ CH(CH ₃)COOCH ₃	–22.4	—	—	—
•CH(CH ₃)Br	–22.9	—	–32.6	+406.7 ± 4.2
•CH(CH ₃) ₂ (31)	–23.0	–22.2(G3) ^b	–28.8	+410.5 ± 2.9
	—	–23.7(G3B3)	—	—
•CH(CH ₃)CH ₂ C(CH ₃) ₂ COOCH ₃	–23.0	—	—	—
•CH(CH ₃)OCHO	–23.6	—	—	—
•CH(CH ₃)OC(O)CH ₃	–24.3	–24.3(G3(MP2)-RAD(+))	—	—
•CH(CH ₃)CH(CH ₃) ₂	–24.8	—	—	—
•CH(CH ₃)CH ₂ Cl	–25.2	—	–30.0	+409.3 ± 3.9
•CH(CH ₃)CH ₂ CH(CH ₃) ₂	–25.4	—	—	—
•CH(CH ₂) ₆	—	–26.9(G3) ^b	–52.3	+387.0 ± 4.0
•CH(CH ₃)Cl	–26.7	–27.0(G3) ^b	–32.7	+406.6 ± 1.5
	—	–26.7(G3(MP2)-RAD(+))	—	—
•CH(CH ₃)SiH ₃	–28.8	—	—	—
•CH(CH ₃)Si(CH ₃) ₃	–29.1	—	—	—
•CH(CH ₃)CH(CH ₂) ₂	–29.1	—	—	—
•CH(CH ₃)PH ₂	–31.1	—	—	—
•CH(CH ₃)NO ₂	–32.3	—	–28.8	+410.5
•CH(CH ₂) ₄ (40)	—	–33.0(G3) ^b	–39.3	+400.0 ± 4.2
•CHCl ₂	–32.2	–34.2(G3) ^b	–32.2	+407.1 ± 4.2
•CH(CH ₃)OCH ₃	–36.5	—	—	—
•CH(CH ₃)OCH ₂ CH ₃	–36.5	–34.8(G3) ^b	–50.2	+389.1
•CH(CH ₃)OH	–38.3	–38.2(G3) ^b	–42.7	+396.6
	—	–42.7(CCSD(T)/CBS)	—	—
•CH(CH ₃)P(CH ₃) ₂	–37.8	—	—	—
•CH(CH ₃)CON(CH ₃) ₂	–38.6	—	—	—
•CH(COOCH ₃)CH ₂ C(CH ₃) ₂ COOCH ₃	–39.2	—	—	—
•CH(COOCH ₃)CH ₂ CH(CH ₃)COOCH ₃	–39.4	—	—	—
•CH(CH ₃)CON(CH ₂ CH ₃) ₂	–40.1	—	—	—
•CH(CH ₃)SCH ₂ COOCH ₃	–40.8	—	—	—
•CH(CH ₃)SH	–41.6	—	—	—
•CH(CH ₃)COOC(CH ₃) ₂	–41.8	—	—	—
•CH(CH ₃)COOH	–41.9	—	–40.5	+398.8
•CH(CH ₃)COOCH ₃	–41.9	—	—	—
•CH(CH ₃)COOCH ₂ CH ₃	–42.0	—	—	—

(continued overleaf)

Table 6 (continued)

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
*CH(CH ₃)SC(CH ₃) ₂ CN	–42.0	—	—	—
*CH(CH ₃)CONH ₂	–42.2	—	—	—
*CH(CH ₃)SCH ₂ C ₆ H ₅	–43.7	—	—	—
*CH(OCH ₂ CH ₂ CH ₂)	—	–44.1(G3) ^b	–54.0	+385.3 ± 6.7
*CH(CH ₃)NHCOCH ₃	–44.9	—	—	—
*CH(COOCH ₃)CH ₂ CH(CH ₃) ₂	–45.4	—	—	—
*CH(CH ₃)NHCHO	–45.5	—	—	—
*CH(CH ₃)SCH ₃	–45.6	—	—	—
*CH(CH ₃)CONHCH ₃	–45.7	—	—	—
*CH(CH ₃)SOCH ₃	–46.6	—	—	—
*CH(CH ₃)CN	–48.5	–49.0(G3) ^b –48.5(G3(MP2)-RAD(+))	–46.0	+393.3 ± 12.6
*CH(CH ₃)NH ₂	–49.9	—	–62.3	+377.0 ± 8.4
*CH(CH ₃)COC ₆ H ₅	–50.0	—	–50.6	+388.7
*CH(CH ₃)NHCH ₃	–50.2	—	—	—
*CH(CH ₃)COCH ₃	–53.9	–52.2(G3) ^b	–53.1	+386.2 ± 7.1
*CH(CH ₃)N(CH ₃) ₂	–54.6	—	—	—
*CH(CH ₃)CHO	–56.4	—	—	—
*CH(CH ₃)CCCH ₃	—	–60.7(G3) ^b	–74.0	+365.3 ± 11.3
*CH(CH ₃)CCH	–63.9	–65.1(G3) ^b –70.8(CBS-QB3) ^{c,d}	–66.3	+373.0
*CH(CH ₃)BH ₂	–65.2	—	—	—
*CH(CH ₃)C ₆ H ₅	–68.3	–68.3(G3(MP2)-RAD(+))	–82.0	+357.3 ± 6.3
*CH(CH ₃)C ₆ H ₄ – <i>p</i> OH	–69.4	—	—	—
*CH(CH ₃)C ₆ H ₄ – <i>p</i> OCH ₃	–69.9	—	—	—
*CH(CH ₃)C ₆ H ₄ – <i>p</i> CN	–71.0	—	—	—
*CH(CH ₃)C ₆ H ₄ – <i>p</i> NO ₂	–73.0	—	—	—
*CH(NHCOCH ₃)CONHCH ₃ (35)	–74.1	–75.5(G3B3)	—	—
*CH(Cl)CHCH ₂	—	–83.0(G3) ^b –88.4(CBS-QB3) ^{c,d}	–68.6	+370.7 ± 4.6
*CH(CH ₃)CHCHCH ₃ (<i>E</i>)	–83.4	—	–97.5	+341.8 ± 6.3
*CH(CHCHCH ₂ CH ₂)	—	–83.7(G3) ^b	–92.6	+346.7
*CH(CH ₃)CHCH ₂	–84.6	–81.7(G3) ^b	–88.7	+350.6
*CH(CH ₃)CHC(CH ₃) ₂	–86.5	—	–107.3	+332.0
*CH(C ₆ H ₅) ₂ (32)	–85.5	–72.4(G3B3)	–85.8	+353.5 ± 2.1
*CH(CH) ₄	–87.3	—	—	—
*CH(OH)CHCH ₂	—	–103.6(G3) ^b	–97.9	+341.4 ± 7.5
*CH(CHCHCHCHCH ₂)	—	–118.6(G3) ^b	–134.3	+305.0 ± 21.0
*CH(CHCHCH ₂ CHCH)	—	–119.5(G3) ^b	–119.6	+319.7

^a Taken from Ref. 13 if not specified otherwise.^b Taken from Ref. 23.^c Taken from Ref. 45.^d Taken from Ref. 46.

of these stereoelectronic effects can be assessed separately for the closed and the open shell systems using (10a) and (10b). Using these definitions and heats of formation for all species from experiment, we obtain an overall anomeric stabilization of CHF₃ (**34H**) of –135.7 kJ mol^{–1} and for radical *CF₃ (**34**) of –84.2 kJ mol^{–1}. These values imply that the stereoelectronic effects among the fluorine substituents in closed shell system CHF₃ (**34H**) are significantly larger than those in the corresponding

radical *CF₃ (**34**). The reaction energy for (9) initially used to define the stability of radical **34** is thus more a reflection of changes in stereoelectronic effects among the fluorine substituents than an indicator of the interaction of the unpaired spin with its direct surrounding!

One of the cases where synergistic substituent effects are observed in highly substituted alkyl radicals are donor/acceptor-substituted systems.^{53,55,56} The glycol radical **35** is often discussed as a typical

Table 7 Radical stabilization enthalpies (RSE, in kJ mol⁻¹) at 298.15 K of trisubstituted methyl radicals and C–H bond dissociation energies of the respective closed shell compounds calculated according to (1).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
•CF ₃ (34)	+13.1	+11.6(G3) ^b	+10.1	+449.4
•CF ₂ CF ₃	+1.2	–0.2(G3) ^b	–9.6	+429.7 ± 2.1
•CH ₃ (3)	0.0	0.0	0.0	+439.3 ± 0.4
•CF ₂ Cl	—	–8.9(G3) ^b	—	+421.3 ± 8.3
•C(CH ₃) ₂ OCHO	–17.2	—	—	—
•C(CH ₃) ₂ CF ₃	–17.3	—	—	—
•C(CH ₃) ₂ OC(O)CH ₃	–17.5	—	–47.0	+392.2
•C(CH ₃) ₂ CHF ₂	–17.6	—	—	—
•C(CH ₃) ₂ OCF ₃	–21.0	—	—	—
•C(CH ₃) ₂ CH ₂ OH	–23.3	—	—	—
•C(CH ₃) ₂ CH ₂ F	–23.4	—	—	—
•C(CH ₃) ₂ F	–23.6	—	—	—
•C(CH ₃) ₂ CCl ₃	–24.5	—	—	—
•C(CH ₃) ₂ CH ₂ CH ₃	–25.8	–10.0(G3) ^b	–38.5	+400.8
•C(CH ₃) ₂ CH ₂ CHCH ₂	–26.3	—	—	—
•CCl ₂ F	—	–26.7(G3) ^b	–25.5	+413.8 ± 5.0
•C(CH ₃) ₂ SO ₂ CH ₃	–27.2	—	—	—
•C(CH ₃) ₂ CF ₂ CF ₃	–27.8	—	—	—
•C(CH ₃) ₂ CH ₂ C ₆ H ₅	–27.9	—	—	—
•C(CH ₃) ₂ Br	–27.9	—	—	—
•C(CH ₃) ₂ C(CH ₃) ₃	–28.4	—	—	—
•C(CH ₃) ₃ (4)	–28.5	–29.8(G3B3)	–38.9	+400.4 ± 2.9
•C(CH ₃) ₂ CH(CH ₃) ₂	–29.0	—	–40.1	+399.2 ± 13.0
•C(CH ₃) ₂ CHCl ₂	–30.2	—	—	—
•C(CH ₃) ₂ Cl	–30.6	—	—	—
•C(CH ₃) ₂ CH(CH ₂) ₂	–31.6	—	—	—
•C(CH ₃) ₂ NHC(O)CH ₃	–35.4	—	–49.8	+389.5
•C(CH ₃) ₂ CClH ₂	–35.5	—	—	—
•C(CH ₃) ₂ OCH ₃	–36.3	—	—	—
•C(CH ₃) ₂ OCH ₂ CH ₃	–36.5	—	—	—
•C(CH ₃)Cl ₂	—	–36.9(G3) ^b	–48.7	+390.6 ± 1.5
•C(CH ₃) ₂ NHCHO	–37.8	—	—	—
•C(CH ₃) ₂ P(CH ₃) ₂	–38.6	—	—	—
•C(CH ₃) ₂ C(O)N(CH ₂ CH ₃) ₂	–39.3	—	—	—
•C(CH ₃) ₂ PH ₂	–40.0	—	—	—
•C(CH ₃) ₂ SCH ₂ C ₆ H ₅	–40.0	—	—	—
•C(CH ₃) ₂ OH	–41.1	–40.8(G3) ^b	–42.8	+396.5
•C(CH ₃) ₂ SiH ₃	–41.7	—	—	—
•C(CH ₃) ₂ Si(CH ₃) ₃	–42.0	—	—	—
•C(CH ₃) ₂ NO ₂	–42.2	—	–44.4	+394.9
•CCl ₂ CHCl ₂	—	–42.3(G3) ^b	–46.3	+393.0 ± 8
•CCl ₃	–42.5	—	–46.8	+392.5 ± 2.5
•C(CH ₃) ₂ SC(CH ₃) ₂ CN	–43.3	—	—	—
•C(CH ₃) ₂ SH	–44.3	—	—	—
•C(CH ₃) ₂ C(O)N(CH ₃) ₂	–44.6	—	—	—
•C(CH ₃) ₂ SCH ₃	–45.6	—	—	—
•C(CONHCH ₃)	–46.3	–47.8(IMOMO)	—	—
–(N(COCH ₃)(CH ₂) ₃)	—	—	—	—
•C(CH ₃) ₂ SCH ₂ COOCH ₃	–46.9	—	—	—
•C(CH ₃) ₂ C(O)NHCH ₃	–49.6	—	—	—
•C(CH ₃) ₂ N(CH ₃) ₂	–49.6	—	—	—
•C(CH ₃) ₂ CONH ₂	–50.8	—	—	—
•C(CH ₃) ₂ NHCH ₃	–50.9	—	—	—
•C(CH ₃) ₂ NH ₂	–51.5	—	–67.3	+372.0 ± 8.4
•C(CH ₃)(COOCH ₃)	–52.3	—	—	—
–CH ₂ C(CH ₃) ₂ COOCH ₃	—	—	—	—

(continued overleaf)

Table 7 (continued)

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
*C(CH ₃) ₂ COOC(CH ₃) ₃	–53.9	—	—	—
*C(CH ₃) ₂ SOCH ₃	–54.0	—	—	—
*C(CH ₃) ₂ COOCH ₃	–54.6	—	—	—
*C(CH ₃) ₂ COOCH ₂ CH ₃	–54.7	—	–51.9	+387.4
*C(CH ₃) ₂ (COOCH ₃)	–55.2	—	—	—
–CH ₂ CH(CH ₃)COOCH ₃	—	—	—	—
*C(CH ₃) ₂ COOH	–55.7	—	–50.3	+389.0
*C(CH ₃) ₂ (COOCH ₃)	–57.4	—	—	—
–CH ₂ CH(CH ₃) ₂	—	—	—	—
*C(CH ₃) ₂ CN	–58.3	–60.3(G3) ^b –58.3(G3(MP2)-RAD(+))	–54.8	+384.5
*C(CH ₃) ₂ COC ₆ H ₅	–58.8	—	–63.2	+376.1
*C(CH ₃) ₂ COCH ₃	–64.4	—	—	—
*C(NHCOCH ₃)	–64.8	–66.3(IMOMO)	—	—
–(CONHCH ₃)(CH ₂ SH)	—	—	—	—
*C(NHCOCH ₃)	–65.5	–67.0(IMOMO)	—	—
–(CONHCH ₃)(CH ₃)	—	—	—	—
*C(NHCOCH ₃)	–69.1	–70.6(IMOMO)	—	—
–(CONHCH ₃)(CH ₂ C ₆ H ₅)	—	—	—	—
*C(NHCOCH ₃)	–69.4	–70.9(IMOMO)	—	—
–(CONHCH ₃)(CH ₂ C ₆ H ₄ - <i>p</i> OH)	—	—	—	—
*C(CH ₃) ₂ C ₆ H ₅	–69.7	—	—	—
*C(CH ₃) ₂ C ₆ H ₄ - <i>p</i> OH	–70.1	—	—	—
*C(CH ₃) ₂ C ₆ H ₄ - <i>p</i> OCH ₃	–70.8	—	—	—
*C(CH ₃) ₂ CCCH ₃	—	–71.3(G3) ^b	–95.0	+344.3 ± 11.3
*C(CH ₃) ₂ CCH	–72.0	–71.9(G3) ^b –80.5(CBS-QB3) ^{c,d}	–94.1	+345 ± 8.4
*C(CH ₃) ₂ C ₆ H ₄ - <i>p</i> NO ₂	–73.2	—	—	—
*C(CH ₃) ₂ C ₆ H ₄ - <i>p</i> CN	–73.6	—	—	—
*C(CH ₃) ₂ C ₆ H ₄ - <i>p</i> CHO	–73.7	—	—	—
*C(CH ₃) ₂ CHC(CH ₃) ₂	–77.8	—	—	—
*C(CH ₃) ₂ C(CH ₃)CH ₂	—	–80.0(G3) ^b –87.3(CBS-QB3) ^{c,d}	–88.2	+351.1
*C(CH ₃) ₂ CHCHCH ₃	–87.2	—	—	—
*C(CH ₃) ₂ CHCH ₂	–88.7	–89.0(G3) ^b –95.4(CBS-QB3) ^{c,d}	–106.7	+332.6 ± 7.1
*C(CH ₃) ₂ BH ₂	–91.0	—	—	—

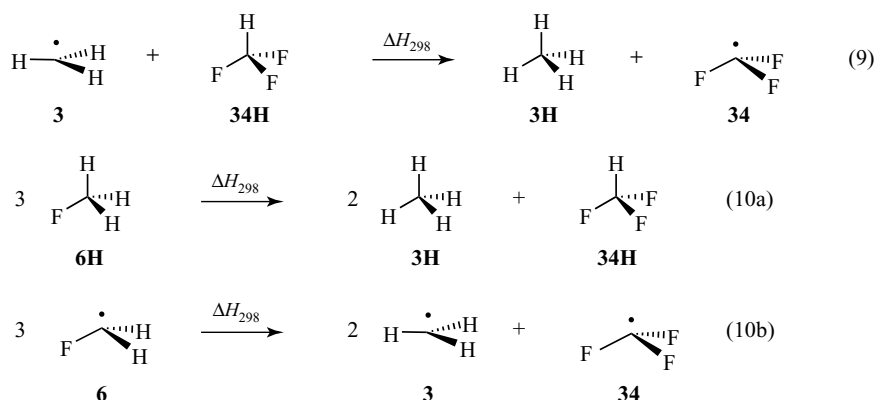
^aTaken from Ref. 13 if not specified otherwise.^bTaken from Ref. 23.^cTaken from Ref. 45.^dTaken from Ref. 46.

and is also important example owing to its high stability^{57–61} and its involvement in enzymatic catalysis (Figure 4).^{6,8,47–50}

The radical center is here flanked on one side by a carbonylamino substituent and on the other side by a aminocarbonyl substituent. The individual effects of these substituents can be quantified by donor-substituted radical **36** with RSE(**36**) = –43.0 kJ mol^{–1} and acceptor-substituted radical **37** with RSE(**37**) = –23.1 kJ mol^{–1}. If these effects were additive, we may expect radical **35** to be quite

stable with a stabilization energy of –66.1 kJ/mol relative to methyl radical **3**. The stabilization energy actually calculated for radical **35** at G3(MP2)-RAD level is RSE(**35**) = –74.1 kJ mol^{–1}, 8 kJ mol^{–1} more than the sum of the individual effects. This increase is commonly rationalized by donor/acceptor (or “captodative”) interactions between the two substituents as expressed by Lewis structure **35b**.

In how far the electronic substituent effects discussed for singly substituted alkyl radicals can act on the radical center is also determined by



Scheme 4 Isodesmic equations to define the stability of radical **34** and the size of stereoelectronic effects in trifluoromethane **34H** and radical **34**.

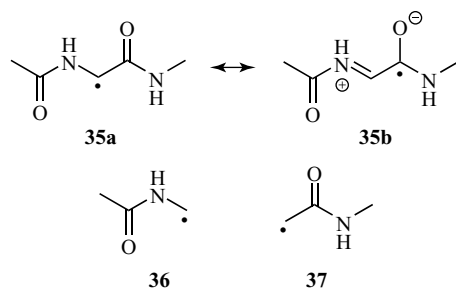


Figure 4 Donor/acceptor-substituted glycol radical **35**, the donor-substituted radical **36**, and the acceptor-substituted radical **37**.

steric effects or other geometrical constraints. This is particularly relevant for radicals in small ring systems, where the orientations of substituents are strictly controlled by ring geometry. In addition, the size of RSE values of cyclic radicals may also reflect changes in ring strain energies between the radical and its closed shell parent. The stability of cycloalkyl radicals of various ring sizes as calculated at G3 level are collected in Figure 5 together with the RSE value for the isopropyl radical (**31**) as the acyclic reference system.

The very low stability of cyclopropyl radical **38** with $\text{RSE}(\mathbf{38}) = +13.1 \text{ kJ mol}^{-1}$ is mainly a reflection of differences in ring strain between cyclopropane (**38H**) and radical **38** and implies, that the C–H bonds in cyclopropane (**38H**) are stronger than in methane (**3H**). These effects are diminished, but still present in cyclobutyl radical (**39**) with $\text{RSE}(\mathbf{39}) = -15.1 \text{ kJ mol}^{-1}$. The

38	39	40	41	31
RSE(G3)	+13.1	-15.1	-33.0	-20.0
(kJ mol ⁻¹)				-22.2

Figure 5 Radical stabilization energies for cycloalkyl radicals and the isopropyl radical (**31**) as obtained at G3 level.²³

stability of cyclopentyl radical **40** at $\text{RSE}(\mathbf{40}) = -33.0 \text{ kJ mol}^{-1}$ is actually larger than that of the acyclic isopropyl radical **31**, whose stability at G3 level amounts to $\text{RSE}(\mathbf{31}) = -22.2 \text{ kJ mol}^{-1}$, while the stability of cyclohexyl radical **41** is almost identical to this acyclic reference system at $\text{RSE}(\mathbf{41}) = -20.0 \text{ kJ mol}^{-1}$ (Figure 6).

4.3 The Stability of Other C-Centered Radicals

A larger number of C-centered radicals exist in which the formal radical center is bound to only two neighbors. This is the case for all radicals, which are at least formally generated through hydrogen atom abstraction from C(sp²) hybridized carbon atoms and the term *σ-type radicals* is frequently used to reflect this point. The stability of these systems can be defined as before relative to the methyl radical/methane reference pair using hydrogen transfer reaction (11) (Scheme 5, Table 8).

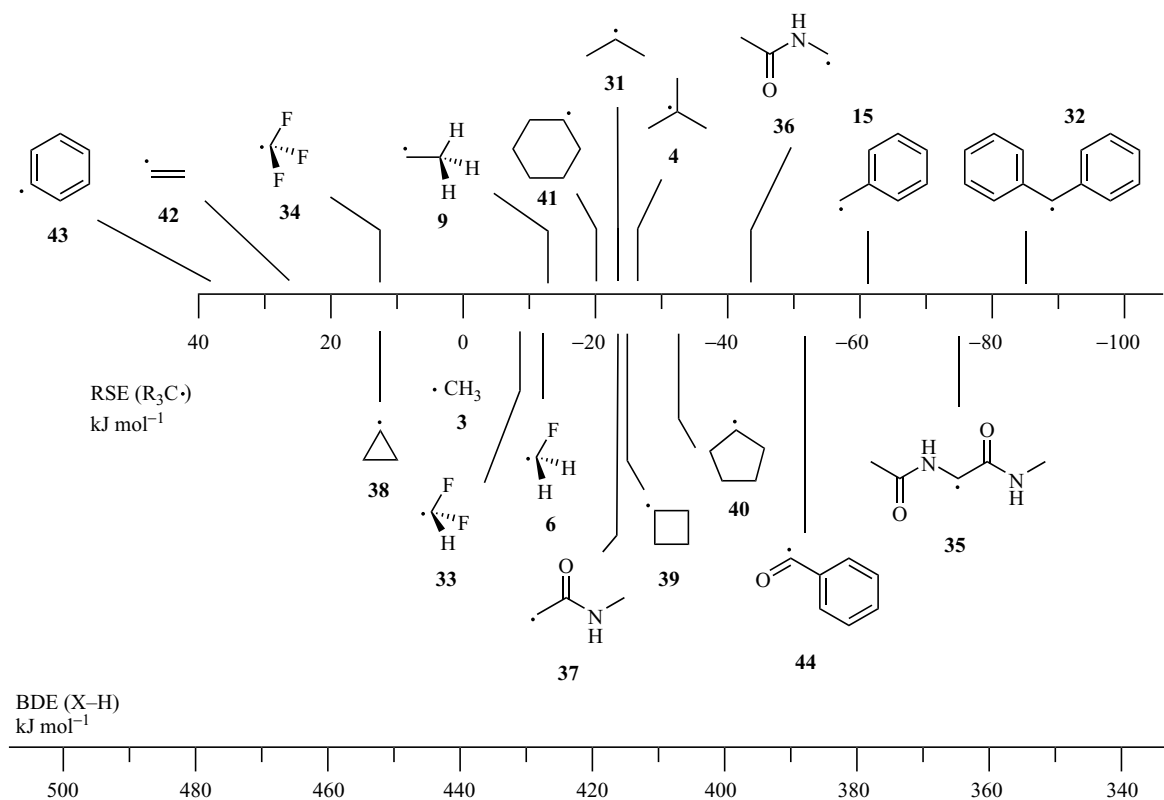
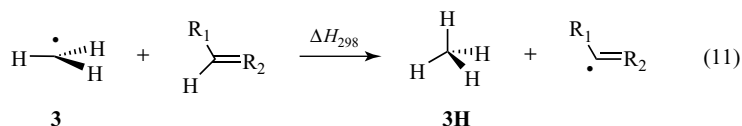


Figure 6 Graphical representation of RSE values for di- and trisubstituted alkyl radicals together with the C–H BDE values of the corresponding closed shell parent systems.



Scheme 5 Hydrogen transfer reaction used to define the stability of σ -type C-radicals.

Even though (11) is not an isodesmic reaction anymore, it allows for the direct comparison with all other C-centered radicals. Vinyl radical (**42**) and phenyl radical (**43**) are two of the best-known systems from this class. Using the definition in (11) both system are highly destabilized relative to methyl radical **3** with $\text{RSE}(\mathbf{42}) = +26.0 \text{ kJ mol}^{-1}$ and $\text{RSE}(\mathbf{43}) = +37.0 \text{ kJ mol}^{-1}$, thus reflecting the much larger C–H BDEs in ethylene and benzene as compared to methane. Large stabilizing effects are observed in this class of radicals when the doubly bonded substituents R^2 are heteroatoms carrying lone-pair electrons. As a consequence the C–H bond

energies in formic acid derivatives and aldehydes are significantly smaller than those in methane. An example in case is radical **44** derived from benzaldehyde with $\text{RSE}(\mathbf{44}) = -52.4 \text{ kJ mol}^{-1}$ (Figure 7).

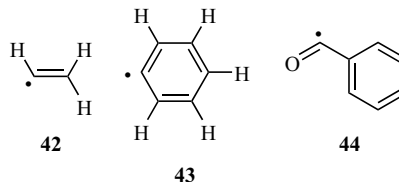


Figure 7 Structures of σ -type radicals **42–44**.

Table 8 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of σ -type C-centered radicals and C–H bond dissociation energies of the respective closed shell compounds calculated according to (1).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(C–H) exp. ^a
•CCH	+117.6	+122.6(G3) ^b	+117.3	+556.6 ± 2.9
•CN	+93.8	+100.9(G3) ^b	+88.3	+527.6 ± 1.7
•CFCF ₂	—	+58.4(G3) ^b	—	—
		+53.1(CBS-QB3) ^{c,d}		
•CFCFCI	—	+52.0(G3) ^b	—	—
•CFCFH	—	+47.4(G3) ^b	—	—
•C ₆ H ₄ - <i>p</i> OH	+41.9	—	—	—
•C ₆ H ₄ - <i>p</i> OCH ₃	+41.6	—	—	—
•C ₆ H ₄ - <i>p</i> NO ₂	+40.4	—	—	—
•C ₆ H ₄ - <i>p</i> CN	+39.4	—	—	—
•C ₆ H ₅ (43)	+37.0	+48.4(G3) ^b	+32.9	+472.2 ± 2.2
•CCICFCI	—	+38.3(G3) ^b	—	—
•CHC(CH ₃) ₂	+34.3	—	—	—
•CHCCH ₃ (<i>E</i>)	+32.0	—	+25.5	+468.8
•CCICHCI	—	+29.5(G3) ^b	—	—
•CHCH ₂ (42)	+26.0	+25.3(G3) ^b	+26.0	+465.3 ± 3.3
•CHCO	—	+12.8(G3) ^b	—	—
•CH ₃ (3)	0.0	0.0	0.0	+439.3 ± 0.4
•COOH	−14.2	—	−35.1	+404.2
•COOCH ₃	−16.2	−18.0(G3) ^b	−40.1	+399.2 ± 8.4
		−21.4(CBS-QB3) ^{c,d}		
•COOCH ₂ CH ₃	−18.1	—	—	—
•COOC(CH ₃) ₃	−24.6	—	—	—
•C(O)N(CH ₃) ₂	−37.8	—	—	—
•C(O)NHCH ₃	−38.1	—	—	—
•C(O)N(CH ₂ CH ₃) ₂	−38.6	—	—	—
•C(O)NH ₂	−39.6	—	—	—
•C(O)CF ₃	—	−46.9(G3) ^b	—	—
•C(O)C ₆ H ₅ (44)	−52.4	—	−68.2	+371.1 ± 10.9
•C(O)CHCH ₂	—	−54.5(G3) ^b	—	—
•C(O)CH ₃	−59.8	−62.0(G3) ^b	−65.3	+374.0 ± 1.3
•C(O)CH ₂ CH ₃	—	−61.1(G3) ^b	—	—
•C(O)H	−64.6	−66.3(G3) ^b	−70.9	+368.4 ± 0.7

^aTaken from Ref. 13 if not specified otherwise.^bTaken from Ref. 23.^cTaken from Ref. 45.^dTaken from Ref. 46.

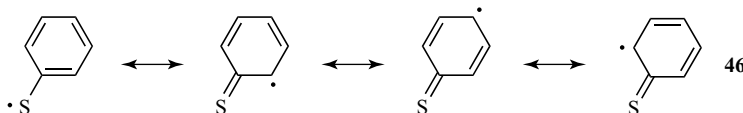
5 THE STABILITY OF SULFUR-CENTERED RADICALS

Aliphatic and aromatic thiols are effective hydrogen atom donors owing to the comparatively weak S–H bond in these compounds. This is evident already for the smallest thiol H₂S (**7H**) with BDE(S–H) = +381.2 kJ mol^{-1} , 58.1 kJ mol^{-1} less than the C–H BDE value in methane (Table 9).¹³ The introduction of alkyl or aryl substituents leads to a further reduction of the S–H BDE as is readily seen in the stability values of the resulting thiyl radicals (Table 9). Alkyl substituents influence the stability of thiyl radicals in a similar way as is observed for alkyl

radicals. A point in case is methylthiyl radical **10** with RSE(**10**) = −18.1 kJ mol^{-1} , which represents a slightly larger effect than is observed for ethyl radical **9** with RSE(**9**) = −13.5 kJ mol^{-1} . An interesting system from this group is cysteinyl radical **45** with RSE(**45**) = −13.7 kJ mol^{-1} obtained through hydrogen abstraction from the thiol side chain of cysteine diamide **45H** (see structure in Figure 12).⁸ Cysteine radicals play a central role in many radical enzymes, where they are directly involved in substrate turnover. A recent comparison of radicals involved in enzymatic catalysis has shown that the stability of these radicals hardly differ from those of simple alkyl thiyl radicals such as **10**.⁸ A more

Table 9 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of sulfur-centered radicals and S–H bond dissociation energies of the respective closed shell compounds calculated according to (4).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(S–H) exp. ^a
*SH (7)	0.0	0.0	0.0	+381.2 $\pm$ 0.1 +376.2 $\pm$ 0.1 (0 K) ^c +362.3 $\pm$ 9.2
*SC(CH ₃) ₃	–12.1	–12.3(G3B3) ^b –15.1(CBS-QB3) ^e	–18.9	
*SCH ₂ CH ₃ (72)	–16.9	–21.9(CBS-QB3) ^e	–15.9	+365.3
*SCH ₃ (10)	–18.1	–18.2(G3B3) ^b –19.9(CBS-QB3) ^e	–15.5	+365.7 $\pm$ 2.1
*S-Cys (45)	–13.7	–14.4(G3B3) ^b	—	—
*SC ₆ H ₅ - <i>p</i> NO ₂ (47)	–35.1	—	–39.8	+341.4
*SC ₆ H ₅ (46)	–43.6	–38.2(G3B3) ^b –45.0(CBS-QB3) ^e	–31.8 –40.9 (0 K) ^{b,d} –40.8(298 K) ^b	+349.4 $\pm$ 4.5 +335.3 $\pm$ 1.2 (0 K) ^{b,d}
*SC ₆ H ₅ - <i>p</i> NH ₂ (48)	–57.6	—	–88.3	+292.9
*SSCH ₃	—	–87.9(CBS-QB3) ^e	–50.7	+330.5 $\pm$ 14.6

^a Taken from Ref. 13 if not specified otherwise.^b Taken from Ref. 8.^c Taken from Ref. 62.^d Taken from Ref. 63.^e Taken from Ref. 64.**Figure 8** Resonance stabilization of phenylthiyl radical (46).

strongly stabilized thiyl radical is obtained in the presence of aromatic substituents as in thiophenyl radical **46** with $\text{RSE}(\mathbf{46}) = -43.6 \text{ kJ mol}^{-1}$ because of extensive delocalization of the unpaired spin (Figure 8).

In contrast to benzyl radical **15**, however, the stability of phenylthiyl radical (**46**) is significantly influenced by the presence of substituents in *para* position of the aromatic ring system. While the presence of acceptor substituents as in nitro-substituted radical **47** leads to lower RSE values ($\text{RSE}(\mathbf{47}) = -35.1 \text{ kJ mol}^{-1}$), a significant enhancement of stability is achieved through donor-substituents as in amino-substituted radical **48** ($\text{RSE}(\mathbf{48}) = -57.6 \text{ kJ mol}^{-1}$). The oxidation of thiols to sulfenic acids (RS(O)H) and sulfinic acids ($\text{RS(O)}_2\text{H}$) leads to a strong reduction in S–H bond strength, making both compound classes interesting as antioxidants.^{65–67} These compounds can exist in O- and S-tautomeric forms, the former of which is significantly more stable (Figure 9). The corresponding BDE values are therefore discussed in the following section on O-centered radicals.

6 THE STABILITY OF OXYGEN-CENTERED RADICALS

The stability of oxygen-centered radicals depends much more strongly on the substitution pattern than is the case for carbon- or sulfur-centered radicals of otherwise comparable structure. The reference point for the definition of radical stability in (5) is in this case given by H_2O with its rather strong O–H bond ($\text{BDE}(\text{O–H}) = +497.1 \text{ kJ mol}^{-1}$, Table 10). Since the performance of the G3(MP2)-RAD method for O-centered radicals is less satisfactory than for other radical classes, the following discussion is based on results obtained at the (higher) G3B3 level. The $\cdot\text{OH}$ radical can be stabilized quite effectively through alkyl groups as is apparent from the stability value for methoxy radical $\cdot\text{OCH}_3$ (**12**) with $\text{RSE}(\mathbf{12}) = -55.7 \text{ kJ mol}^{-1}$. Even more stable radicals are obtained in the presence of aromatic substituents and the value of the *para*-methylphenoxy radical with $\text{RSE}(\mathbf{49}) = -129.4 \text{ kJ mol}^{-1}$ may be typical here. These very high stability values imply rather low O–H BDE values in the respective

Table 10 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of oxygen-centered radicals and O–H bond dissociation energies of the respective closed shell compounds calculated according to (5).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(O–H) exp. ^a
$\cdot\text{OCF}_3$	+4.4	+4.9(G3B3)	—	—
$\cdot\text{OH}$ (1)	0.0	0.0	0.0	+497.1 $\pm$ 0.3
$\cdot\text{OC}(\text{CH}_3)_3$	– 47.5	– 47.7(G3B3)	– 52.2	+444.9 $\pm$ 2.8
$\cdot\text{OCH}_2\text{CH}_3$	– 54.5	– 54.8(G3B3)	– 56.1	+441.0 $\pm$ 5.9
$\cdot\text{OCH}_3$ (12)	– 55.4	– 55.7(G3B3) – 57.7(CBS-QB3) ^{b,c}	– 56.9	+440.2 $\pm$ 3.0
$\cdot\text{O}(\text{H})\text{Bme}_3$	– 97.3 ^d	—	—	—
$\cdot\text{OC}_6\text{H}_5$ - <i>p</i> -NO ₂	– 121.5	– 105.5(G3B3) ^e	—	—
$\cdot\text{OOH}$	– 130.4	– 129.6(G3B3) – 130.9(CBS-QB3) ^c	– 131.0	+366.1 $\pm$ 0.3
$\cdot\text{OOCH}_3$	—	– 138.1(CBS-QB3) ^{f,c}	– 126.8	+370.3 $\pm$ 2.1
$\cdot\text{OCHCH}_2$ (13b)	– 135.3	—	—	—
$\cdot\text{OOC}(\text{CH}_3)_3$	—	– 143.8(CBS-QB3) ^{c,g}	– 144.8	+352.3 $\pm$ 8.8
$\cdot\text{OC}_6\text{H}_5$ - <i>p</i> -CH ₃ (49)	– 148.9	– 129.4(G3B3) – 140.7 ^{h,i}	– 136.9	+360.2 $\pm$ 2.1
$\cdot\text{O-Tyr}$ (71)	– 151.0	– 131.5(IMOMO) ^h	—	—
$\cdot\text{OC}_6\text{H}_5$ - <i>p</i> -NH ₂	– 154.7	– 152.8(G3B3) ^e	—	—
$\cdot\text{OC}_6\text{H}_5$	– 155.7	– 121.6(G3B3) – 133.9(CBS-QB3) ^{b,c}	– 134.4 ^b – 132.3 ^{h,j}	+362.8 $\pm$ 2.9 ^b
$\cdot\text{OS}(\text{O})\text{CH}_3$ (51)	– 156.9	– 162.2(G3B3)	—	—
$\cdot\text{ONH}_2$ (50)	– 165.7	– 164.6(G3B3) – 173.6(CBS-QB3) ^c	– 175 – 183	+314–322
$\cdot\text{OSH}$	—	– 192.4(CBS-QB3) ^{f,c}	—	—
$\cdot\text{TEMPO}$ (2)	—	—	– 205.9 ^k	+291.2 ^k
$\cdot\text{OSCH}_3$ (52)	– 216.5	– 205.3(G3B3) – 212.1(CBS-QB3) ^{f,c}	—	—

^a Taken from Ref. 13 if not specified otherwise.^b Taken from Ref. 70.^c Taken from Ref. 45.^d Taken from Ref. 68.^e Using 6D/10F polarization functions in UMP4(FC)/6-31G(2df,p) and UMP2(FULL)/G3Large.^f Taken from Ref. 67.^g Taken from Ref. 64.^h Taken from Ref. 8.ⁱ Taken from Ref. 69.^j Taken from Ref. 71.^k Taken from Ref. 72.

closed shell phenols, many of which are known to have antioxidative properties. Previous studies on borane/water and borane/alcohol complexes also indicate that O–H bond energies are substantially lower in these complexes as compared to the free protic compounds.⁶⁸ Nitroxide radicals derived through hydrogen abstraction from hydroxylamines represent another class of very stable O-centered radicals. Even the smallest of these systems $\cdot\text{ONH}_2$ (**50**) is strongly stabilized with $\text{RSE}(\text{50}) = -164.6 \text{ kJ mol}^{-1}$. The “persistent” TEMPO radical **2** thus derives its lack of reactivity from both a high thermodynamic stability as well as substantial steric hindrance. The

previously discussed oxidation products of thiols such as methylsulfenic acid **52H** and methylsulfinic acid **51H** are known to exhibit S/O-tautomerism (Figure 9). Both theoretical and experimental studies on these compounds have shown that the respective O-tautomers (**51bH** and **52bH**) predominate over the S-tautomers (**51aH** and **52aH**). Using enthalpies obtained at G3B3 level indicates that tautomer **52aH** is 51.0 kJ mol^{-1} less stable than tautomer **52bH**.

Hydrogen atom abstraction from either of these tautomeric forms yields the same open shell species **51** and **52**, in which the unpaired spin is delocalized over the S and O atoms. The stabilities

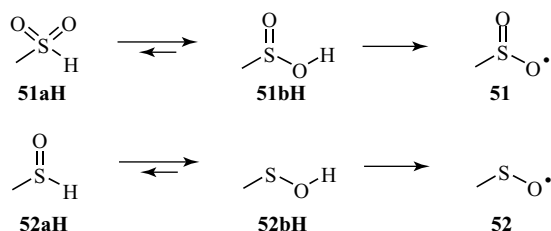


Figure 9 Tautomeric forms of methylsulfinic acid (**51H**) and methylsulfenic acid (**52H**) together with the corresponding sulfinyl radical **51** and sulfenyl radical **52** formed after hydrogen abstraction.

of the radicals relative to the O-protonated tautomeric forms ($\text{RSE}(\mathbf{51}) = -162.2 \text{ kJ mol}^{-1}$ and $\text{RSE}(\mathbf{52}) = -205.3 \text{ kJ mol}^{-1}$) are indicative of the highly stabilized nature of these radicals and the correspondingly weak O–H bonds in the precursor sulfenic and sulfinic acids.

7 THE STABILITY OF NITROGEN-CENTERED RADICALS

The homolytic N–H BDE in NH_3 (**8H**) of $+450.1 \pm 0.24 \text{ kJ mol}^{-1}$ (Table 11) indicates a slightly stronger bond than the C–H bond in methane. Despite this similarity, the substituent

effects observed for N-centered radicals can be distinctly different as compared to those seen for C-centered radicals. Alkyl substitution is strongly stabilizing as in primary aminyl radical **11** with $\text{RSE}(\mathbf{11}) = -30.0 \text{ kJ mol}^{-1}$. The addition of a second alkyl group as in secondary aminyl radical **53** is slightly less effective with $\text{RSE}(\mathbf{53}) = -52.6 \text{ kJ mol}^{-1}$, showing the saturation behavior already noted for C-centered radicals. Single and double phenyl substituents as in *N*-phenylaminyl radical **54** and *N,N*-diphenylaminyl radical **55** also show slightly larger stabilities than is seen in the analogous C-centered radicals. Surprisingly, acceptor substituents such as carbonyl groups have a clearly destabilizing effect on aminyl radicals, leading to rather strong N–H bonds in amide groups. A comparison of stability values for aminyl radicals with different acceptor substituents such as formyl-substituted radical **56** with $\text{RSE}(\mathbf{56}) = +28.8 \text{ kJ mol}^{-1}$, acetyl-substituted radical **57** with $\text{RSE}(\mathbf{57}) = +22.1 \text{ kJ mol}^{-1}$, or urea-derived radical **58** with $\text{RSE}(\mathbf{58}) = +5.2 \text{ kJ mol}^{-1}$ also indicates a stronger destabilization for systems carrying more strongly electron-withdrawing substituents. Analysis of the wavefunction of these systems reveals the existence of two close lying electronic states, an energetically preferred state of *A''* symmetry

Table 11 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of nitrogen-centered radicals and N–H bond dissociation energies of the respective closed shell compounds calculated according to (6).

System	G3(MP2)-RAD	Other	RSE exp. ^a	BDE(N–H) exp. ^a
*NHCHO (56)	+28.8	—	+3.9	+454.0
*NHCOCH ₃ (57)	+22.1	—	−0.3	+449.8
*NH(CO)CH ₂ NH ₂	+29.6	—	—	—
*N(CH ₂ CONH ₂)COCH ₃	+14.9	—	—	—
*N(CH ₂ CHO)CHO	+14.3	—	—	—
*NHCF ₃	+11.4	—	—	—
*N(CH ₃)CHO	+8.7	—	—	—
*N(CH ₂ CHO)COCH ₃	+10.3	—	—	—
*NH(CO)NH ₂ (58)	+5.2	—	—	—
*N(CH ₃)COCH ₃	+2.0	—	−4.5	+445.6
*NH ₂ (8)	0.0	0.0	0.0	+450.1 ± 0.24 ^[b]
*NHCH ₂ CHO	−24.5	—	—	—
*NHCH ₂ CONH ₂	−29.3	—	—	—
*NHCH ₃ (11)	−30.0	−30.4(G3B3)	−25.0	+425.1 ± 8.4
*N(CH ₃) ₂ (53)	−52.6	−53.2(G3B3)	−54.3	+395.8 ± 8.4
*NHC ₆ H ₅ (54)	−65.7	—	−64.3	+385.8
*N(C ₆ H ₅) ₂ (55)	−89.7	—	—	—

^aTaken from Ref. 13 if not specified otherwise.

^bTaken from Ref. 76.

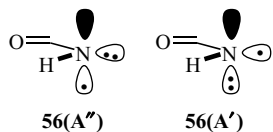


Figure 10 Different electronic states for aminyl radical **56**.

and a higher lying state of A' symmetry (assuming a C_s symmetric structure for both states).^{59, 73–75}

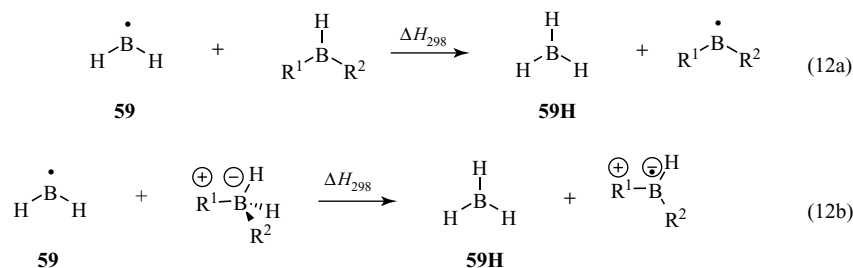
The orbital occupations in these two states can approximately be described with the cartoons shown in Figure 10. In the energetically less favorable A' state, the nitrogen lone-pair electrons are localized in a p-type atomic orbital optimally aligned for resonance delocalization into the adjacent C–O double bond. At the same time, this leaves the unpaired electron in an orbital oriented orthogonally to the C–O π -systems and thus unable to attain the stabilization available in other heteroallylic radicals. In the energetically more favorable A'' state, the orbital occupations at nitrogen are interchanged, now allowing for resonance delocalization of the unpaired electron into the C–O π -systems. This now leaves the nitrogen lone-pair electrons in the orbital oriented orthogonally to the C–O π -systems and thus unable to attain the stabilization available in the parent amide systems. It is this loss of resonance delocalization of the nitrogen lone-pair electrons that ultimately leads to the low stability of radical **56**.

8 THE STABILITY OF BORON-CENTERED RADICALS

The stability of boron-centered radicals is a key factor in rationalizing the properties of boranes as

hydrogen atom donors^{38, 77–80} and as reagents in transition-metal-mediated reactions.^{81, 82} In analogy to other open shell systems discussed before a quantitative definition of the stability of boryl radicals can be given using isodesmic equation (12a). For boranes complexed to Lewis bases this takes on the form of (12b) (Scheme 6).

However, in remarkable contrast to the systems discussed before, the B–H BDE in the reference borane BH_3 (**59H**) seems not to be well established. The single experimental study on the heat of formation of BH_2 radical **59** implies a BDE(B–H) value of $+312 \text{ kJ mol}^{-1}$, more than 100 kJ mol^{-1} less than found by most theoretical studies.^{13, 38, 81–83} Benchmark-quality calculations at W4.3 level put the B–H bond energy in BH_3 at $+441.14 \text{ kJ mol}^{-1}$, a value in close proximity to the C–H bond energy in methane (CH_4). This value is, in the following, used to quantify radical stability according to (12a, 12b). While the effect of alkyl substituents attached to the boron atom on the B–H bond energies is quite moderate, the complexation of boranes to Lewis bases leads to large changes in B–H bond energies. Even weakly coordinating Lewis bases such as amines and phosphanes lead to a significant stabilization of boryl radicals as can be seen from the stability values for borane complexes $H_2B^*NH_3$ (**60**) and $H_2B^*PH_3$ (**61**) with $RSE(\mathbf{60}) = -13.7 \text{ kJ mol}^{-1}$ and $RSE(\mathbf{61}) = -54.3 \text{ kJ mol}^{-1}$, respectively (Table 12). Significantly lower BDE(B–H) values and thus more stable boryl radicals are obtained through complexation with Lewis bases including a π -system. This is readily seen for boryl radicals **62** and **63** with stability values of $RSE(\mathbf{62}) = -112.5 \text{ kJ mol}^{-1}$ and $RSE(\mathbf{63}) = -116.3 \text{ kJ mol}^{-1}$. The spin density distribution is in these cases not well described with



Scheme 6 Hydrogen transfer reactions used to define the stability of boryl radicals.

Table 12 Radical stabilization enthalpies (RSE, in kJ mol^{-1}) at 298.15 K of boron-centered radicals and B–H bond dissociation energies of the respective closed shell compounds calculated according to (12a, 12b).

System	G3(MP2)-RAD ^a	Other	RSE exp.	BDE(B–H) exp. ^b
[•] BH ₂ (59)	0.0	0.0	0.0	+312.1 (+441.14) ^c
[•] BH ₂ -NMe ₃	–12.6	—	—	—
[•] BHMe-NMe ₃	–12.8	—	—	—
[•] BH ₂ -NH ₃ (60)	–13.7	–12.6(G2) ^d	—	—
[•] BH ₂ -Quinuclidine	–14.0	—	—	—
[•] BH ₂ -NH(SiMe ₃) ₂	–16.7	—	—	—
[•] BH ₂ -NH(SiH ₃) ₂	–24.6	—	—	—
[•] BH ₂ -PMe ₃	–52.1	—	—	—
[•] BH ₂ -PH ₃ (61)	–54.3	–53.1(G2) ^d	—	—
[•] BH ₂ -N(CHCHNHCH) (65)	–77.3	—	—	—
[•] BH ₂ -N(CHCHN(SiMe ₃)CH)	–79.4	—	—	—
[•] BH ₂ -N(CHCHCHNH)	–95.2	—	—	—
[•] BH ₂ -N(CHCH(O)CH) (66)	–97.9	—	—	—
[•] BH ₂ -OCH(NMe ₂)	–108.9	—	—	—
[•] BH ₂ -C(NHCHCHNH)	–110.7	—	—	—
[•] BH ₂ -C(NMeCHCHNMe) (62)	–112.5	—	—	—
[•] BH ₂ -DMAP (63)	–116.3	—	—	—
67	–116.6	—	—	—
[•] BH ₂ -C(NHCH ₂ CH ₂ NH)	–116.9	—	—	—
[•] BH ₂ -N(CHCH(S)CH) (68)	–117.7	—	—	—
[•] BH ₂ -N(CHCHCH(O))	–137.2	—	—	—
69	–138.7	—	—	—
[•] BH ₂ -N(CHCHCHCHCH) (70)	–144.3	—	—	—
[•] BH ₂ -N(CHCHCH(S))	–146.6	—	—	—
[•] BH ₂ -N(CH(N)CHCHCH)	–152.5	—	—	—
[•] BH ₂ -OC(CH ₃) ₂	–163.6	—	—	—
[•] BH ₂ -N(CHCH(N)CHCH)	–165.8	—	—	—
[•] BH ₂ -OCH(CH ₃) (64)	–184.0	—	—	—

^aG3(MP2)-RAD//MPW1K/6-31+G(d).^bTaken from Ref. 13.^cValue obtained at W4.3 level of theory as taken from Ref. 38.^dTaken from Ref. 81, 82.

the canonical Lewis structures in Table 12 as substantial parts of the unpaired spin density are delocalized into the adjacent π system. The most stable boryl radicals are obtained through complexation to carbonyl groups as in radical **64** with $\text{RSE}(\mathbf{64}) = -184.0 \text{ kJ mol}^{-1}$. The unpaired spin density is in this system localized almost exclusively on the carbonyl carbon atom and radical **64** should, therefore, best be seen as a borylketyl radical (Figure 11).

9 RELATIVE STABILITY SCALES FOR C-, S-, O-, N-, AND B-CENTERED RADICALS

The equivalence of differences in RSE and differences in BDE mentioned before provides a basis for the comparison of stability values for radicals of different type. This is shown

graphically in Figure 12, in which the origins of all individual stability scales are anchored onto a global (absolute) BDE scale. The strongest bond in the reference systems is the O–H bond in water (**1H**) with $\text{BDE}(\text{O–H}) = +497.1 \text{ kJ mol}^{-1}$, followed by the N–H bond in ammonia (**8H**) with $\text{BDE}(\text{N–H}) = +450.1 \text{ kJ mol}^{-1}$, the B–H bond in borane (**59H**) with $\text{BDE}(\text{B–H}) = +441.1 \text{ kJ mol}^{-1}$, the C–H bond in methane (**3H**) with $\text{BDE}(\text{C–H}) = +439.3 \text{ kJ mol}^{-1}$, and the S–H bond in H_2S (**7H**) with $\text{BDE}(\text{S–H}) = +381.2 \text{ kJ mol}^{-1}$. This implies, for example, that the origin of the O-radical scale is shifted to the origin of the C-radical scale by 57.8 kJ mol^{-1} to higher energies. A direct comparison of radicals of different type is most easily accomplished by combination of the (experimentally measured) BDE values for the reference systems with the (theoretically calculated) RSE

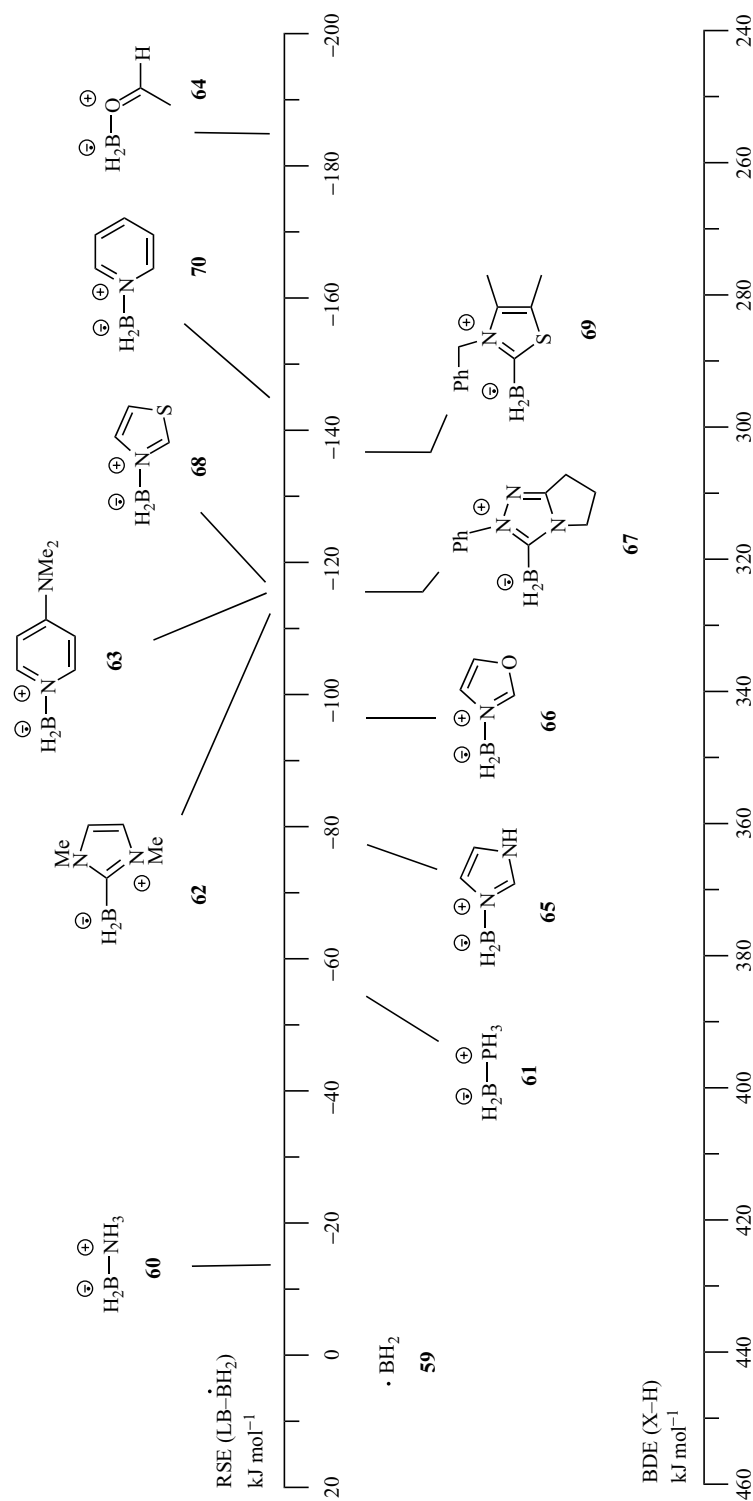


Figure 11 Graphical representation of the Lewis-base-boryl-radical stability at G3(MP2)-RAD//MPW1K/6-31+G(d) level of theory.

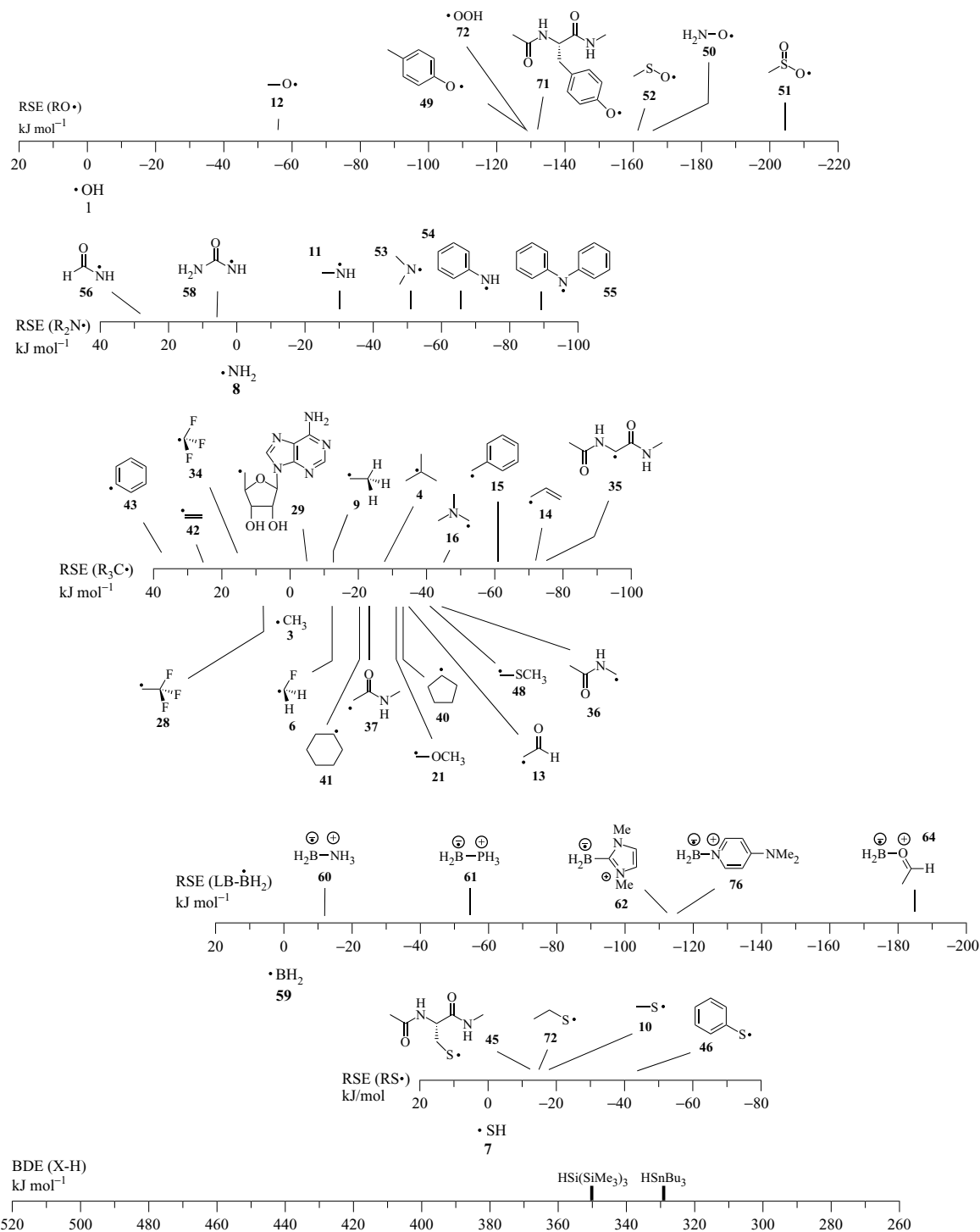


Figure 12 Relative stability scales for C-, S-, O-, N-, and B-centered radicals.

values of a particular radical. The strength of the central C–H bond in 2-methylpropane ((CH₃)₃C–H, **4H**), for example, can be calculated through combination of the RSE value for *tert*-butyl radical (**4**) of RSE(**4**) = –28.5 kJ mol^{–1} with the C–H BDE in methane (**3H**) of BDE(C–H) = +439.3 kJ mol^{–1} to give BDE(C–H, **4H**) = 439.3 – 28.5 = +410.8 kJ mol^{–1}. In a completely analogous way, the BDE(O–H) value in 4-methylphenol (**49H**) can be calculated as BDE(O–H, **49H**) = 497.1 – 129.4 = +367.7 kJ mol^{–1}, and the BDE(N–H) value in aniline (**54H**) can be calculated as BDE(N–H, **54H**) = 450.1 – 65.7 kJ mol^{–1} = +384.4 kJ mol^{–1}. These values imply that hydrogen abstraction through *tert*-butyl radical (**4**) from 4-methylphenol (**49H**) is exothermic by $\Delta H_{298} = 367.7 - 410.8 \text{ kJ mol}^{-1} = -43.1 \text{ kJ mol}^{-1}$ and from aniline (**54H**) is exothermic by $\Delta H_{298} = 384.4 - 410.8 \text{ kJ mol}^{-1} = -26.4 \text{ kJ mol}^{-1}$. These two examples illustrate the fact that the radicals shown in the global stability scale in Figure 12 can be converted from the left to the right side in an exothermic fashion using the appropriate hydrogen transfer reactions. One striking result of this type of global stability comparison is the largely similar stability of tyrosyl radical (**71**), glycyl radical (**35**), and cysteinyl radical (**45**), three amino acid-derived radicals of outstanding importance in enzymatic catalysis. One additional advantage of the combined RSE/BDE scales in Figure 12 is the ease of combination of theoretically calculated and experimentally measured BDE values. Tin hydride H–SnBu₃ (see **Tin Hydrides and Functional Group Transformations**) and silane H–Si(SiMe₃)₃ (see **Silanes as Reducing Reagents in Radical Chemistry**), for example, have experimentally determined X–H BDE values of BDE(Sn–H) = +328.9 kJ mol^{–1} and BDE(Si–H) = +351.5 kJ mol^{–1}, respectively.^{84,85} Using the data derived above for *tert*-butyl radical (**4**), these values imply that reaction of radical **4** with these hydrogen donors is exothermic by $328.9 - 410.8 \text{ kJ mol}^{-1} = -81.9 \text{ kJ mol}^{-1}$ (HSnBu₃) or by $351.5 - 410.9 \text{ kJ mol}^{-1} = -59.4 \text{ kJ mol}^{-1}$ (HSi(SiMe₃)₃).

10 CONCLUSIONS

The stabilities of a variety of radicals can be determined quantitatively using reaction energies for

hydrogen transfer reactions with an appropriately selected reference system. Despite the fact that this definition is, to a certain extent, arbitrary and that the obtained stability values may not always reflect substituent effects on the unpaired spin alone, the resulting energies are nevertheless helpful owing to the flexibility of this type of definition and the wide occurrence of hydrogen transfer reactions in open shell systems. One particular strength of this type of thermodynamic data is the possibility to predict exothermic and endothermic processes with equal accuracy, and the facile combination of experimentally measured and theoretically calculated data.

ACKNOWLEDGMENTS

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Free Radical Chemistry in Room-Temperature Ionic Liquids

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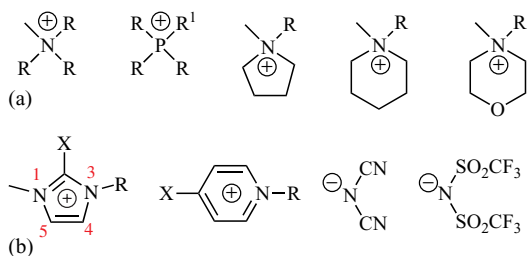
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1 INTRODUCTION

Room-temperature ionic liquids (ILs) are fascinating new solvents consisting of oddly shaped organic cations and organic or inorganic ions.^{1,2} These compounds bridge the divide between molecular liquids and ionic solids. Some of the typical ions that are used in the synthesis of ILs are shown in Scheme 1. Owing to the irregular shapes of the constituting organic cations (such as alkyl-substituted ammonium, phosphonium, pyrrolidinium, morpholinium, pyridinium, imidazolium, and other cations), the melting points of these ionic compounds are often below room temperature. Although their characteristics can vary over a tremendous range, ILs generally possess low volatility, good electric conductivity, moderate to high viscosity, and microheterogeneity that produces different local environments favoring simultaneous solubility of polar and nonpolar compounds.³ Since the development of air- and water-stable ILs, the field has exploded and the present and potential applications of these new solvents have increased exponentially.^{1,2,4} These applications presently span the whole range of synthetic and industrial chemistry: from electrolytes in oxide-based solar cells¹ to extraction solvents in spent nuclear fuel processing^{5,6} to cellulose extraction and chemical processing⁷ to the control of organosynthetic reactions⁸ to a Moon telescope,⁹ just to name a few such possible applications. It

has been realized that ILs may constitute the largest class of organic liquids, because the number of combinations of the possible cations and anions is astronomical. As such, to exhaustively review free radical behavior in ILs would be comparable in scope to reviewing this behavior in all of molecular liquids that are presently known. Furthermore, as any radical that can be generated in a molecular liquid can also be generated in ILs, the potential scope of such a review would be limitless. The common methods for production of organic radicals, such as thermolysis, photolytic cleavage, electron transfer, electrochemistry, introduction of chemically stable radicals (such as FeCl_4^{-10} and superoxide anion¹¹), or the use of spin traps for converting short-lived reaction intermediates to stable radicals—all of such methods have been realized in ILs. However, providing a comprehensive list of such radicals in the ILs would be impractical and beyond the scope of this review. Instead, we present some examples of how radical solutes have been used to probe the properties of ILs and how ILs influence radical reactivity, but we focus primarily on the radicals derived from ILs themselves, and their reactivity.

To date, the most investigated class of ILs contain 1-methyl-3-alkylimidazolium cations (C_Nmim^+ , where N is the carbon number for the alkyl chain in the long arm, Scheme 1 for $X = \text{H}$) and the corresponding 2-alkyl derivatives (e.g., $X = \text{Me}$).



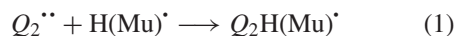
Scheme 1 Typical constituent ions in room-temperature ionic liquids. (a) “Aliphatic cations”: alkylated ammonium and phosphonium, pyrrolidinium, piperidinium, and morpholinium cations. (b) Alkylated imidazolium (X = H, Me) and pyridinium cations (“aromatic cations”) and dicyanamide and bistriflimide (NTf₂⁻) anions.

For such cations, we shall adopt a nomenclature in which the residue of the imidazolium cation with respect to substitution in the n -th atom in the ring (Scheme 1) is designated as Q_n . In this nomenclature, the 2-imidazolyl radical is $Q_2H^\bullet$, the N -heterocyclic carbene (NHC) is $Q_2^{2\bullet}$, and so on.

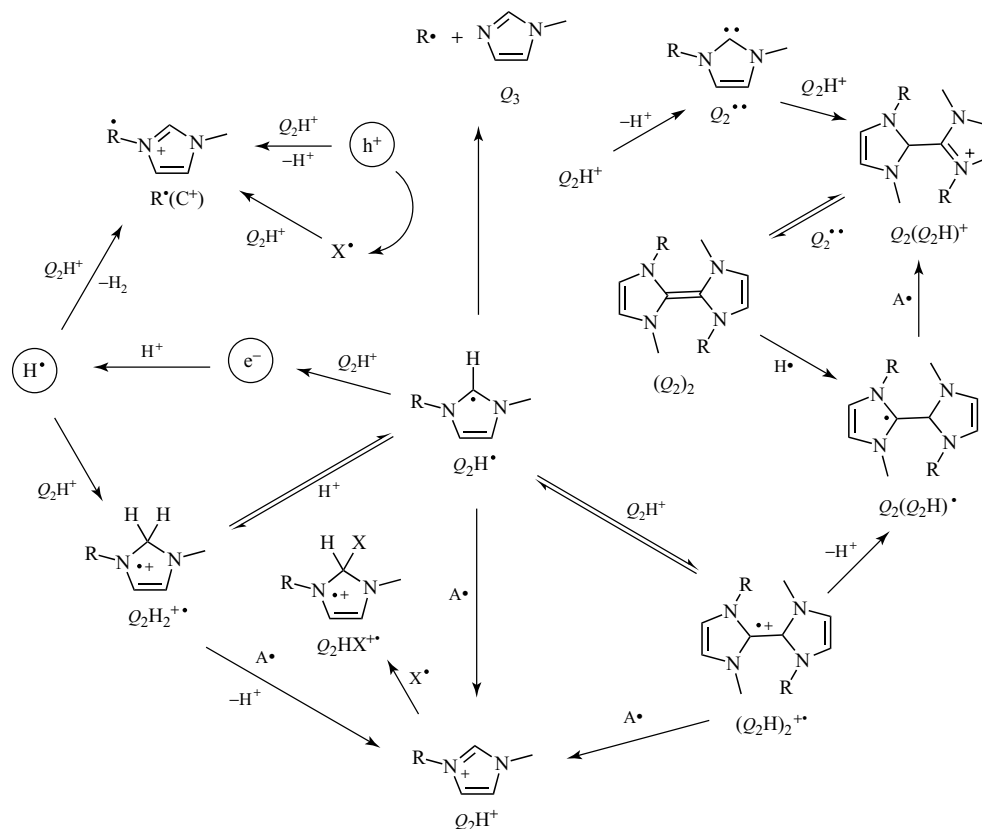
The solvation and dynamics of radical intermediates and spin probes in ILs have been frequent subjects of studies.^{12–24} Such experiments go back to the pioneering work of Noel, Allendoerfer, and Osteryoung,¹² who used electron paramagnetic resonance (EPR) spectroscopy to study the rotational dynamics of nitroxide radicals in the mixtures of C₂mim Cl and AlCl₄. Detailed studies of rotational dynamics of neutral and charged stable nitroxide radicals aiming to determine the microviscosity of the IL have been reported. An elegant application of this method by Compton's group at Oxford was the recent demonstration of viscosity reduction when hydrophobic C₂mim NTf₂ (Scheme 1) was saturated by SO₂ and CO₂.²⁴ Another study used methylviologen radical cation (MV²⁺) to estimate the rates of diffusion-controlled electron self-exchange with MV²⁺, thus investigating translational rather than rotational dynamics.²¹ A somewhat similar method was used to study the effect of ILs on the conformational dynamics of stable biradicals through the exchange interaction between the termini bearing the unpaired electrons.^{22,23} The drawback of such studies is that the inferences of molecular detail in the solute–solvent and solvent–solvent interactions are indirect and often qualitative. In this sense, the current realizations of the method may provide less insight than ultrafast laser studies reviewed elsewhere.^{25–27}

In general, the rotational and translational dynamics in ILs tend to be slow^{12–21} owing to their generally higher viscosity and strong solute–solvent interactions, and these features have significant effects on charge separation and charge recombination dynamics.²⁸ Such properties of the ILs can be exploited for macromolecular synthesis involving (living) radical and ionic polymerization^{29–33} and catalysis,^{34,35} which was quickly realized following the discovery of air- and water-stable ILs. The classical example of such reactions are Cu(I)- N -propyl-2-pyridylmethanimine-mediated living radical polymerization of methyl methacrylate³⁶ and radical C–C cyclizations induced by Mn(III)(OAc)₃.³⁷ One-electron redox reactions of aromatic molecules in imidazolium ILs, whether chemical or electrochemical, are very facile and the resulting radical ions are stabilized by π – π solute–solvent interactions.^{38–43} Among such reactions, halogen anion elimination shows very strong solvent effects as compared to common polar solvents (such as acetonitrile).^{38,40,44} Normally, the solvation of the leaving halide anion disfavors cleavage via the entropy term. As the ILs are composed of bulky cations, this term is much lower in the ILs.³⁸ This is the fairly common theme in the chemistry of radical intermediate in the ILs: the strength of the solvent–solute interactions is modulated by steric and crowding effects in such ILs.

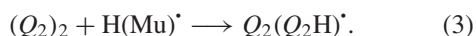
Some methods of free radical generation, however, are more peculiar to the ILs and closely related to the structure of the constituent ions. These methods include radiolysis,^{45–52} photoionization and photoinduced charge separation involving the excited constituent ions,⁵³ and electrochemical breakdown of neat ILs.^{54–58} A more exotic radical chemistry is possible for imidazolium ILs. The cation ($C^+ = Q_2H^+$) easily deprotonates from 2-position in the presence of weak bases and the resulting carbene $Q_2^{2\bullet}$ (2-ylidene) can react with H⁺ atoms or muonium (Mu), μ^+e^- (the heavy “isotope” of H⁺), yielding 2-(Mu)-imidazolyl radicals



observed by muon spin resonance spectroscopy.^{59–61} A recent example of this method is the attachment of the muonium to the dimer form of the carbene, $(Q_2)_2$ (also known as the *electron-rich olefin* or the *symmetric dimer*) to produce the corresponding dimer radical $Q_2(Q_2H)^\bullet$



(Scheme 2), which can also be produced in a reduction of C_N mim $Cl-AlCl_3$ by metallic lithium. The electron-rich olefin is the product of the Lemal (equilibrium) reactions well known in NHC chemistry⁶²: the carbene attaches to the C(2) position of the parent cation and the resulting “asymmetric dimer” $Q_2(Q_2H)^+$ cation reacts with another carbene, yielding the symmetric dimer and recovering the parent cation:



($Q_2Ar^{\cdot}$, where Ar is an aryl group) are produced through photoinduced N–C bond cleavage of *o*-chlorohexaarylbisimidazole (*o*-Cl-HABI). Normally radical–radical reactions are diffusion limited, but the recombination of lophyl radicals is typically slow in molecular solvents ($k_{\text{rec}} = 300\text{--}8000\text{ M}^{-1}\text{ s}^{-1}$)⁶⁵ because the planar radicals have to distort significantly to form the asymmetric, strained HABI molecule.⁶⁶ Strehmel *et al.*⁶⁷ examined lophyl radical cage escape yields and recombination rates in three ILs of varying viscosities in comparison with dimethylsulfoxide. Cage escape yields were reduced by half in the ILs relative to dimethylsulfoxide, indicating longer cage retention times in the ILs facilitating fast recombination. Remarkably, the radical recombination rate constants for $\text{C}_4\text{mim NTf}_2$, $\text{C}_6\text{mim PF}_6$, and $\text{C}_4\text{mim BF}_4$ were 95 000, 21 000, and 18 000 $\text{M}^{-1}\text{ s}^{-1}$ respectively, whereas the rate constant in dimethylsulfoxide

(20–200 times less viscous) was $5300 \text{ M}^{-1} \text{ s}^{-1}$. It appears that lophyl radical recombination is promoted by the IL environment, possibly through transition state stabilization by means of yet unknown interactions.

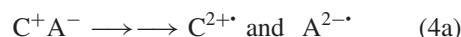
Although it is clear that ILs can have significant effects on the reactions and dynamics of solute radicals, there is a much richer chemistry of radicals derived from the ILs themselves. This chemistry is not only determined by the type of anion or cation from which a particular radical is derived but it can also be profoundly influenced by the chemistry of the respective counterion. Ionizing radiation, photochemistry, and electrode reactions can serve as the means of “ionizing the ions.” The thrust of this article is to describe the chemistry of such reactions and the nature and reactivity of radicals thus formed.

2 “IONIZATION OF THE IONS”

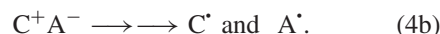
In a molecular liquid, ionization (or, more generally, oxidation and reduction of the constituent solvent molecules) produces the so-called *excess electrons* (e^-) and *holes* (h^+), that is, solvent molecules from which the electron has been detached (forming a parent radical cation, which may be stable or unstable) and rapidly relocalized in the bulk solvent. If the solvent molecules have no electron affinity or accessible antibonding orbitals, the excess electron localizes in the voids between the solvent molecules as a “solvated electron”⁶⁸; otherwise the excess electron attaches to a solvent molecule to form a molecular anion. Sometimes, dimer or multimer anions are formed instead, bridging the two extremes of the electron localization: molecular ions and solvated electrons, which can be viewed as clusters of electrons and their solvent cages. Radical cations of nonaromatic molecules tend to deprotonate rapidly, yielding secondary neutral radicals. Sometimes, such “holes” and “electrons” (or their incompletely localized precursors) can migrate faster than molecular diffusion, by a resonance charge-hopping mechanism, and so the charge transfer to the solute is very rapid and efficient, despite the relatively short lifetime of these primary species. This lifetime is, typically, reduced by charge recombination, especially in liquids of low and medium polarity: the Coulomb attraction

between the opposite charges in the geminate pairs (or clusters of such pairs in radiolytic spurs) generated in the ionization or charge separation events pulls the radical ions toward each other. Some reactive species escape, but the majority recombine.

Many of these common intuitions about ionization in organic liquids fail when these liquids are composed of ions. Very generally,^{69,70} the “ionization of ions” produces either radical dications and dianions (if the electron is removed from a cation and accepted by an anion)



or neutral radicals (if the electron is accepted by a cation or removed from an anion)

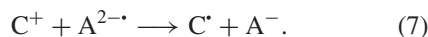


It is also possible that the electron detached from either of the constituent ions is trapped in anion vacancies and/or interstitials between the cations, similarly to F-centers in irradiated NaCl and other inorganic ionic solids.

Naturally, these doubly charged radicals are inherently unstable, owing to the strong internal Coulomb repulsion, and so such a species rapidly eliminates one of the charges via fragmentation. The typical examples of such fragmentation reactions are deprotonation of radical dications from the aliphatic arms (with the formation of the corresponding alkyl radical in the arm; see Scheme 2)⁷⁰



and halide elimination from the radical dianions of fluorinated anions (reactions 27 and 28 below). These ultrafast fragmentation reactions compete with the equally rapid electron transfer involving the neighboring ion; for example,^{69,70}



The formation of the doubly charged radical ions may seem counterintuitive, as from the energetics standpoint, it appears more likely that the negative charge (“electron”) would be trapped by the constituent cation, whereas a positive charge (“hole”)

would be trapped by the constituent anion. This may indeed be the case in one- or multiphoton ionization and this is certainly the case in electrochemical experiments, but this is not the case in the radiolysis of ILs. Indeed, the typical energies involved in the generation of two to five ion pairs in 5–10 nm spurs through interaction with fast (>0.1 MeV) electrons is 10–20 eV per ionization event, and this energy is more than sufficient to produce superexcited electronic states of the constituent ions, electronically and vibrationally excited neutral radicals, and radical dications and dianions (that otherwise belong to the curiosity cabinets of physical organic chemistry). Furthermore, the excess electron is a highly reducing species that can easily react with certain anions, among them nitrate (*vide infra*).

As both the proton transfer (5) and electron transfer reactions (6) are very rapid and involve the same acceptor (the neighboring anion), the branching ratio of these two reactions largely depends on the stability of the radical dication to deprotonation. Aliphatic cations (such as quaternary ammonium cations) very readily deprotonate from the terminal and penultimate sites of their alkyl arms, because these are the sites of the maximum unpaired electron density in the C^{2+} . Consequently, the yield of the deprotonation is large and $R^+(C^+)$ radicals are the main form of the cation-derived radical in the corresponding ILs.⁷⁰ By contrast, in aromatic cations, the unpaired electron density is mainly on the ring, and the deprotonation from the aliphatic arms is significantly reduced, though it is by no means negligible. Owing to the occurrence of reaction (6), the main form of the “hole” generated in an IL is radical $A^{\bullet}$, irrespective of whether the ionization proceeds from the cation or the anion.

The routine formation of doubly charged radicals makes the radical chemistry of the ILs delightfully exotic, as such species seldom occur in “normal” liquids. However, even the neutralization reaction (4b) results in the unusual situation: the formation of the geminate pair of neutral radicals surrounded by ions (as opposed to the normal situation, which is the geminate pair of radical ions surrounded by neutral molecules).^{69–71} Since there is no direct electrostatic interaction of neutral radicals in an ionic fluid, the radicals may readily escape from such geminate pairs and the chemistry may be dominated by cross-reactions of such escaped radicals as opposed to rapid recombination of geminate radical ion pairs.

At present, little is known about the geminate dynamics of such neutral radicals in ILs, though some classes of ILs have been extensively studied using pulse radiolysis and ultrafast laser spectroscopy.^{72,73} Such geminate pairs are not the general rule, as the neutral radicals that are surrounded by ions can convert to dimeric radical ions by forming two-center three-electron $\sigma^2\sigma^{*1}$ bonds with the parent ions,^{71,73}



restoring “normalcy” (having ionic radical intermediates similar to molecular liquid mechanisms). This is not the only way of such “normalization,” the IL systems exploit several such ways (as discussed in the subsequent sections). The formation of metastable neutral radicals via reaction (4b) is much less frequent than could be expected on the general grounds. Since in the ILs, the (radical) ions are more strongly solvated than neutral radicals, *if a reaction intermediate can be converted to a charged species, then it is typically converted to such a species*. This is one of the most general patterns of radical behavior in the ILs—these liquids “want” to stay ionic!

The hemicolligation reactions mentioned above have precedence in inorganic solids. The ionization of alkali halides, Alk^+X^- , yields an anion-vacancy-trapped electron interacting with six neighboring alkali cations and the $X_2^{\bullet-}$ anion. The latter is formed when the $X^{\bullet}$ atom generated by electron detachment from the parent halide anion forms the $\sigma\sigma^*$ bond with the interstitial X^- . The same reaction also occurs in the ILs composed of Br^- and I^- anions.^{53,57,74,75} Given the high concentration of the parent anions in such neat ILs, reaction (8b) occurs in <100 fs.⁷³ The similar reactions should occur in ILs composed of pseudohalide anions (such as SCN^-), including the popular choice for a chemically inert, hydrophobic anion, the dicyanamide $((NC)_2N^-$, Scheme 1). It was shown⁷¹ that the radical $(NC)_2N^{\bullet}$ derived via reaction (4b) forms the C_2 symmetric $[(NC)_2N-N(CN)_2]^{\bullet-}$ radical anion. For other (pseudohalide) imide anions, which have bulkier substituting groups (such as the NTf_2^- anion, where $Tf = CF_3SO_2$; see Scheme 1), steric hindrance prevents the formation of the dimer anion and neutral Tf_2N radicals are observed instead.⁷⁰ In ILs composed of aliphatic cations (Scheme 1), there

are no accessible antibonding orbitals for the excess electrons to occupy, and the electrons do not attach to such cations. If the ground state anions in such aliphatic IL also have low or negative electron affinity, such electrons can form cavity-trapped “solvated electron” species that are electrostatically bound to several cations forming the cavity.^{48–50,53} It is possible that such cavities originate as anion vacancies.⁷¹ The electron is partially screened from the cation’s positive center by its aliphatic groups, and the optical absorption spectra of such “solvated electrons” resemble those of medium-polarity molecular liquids, suggesting only weak electrostatic interactions with the bulky cations. The reaction and solvation dynamics of such electrons are the subject of active investigation, and we refer the reader to recent reviews.^{52,76,77} Solvated electrons in some ILs may persist for about a microsecond before they decay through geminate recombination with holes or their successor species, including radiolytically generated protons, or they may disappear more quickly by reactions with adventitious scavengers (impurities in the IL). It is also possible that such solvated electrons slowly react with the constituent NR_4^+ cations, with the formation of the corresponding amine NR_3 and the elimination of the terminal $\text{R}^\bullet$ radical, as occurs in water.⁷⁸ The decay of these solvated electrons, either via photoassisted recombination or alkyl arm elimination, can be induced by photoexcitation in the visible region (resulting in <1 ns photobleaching).⁷⁹

In ILs composed of aromatic cations, the π -systems of the cations can readily accommodate the negative charge, and so electrons are promptly trapped therein. It is possible that excess electrons exist fleetingly in aromatic cation ILs, and there is some support to this conjecture both from the experiment^{72,73} and theory^{80,81}. However, such excess electrons would be inherently unstable with respect to attachment after the solvation dynamics have come to equilibrium. The typical examples of such electron-accepting cations (C^+) are “aromatic” cations shown in Scheme 1; neutralization of these cations results in the formation of trigonally distorted 2-imidazolyl (Scheme 2) and planar 4-pyridinyl radicals ($\text{C}^\bullet$). The latter radicals and 2-alkyl-substituted imidazolyl radicals are unreactive toward their parent cations, whereas in some ILs, the 2-imidazolyl radicals attack the parent cation at the 2-position (reaction 8b) to form a $\text{C}(2)\text{--C}(2)$ $\sigma\sigma^*$ bound C_2 symmetrical “gauche”

dimer radical cation $\text{C}_2^{+\bullet}$, which exhibits a low energy $\sigma\leftarrow\sigma^*$ absorption band.⁷¹ Since this $\sigma\sigma^*$ bond is rather weak, reaction (8b) is reversible and the dimerization is favorable in some ILs but not in others. If the anions are compact, strong solvation interactions with the parent cation shift the equilibrium to the left side of reaction (8b); if the interactions are weaker (which is the case for bulky and extended anions that also tend to cluster, such as NTf_2^-), the equilibrium is shifted right to the dimer radical cation. The resulting $\text{C}_2^{+\bullet}$ cation radicals formed in reaction (8b) resemble the A_2^{--} anion radicals formed in reaction (8b). A peculiarity of such “double dimerization” is that the recombination can occur in the following two ways:



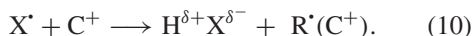
In halide ILs, the signature of this branched dimerization is a very rapid (geminate) generation of X_3^- (from $\text{X}^- + \text{X}_2$). If reaction (9b) does not occur, the only chemical pathway to X_3^- is via the disproportionation of the escaped X_2^{--} radicals, which is slow. Time-resolved Br K-edge X-ray absorption studies on C_6mim Br photoexcited by a 200-nm laser suggest rapid (<1 ns) formation of a closed-shell species with the Br–Br bond, consistent with the occurrence of reaction (9b).⁶²

How extensive is the fragmentation of the constituent ions in the “ionization of the ions?” The overall degradation of NTf_2^- in irradiated C_4mim NTf_2 was estimated as 2.2 species per 100 eV absorbed energy.⁸² Given that the typical ionization yield in an organic liquid is three to five ion pairs per 100 eV, it is seen that the “ionization of the ions” generally results in their fragmentation (which competes with the recombination). We proceed to look more closely at the radicals derived from the constituent ions.

3 NONAROMATIC ANIONS

Although the formation of Br_2^{--} and I_2^{--} in aliphatic and aromatic ILs is well established,^{53,74,75,83} no such species were apparent for chloride ILs.⁸⁴ This suggests that reaction

(8b) competes with hydrogen abstraction from the organic cation:



The energies of the H–X bond change from 5.9 to 4.5 to 3.8 eV from F to Cl to Br, hence reaction (10) can outcompete reaction (8b) for chlorine but not bromine, and $Cl_2^{\cdot-}$ is not formed. Consequently, no chloride-derived radicals can be traced to the anion, as $R^{\cdot}(C^{+})$ can also be generated via reactions (5) and by $H^{\cdot}$ atom abstraction reaction



Similarly, no distinctive anion-derived radicals are observed in ILs composed of BF_4^{-} and PF_6^{-} . For PF_6^{-} and BF_4^{-} , mass spectrometry analyses indicate the occurrence of $F^{\cdot}$ atom substitution/addition products,^{82,85}



whereas EPR spectra indicate no anion-related radicals. Since the irradiation of KPF_6 and KBF_4 yields various P- and B-centered radicals, the absence of such anion-derived radicals in the ILs suggests that $F^{\cdot}$ atoms promptly abstract hydrogen via reaction (10). When tetracyanoborate anion, $B(CN)_4^{-}$, replaces the BF_4^{-} anion, two B-centered radicals are observed that are formed via reactions



In the gas phase, BF_3 has near-zero or negative electron affinity versus 3.4 eV for $B(CN)_3$ and 3.94 eV for C_1mim^{+} .⁸⁴ Had the $BF_3^{\cdot-}$ radical been formed via reaction (13), it would promptly donate the electron to any acceptor including the constituent cation. Equally, significant is nonobservation of the $\cdot BF_2$ radical. The dissociation energy for F_2 (1.61 eV) is considerably lower than this energy for C_2N_2 (5.78 eV). Consequently, the $BX_3 + X^{\cdot}$ pathway is preferred to the $\cdot BX_2 + X_2$ pathway by almost 5.7 eV for $X = F$, whereas the second pathway is preferred by 0.7 eV for $X = CN$. Therefore,

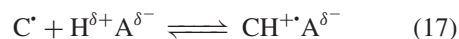
while reaction (12) occurs for the tetrafluoroborate anions, reaction (14) is preferred for the tetracyanoborate anions. Turning to more complex inorganic anions, a very important example is hydrogen sulfate, which can be used to generate $H^{\cdot}$ atoms:



The $H^{\cdot}$ atoms abstract hydrogen from the alkyl arms of the cations (reaction 11), but for aromatic cations, the main reaction is H-atom addition



For imidazolium cations, this addition is in the C(2) position, yielding $Q_2H_2^{+*}$; for pyridinium cations, it is in the C(4) position. The same radical cation adduct CH^{+*} can be formed via the reversible protonation of $C^{\cdot}$ radical by acids:



and both pathways (16) and (17) to this radical cation have been observed experimentally.^{84,86} Such proton adducts are remarkably stable (some of these species persist to 350 K) and probably decay via the reaction

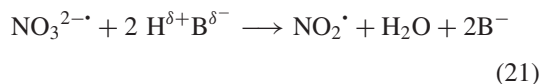


The $H^{\cdot}$ atom formation does not necessarily involve reaction (15); the electron can be scavenged by any protic impurity in the IL, including the one that is photo- or radiolytically generated (such as $H^{\delta+}A^{\delta-}$ and H_3O^{+}). Another likely source of the $H^{\cdot}$ atoms is the homolysis of the C–H bonds in the electronically excited states of the cations that are generated either by charge recombination or direct excitation (e.g., during radiolysis),

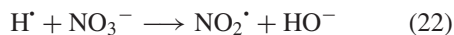


Another inorganic anion of practical interest is nitrate, as nuclear separations based on ILs typically involve 1–5 M nitric acid solutions in contact with the IL, and the nitrate anion is extracted from such aqueous solutions.⁸⁷ Radiolysis of $C_4mim NO_3$ results in the accumulation of $NO_2^{\cdot-}$ anions.⁴⁷ In the EPR spectra obtained from irradiated $C_2mim BF_4/C_2mim NO_3$, the strongest resonance lines are from the $NO_2^{\cdot}$ and NO_3^{2-*} radicals.⁸⁴ In KNO_3

(serving as a reference system), there is also the $\text{NO}_3^\bullet$ radical that is lacking in the ILs. In both aliphatic and aromatic IL nitrates, the radicals derived from the organic cation (such as $\text{C}^\bullet$) are missing. In aqueous solutions, the $\text{NO}_2^\bullet$ radicals form not only via the prompt homolysis of the excited $\text{NO}_3^{2-\bullet}$ anion but also via a slower reaction of $\text{NO}_3^{2-\bullet}$ (or HNO_3^{--}) with acids, $\text{H}^{\delta+}\text{B}^{\delta-}$ (including water), yielding the corresponding oxide anion as a by-product:



The $\text{NO}_3^{2-\bullet}$ radical is readily protonated by weak acids, and it is likely that the $\text{NO}_2^\bullet$ radicals observed in the ILs are generated in these secondary reactions. The $\text{NO}_2^\bullet$ radical can also be produced in reactions of $\text{H}^\bullet$ atoms and NO_3^- :



When tetrabutylammonium nitrate is irradiated at 77 K and then warmed to 225 K, the $\text{NO}_3^{2-\bullet}$ and $\text{NO}_2^\bullet$ radicals decay, and the signal of the $\text{NO}_2^{2-\bullet}$ (or HNO_2^{--}) radical appears. The formation of this radical could be due to electron transfer from $\text{NO}_3^{2-\bullet}$ to NO_2^- ; the nitrite (found among the stable radiolytic products) might be formed via the dissociation of the excited state NO_3^- anion. In $\text{C}_2\text{mim NO}_3/\text{BF}_4$, this $\text{NO}_2^{2-\bullet}$ radical is not observed; instead, at 175–180 K, the $\text{NO}_3^\bullet$ radical is observed. The observed low yield of the $\text{NO}_3^\bullet$ radicals in the irradiated ILs as compared to inorganic nitrates can be accounted for by high reactivity of this radical, by H abstraction or electron transfer.

A large subset of the simple anions that are used in IL synthesis can be represented as RB^- , where R- is an alkyl or alkoxy group (or their perfluorinated analogs) and -B is an inorganic base (such as $-\text{SO}_3^-$, $-\text{CO}_2^-$, and $-\text{PO}_2^{2-}$). One-electron oxidative fragmentation of several such anions is well known (e.g., Kolbe reaction for the carboxylates),^{84,88} and these better-known reactions exemplify a more general pattern of the loss of base upon neutralization

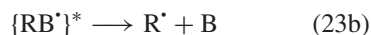


Table 1 Radical products derived from the constituent anions and identified in the frozen ILs using EPR spectroscopy (the deprotonated forms of the radicals are given).⁸⁴

Anion	Radicals observed
X^{-a}	$\text{X}_2^{-\bullet}$
HSO_3^-	$\text{H}^\bullet$
NO_3^-	$\text{NO}_3^{2-\bullet}$, $\text{NO}_2^\bullet$, $\text{NO}_2^{2-\bullet}$
$\text{CR}_3\text{CO}_2^{-b}$	$^\bullet\text{CR}_3$, $^\bullet\text{CR}_2\text{CO}_2^-$
$\text{CR}_3\text{SO}_3^{-b}$	$^\bullet\text{CR}_3$, $^\bullet\text{CR}_2\text{SO}_3^-$, $\text{CR}_3\text{SO}_3^\bullet$
$\text{CF}_3\text{CF}_2\text{CO}_2^-$	$^\bullet\text{CF}_2\text{CF}_2\text{CO}_2^-$, $\text{CF}_3^\bullet\text{CFCO}_2^-$
$\text{CH}_3\text{OSO}_3^-$	$^\bullet\text{CH}_2\text{OH}$, $^\bullet\text{CH}_2\text{OSO}_3^-$, $\text{CH}_3\text{OSO}_3^\bullet$
$(\text{CH}_3\text{O})_2\text{PO}_2^-$	$^\bullet\text{CH}_2\text{OH}$
$\text{B}(\text{CN})_4^-$	$^\bullet\text{B}(\text{CN})_2$, $\text{B}(\text{CN})_3^\bullet$
$\text{B}(\text{ox})_2^{-c}$	$(\text{ox})\text{BO}^\bullet\text{C}=\text{O}$
NTf_2^-	$^\bullet\text{CF}_3$, $^\bullet\text{CF}_2\text{SO}_2\text{NTf}^-$, $^\bullet\text{NTf}_2$

^aX = Br or N(CN)₂.

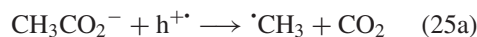
^bR = H or F.

^cox = oxalato.

which yields the corresponding fragment radical $\text{R}^\bullet$ (Table 1). Reaction (23) occurs in most of the ILs composed of RB^- anions, even if the ground state of the intermediate radical $\text{RB}^\bullet$ is relatively stable. This is explained by the fact that reaction (23a) is strongly exergonic and the neutral radical $\text{RB}^\bullet$ is generated in an electronically and/or vibrationally excited state. The potential presence of water increases the likelihood of reaction (23b) involving the relaxed $\text{RB}^\bullet$ radical through the hydration of residue B with the formation of acids



Reaction (24) causes a radiation-induced increase in proticity.⁸⁹ The fluorination of the RB^- anions (which is a popular approach to increasing the hydrophobicity and chemical durability of ILs) has little effect on the facileness of reactions (23). For alkyl and alkoxy RB^- anions, intra- or intermolecular deprotonation from the aliphatic moiety competes with reaction (23b), for example,



and the latter radical (in deprotonated form) can also be produced via secondary reactions



Table 2 Density functional estimates for adiabatic electron detachment energies (EDE_{ad}), bonding energies for (pseudo)halide anions, and dissociation energies D (reaction 23b) for selected anions.⁸⁴

Anion (A [−])	EDE _{ad} (A [−]) (eV)	A [−] + A [•] (eV) ^a	D (R [•] + B) (eV) ^b
Thiosalicylate	3.36	—	−0.026
Benzoate	3.44	—	−0.006
Picolinate	3.56	—	−0.34
Bromide	3.60	1.44	—
Salicylate	3.64	—	−0.062
Acetate	3.65	—	−0.63
Chloride	3.70	1.50	—
Maleimide	3.90	0.86	—
Phthalimide	3.98	0.58	—
Dicyanamide	4.06	0.86	—
Succinimide	4.12	1.02	—
Methanesulfate	4.26	—	1.04
Tosylate	4.29	—	1.36
(MeO) ₂ PO ₂	4.43	—	1.08
MeOSO ₃	4.62	—	0.77
Triflate	5.20	—	0.30
NTf ₂	5.50	—	—
B(ox) ₂ ^c	6.30	—	−0.20
BF ₄	7.31	—	—
PF ₆	8.02	—	—

^aFor (pseudo)halides only.^bDissociation energy (eV) for reaction (23b); 3,5-dimethylbenzoate (−0.017), naphthalene-2,3-dicarboxylate (−0.30), 1,2,3-benzenetricarboxylate (−0.39), phthalate (−0.43), terephthalate (−0.91), 1,2,4,5-benzenetetracarboxylate (−1.67); α-alanine (−0.73), glycylglycine (−1.05), histidine (−0.95).^cox = oxalato.

Reactions (25) and (26) can be readily generalized to include other RB[−] anions. Table 1 summarizes the radicals observed using EPR spectroscopy.⁸⁴ The product analyses are consistent with these observations: it is precisely because of the occurrence of reaction (23) that most of the commonly used constituent anions undergo appreciable fragmentation upon radiolysis. The stabilization of the anion could be achieved either via (i) preventing reaction (23a) through increasing adiabatic electron detachment energies (EDEs) of the constituent anions (Table 2) or (ii) stabilization of the intermediate radical. Increasing the EDE of the anion has little actual effect on its *radiation* stability, as the ionization events in radiolysis are energetic (5–20 eV) and reaction (23a) still occurs.

The simplest of the RB[−] anions is acetate. In radiolysis of C₂mim and C₄mim CH₃CO₂[−], the EPR spectrum recorded at 50 K exhibits the resonance lines of the methyl radical superimposed on the

broad lines from Q₂H[•] and R[•](C⁺) radicals; there is no evidence of reaction (25b). The high yield of the R[•](C⁺) radical suggests that the methyl radicals can abstract hydrogen from the aliphatic arms of the cation. At 175 K, thermally activated methyl radicals add to Q₂H⁺. When the sample irradiated at 77 K is stored at this temperature, the methyl radical fully decays, and the EPR spectrum reveals the presence of the [•]CH₂CO₂[−] (or the [•]CH₂CO₂H) generated via reaction (26). Thus, the methyl radical released in reaction (23) decay (i) by H abstraction from both of the constituting ions and (ii) by thermally activated addition to the imidazolium cation.

When a trifluoromethyl group replaces the methyl group in acetate, the main feature is a signal from [•]CF₂CO₂[−] radical; there is also a weaker signal from the [•]CF₃ radical. The likely origin of this [•]CF₂CO₂[−] radical is dissociative electron attachment (DEA) to the parent anion proceeding via the radical dianion intermediate:

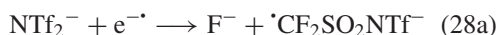


The radiation stability of anions with long fluorinated aliphatic chains (used in some applications where greater IL hydrophobicity is required) is poor. In tetraalkyl ammonium and phosphonium pentafluoroacetate, high yields of CF₃[•]CFCO₂[−] and [•]CF₂CF₂CO₂[−] radicals were observed, while there was no evidence for reaction (23) occurring. The propensity to generate fluoride limits the viability of such anions for applications in high radiation fields. As observed above, aliphatic carboxylates have similar limitations owing to the ease of reaction (23b). Examination of the longer chain homologs of the carboxylates, sulfates, and diphosphates indicates that *the longer was the aliphatic chain in the RB[−] anion, the more extensive was the fragmentation by deprotonation (such as reaction 25b) as compared to reaction (23b).*⁸⁴

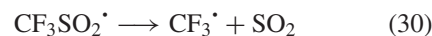
Another representative class of the RB[−] anion is sulfonates. The resonance lines from [•]CH₂SO₃[−], CH₃SO₃[•], and [•]CH₃ are discernible in EPR spectra of irradiated frozen ILs consisting of the methanesulfonate anions. Above, we have compared aliphatic carboxylates and their perfluorinated analogs; the same comparison can be made for the alkylsulfates and alkylsulfonates. One of these fluorinated anions, triflate (TfO[−]), is a popular anion choice for IL synthesis. Radiolysis of C_Nmim CF₃SO₃[−] yields [•]CF₃ and [•]CF₂SO₃[−]

(or its protonated form). Unlike the case of C_N mim $CF_3CO_2^-$, where the $\cdot CF_2CO_2^-$ radical accounts for most of the radicals observed, the yield of these two radicals in the TfO ILs is low (<5% total radical yield). No evidence for the $CF_3SO_3\cdot$ radical (analogous to the $CH_3OSO_3\cdot$ and $CH_3SO_3\cdot$ radicals observed in the reference alkylated anion systems) was found in these ILs, suggesting that this $CF_3SO_3\cdot$ radical is unstable. The estimates for the C–S bond dissociation energies given in Table 2 indicate that the gas-phase C–S dissociation barrier for $CH_3SO_3\cdot$ radical is considerably greater as compared to the $CF_3SO_3\cdot$ radical (1.04 vs 0.3 eV), which may account for the instability of the latter species. Extending the perfluorinated alkyl chain greatly increases the yield of reaction (27) for such anions, as the longer chain provides more sites for fluoride loss and increasing chain length decreases the effect of the negatively charged SO_3^- group (repelling the excess negative charge), resulting in more efficient electron trapping.

A closely related anion to TfO^- is bistriflimide, NTf_2^- , which is widely utilized in IL synthesis owing to its high hydrophobicity.⁹⁰ The three anion-derived radicals observed in the bistriflimide ILs are $\cdot NTf_2$, $\cdot CF_2SO_2NTf^-$, and $\cdot CF_3$ (which accounts for 2–5% of the total radical yield). Therefore, in addition to reaction (4b), bistriflimide might undergo DEA typical of other fluorinated anions, albeit with a small yield, as well as N–S fragmentation.^{55,58}



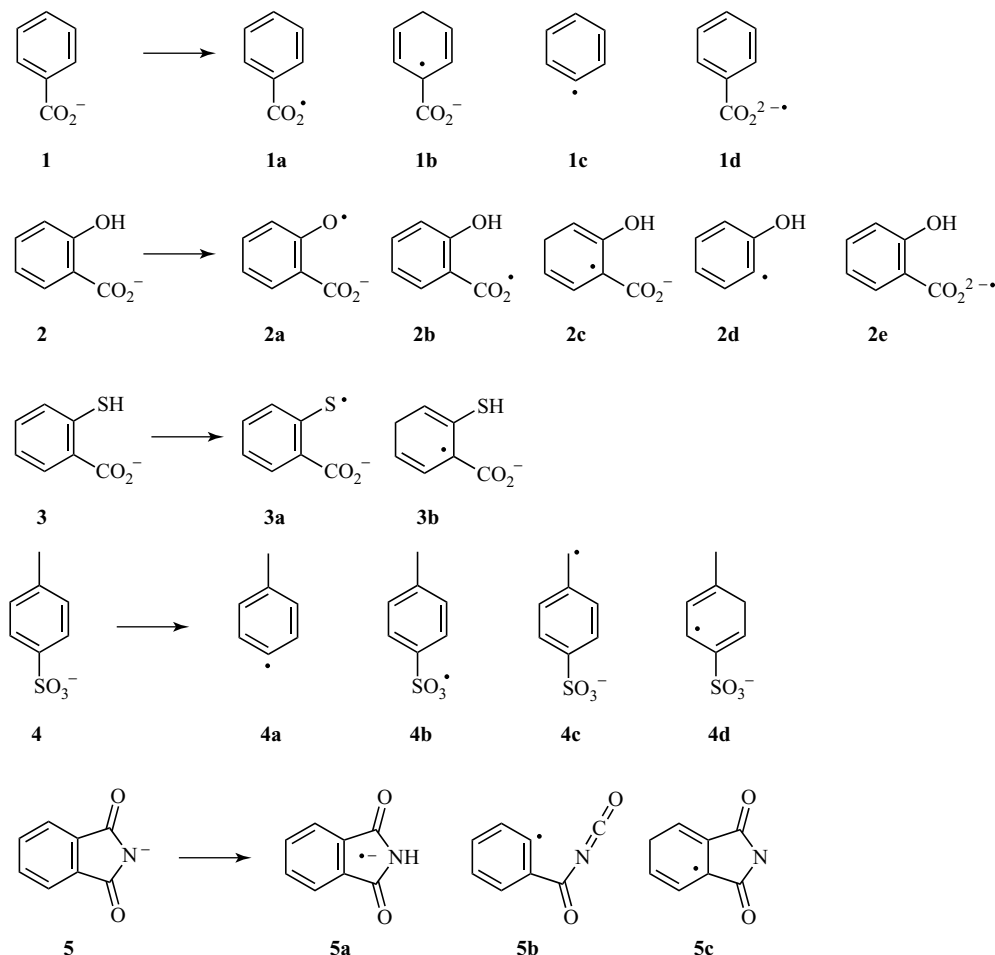
Mass spectrometry data suggest the occurrence of both N–S and S–C scission in this anion, as there are stable products, such as $(CF_3)_2SO_2$, imidazolium cations 2-substituted by $CF_3SO_2^-$ and $TfNH$ -groups,^{82,85} and $TfNH$ adducts of tetraalkylammonium cations,⁹¹ all of which can be explained only through the occurrence of this scission. According to Table 2, the S–C dissociation energy for the $CF_3SO_2\cdot$ and $CF_3SO_3\cdot$ radical are comparable, and both are chemically unstable, undergoing reaction (23b) that accounts for the radiolytic generation of sulfite.⁸⁹ The fragmentation of NTf_2^- is likely to involve electronically excited anion⁸⁴:



4 AROMATIC ANIONS

Given the propensity for RB^- anions to fragment on neutralization, is it possible to stabilize the intermediate radical $A^\cdot$ by π -conjugation? Theoretical calculations^{84,88} indicate that reaction (23a) is least exothermic for monocarboxylated benzenes, such as benzoic (**1** in Scheme 3) and (thio)salicylic acids (**2** and **3**).

Irradiated tetraalkylphosphonium benzoate yields radical **1a** (Scheme 3) that accounts for ~20% of the total radical yield, as determined by EPR spectroscopy.⁸⁴ There is also a weak EPR signal from radical **1b**, but no radical **1c** (generated via reaction 23) is observed. In crystalline tetrabutylammonium benzoate, the lines of radical **1c** are superimposed on the resonance line of radical **1a**. When the same material is quenched from a melt at 77 K, there are resonance lines of radical **1d**. It appears that benzoate serves not only as a hole scavenger (yielding radical **1a**) but also as an electron and H-atom acceptor (yielding radicals **1d** and **1b**, respectively). Neither one of these reaction pathways results in the fragmentation of the anion. In the salicylate IL, there are lines from radicals **2a** and **2b**, with radical **2b** accounting for ~40% of the total radical yield. The phenoxyl radical **2a** decays at 200 K, whereas radical **2b** persists to 220 K; at intermediate temperatures, the narrow line of radical **2b** is superimposed on the weaker lines from radical **2c**. By contrast, the EPR spectrum of irradiated methyltriocetylammmonium salicylate was dominated by radical **2a**, whereas radical **2b** was not observed; instead there were overlapping lines from radicals **2a**, **2c**, and **2d**; the latter radical is the product of reaction (23b). As radical **2a** has an EPR spectrum similar to that of radical **2e**, it is possible that the latter EPR signal originates from electron rather than hole reactions. Similar radical products were also observed for the thiosalicylate. Given these results, one might expect that sulfonated benzenes may also be resistant to fragmentation; however, radicals **4a** and **4c** were



Scheme 3 Fragmentation patterns of complex aromatic anions.

found in irradiated tosylate ILs, indicating the occurrence of reactions (23b) and (25b), and the $\text{H}^\bullet$ adduct **4d** was also observed; such $\text{H}^\bullet$ atom additions also occurred in other ILs composed of aromatic anions.

As both the dicyanamide and bistriflimide yield few radical fragments in radiolysis of the corresponding ILs, we conjectured that combining the $>\text{N}^-$ group with an aromatic π -system may yield hydrophobic anions that are particularly resistant to radiolysis. Phthalimide (**5**) is the simplest such anion. Irradiation of sodium phthalimide produced the protonated form $\text{HA}^{\bullet-}$ (radical **5a**) of the dianion (formed via reaction 4a) and radicals **5c** and **5b** (the latter is formed by ring-opening in the oxidized phthalimide). The EPR spectra for phthalimide ILs exhibit the narrow line of radical **5a** that

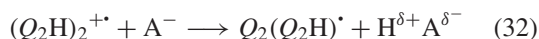
accounts for 20–35% the total radical yield. Above 150 K, there are also weak lines due to radical **5c**. In these ILs, there is no evidence for the occurrence of radical **5b**. Thus, the phthalimide provides another example of a radiation-resistant anion.

To sum up this exposition on anion chemistry, the extent of anion fragmentation greatly varies between ILs. The least stable anions are aliphatic carboxylates, aryl- and alkyl- sulfonates, alkylsulfates, and dialkylphosphates—as well as their fluorinated derivatives. Among the fluorinated sulfonates, only the smallest anion, TfO^- , is relatively stable; longer chain anions are readily defluorinated. The fragmentation also occurs for small inorganic anions, such as nitrate and tetracyanoborate. Nevertheless, there are exceptions to this general rule.

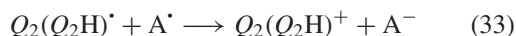
The first exceptional class of anions is the benzoate and its oxo- and thiooxo- derivatives, and the second exceptional class consists of imides (there could be more such classes). The apparent reason for the imide stability is that these anions do not belong to the RB^- class, so their radicals *cannot* undergo reaction (23b). The corresponding N-centered radicals appear to be unreactive toward the constituent cations and so decay by back recombination. For dicyanamide, this N-centered radical undergoes additional stabilization via reaction (8b). While oxidative fragmentation is suppressed for these imides, the phthalimide and succinimide readily trap the electrons and react with $H^\cdot$ atoms.

5 CATION CHEMISTRY

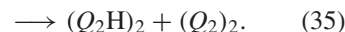
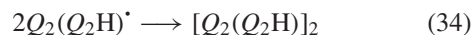
For aliphatic cations, the redox chemistry is simple: the ionization of such cations results in the formation of H-loss $R'(C^+)$ radicals (multiple examples of this kind are given elsewhere).⁷⁰ However, aromatic cations exhibit more complex and interesting radical chemistry. We have already considered several types of reactions involving imidazolium cations (summarized in Scheme 2). In particular, we observed that Q_2H^+ cations can react with the electrons giving either $Q_2H^\cdot$ radicals and/or $(Q_2H)_2^{+\cdot}$ dimer radical cations. The $Q_2H^\cdot$ radicals are readily protonated to yield $Q_2H_2^{+\cdot}$ cations, whereas $(Q_2H)_2^{+\cdot}$ and $Q_2R^\cdot$ radicals (derived from Q_2R^+ cations) are not protonated. The eventual fate of the $(Q_2H)_2^{+\cdot}$ is presently unclear; we have suggested that this radical cation decays by recombination (reaction 9) or proton transfer reaction (32),



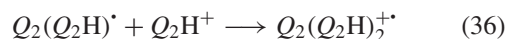
yielding the Q_2 -substituted 2-imidazolyl radical.^{62,86} This radical could be the intermediate in the oligomerization of the imidazolium cations (under mildly reductive conditions) leading to deterioration of IL properties. The $Q_2(Q_2H)^\cdot$ radical can recombine with $A^\cdot$ (or $A_2^{\cdot-}$), yielding the asymmetric dimer cation $Q_2(Q_2H)^+$ (which can also be generated via reaction (2a)),



and two such $Q_2(Q_2H)^\cdot$ radicals can either combine to form a tetramer or they can disproportionate to yield $(Q_2)_2$ (which can also be generated via reactions 1 and 2)



Thus, the same products can be generated via the radical and carbene chemistry.⁶² Theoretical considerations also suggest that the $Q_2(Q_2H)^\cdot$ radical can react with the parent cation,



to yield trimer radical cation $Q_2(Q_2H)_2^{+\cdot}$, which, in turn, can recombine yielding the $Q_2(Q_2H)^+$ or neutral trimer $Q_2(Q_2H)_2$. The C(2)–C(2) conjugation cannot extend over the tetramer, owing to steric hindrance in the resulting oligomers.⁶²

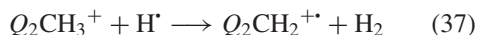
Nuclear magnetic resonance (NMR) provides the most direct structural information on the products formed in the ILs.^{56,62} The calculated proton chemical shifts ($\delta(^1H)$) for the ring protons in C_1mim^+ are ~ 8 ppm for (hereafter, all chemical shifts are given vs tetramethylsilane). In the corresponding $(Q_2H)_2$ dimer, owing to the loss of the aromaticity, the H(2) and H(4,5) protons exhibit $\delta(^1H)$ 4.2 and 5.8–6 ppm, respectively. 1H NMR spectroscopy⁵⁶ of electrochemically degraded $C_4mim BF_4$ does reveal a new set of protons with $\delta(^1H) \approx 5.7$ ppm that are the signature of the neutral oligomers. The estimated carbon-13 chemical shifts for C(4,5) in the $(Q_2H)^+$ and $(Q_2H)_2$ are similar (120 vs 115 ppm), whereas for C(2), the chemical shift changes from 127 to 91 ppm. In ^{13}C NMR spectra taken before the electrolysis of $C_4mim BF_4$, there are lines by C(2) and C(4,5) of the parent cation with $\delta(^{13}C) \sim 134$ and 120 ppm, respectively. After the electrolysis, these two peaks disappear, whereas three new peaks in the 80–95 ppm region appear in the cathodic liquid. These resonance lines are clearly from the *reduced* carbon-2 in (several) neutral oligomers.

While such C(2)–C(2) bonding reactions are prominent in the cathodic fluid, it is not yet clear that the oligomerization of this type is important in radiolytic and photolytic decomposition of the ILs.⁸⁶ The dimer species were observed in the mass spectra of irradiated imidazolium ILs,

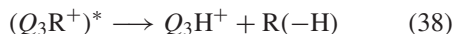
along with several other products that can be considered as the products of cross recombination of various radicals discussed in this article.⁸² The radiolytic yields for decomposition of the cations were ~ 2.8 per 100 eV for C₄mim NTf₂ and ~ 3.7 per 100 eV for C₄mim TfO, respectively.⁸² During this decomposition, ~ 0.26 molecules of H₂ per 100 eV⁹² were generated, indicating considerable loss of hydrogens, primarily from the alkyl arms of the substituted imidazolium cations.

Owing to the formation of radiolytic products, the viscosity of the irradiated IL samples increases considerably.^{47,86} The NMR spectra of C₄mim TfO and C₅mim NTf₂ exposed to 6–8 MGy indicate $\sim 30\%$ loss of α - and β -hydrogens from their long arms. Concomitant with these changes is the appearance of new lines in the ¹³C NMR spectra, at ~ 1 – 10% of the cation concentration. Cross recombination of R'(C⁺) radicals and polymerization of olefinic products of their disproportionation would yield products exhibiting such ¹H and ¹³C NMR spectra. Bridging through the alkyl arms is also suggested by mass spectrometry: there is a diffuse continuum of mass peaks centered at $m/z 670 \pm 300$, stretching out to $m/z 1700$, and accounting for 95% of the total ion count. The yield of the polymer in C₄mim TfO was ~ 0.23 monomer units per 100 eV, which is comparable to the H₂ yield. This behavior is clearly different from electrochemical reduction, where the oligomerization is driven by the C(2)–C(2) condensation. This difference is readily accounted for by the more energetic nature of radiolysis, in which the R'(C⁺) radicals can be formed.

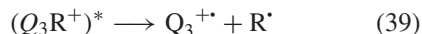
Apart from the reactions that are induced by radiolytic or electrochemical reduction of the imidazolium cations, free radicals derived from the cations can be generated via secondary radical reactions and reactions with the products of carbene chemistry (Section 1). In the case of 2-alkyl-substituted imidazolium cations Q₂R⁺, steric hindrance inhibits C(2)-addition reactions, and abstraction takes place, for example:



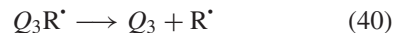
Such reactions do not exhaust the richness of radical chemistry of imidazolium cations. Excitation of the cation may involve N–C cleavage in the excited state of the cation



with the formation of an 1-ene (such reactions were observed in the gas phase)⁸⁶ or homolytic dissociation

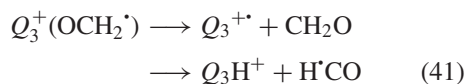


A similar reaction may also occur in the ground or excited states of the 2-imidazolyl radical:



Reaction (38) is a C–N bond scission reaction (39) concerted with H transfer from the leaving group. Irradiation of 1,3-di(*tert*-butyl)imidazolium tetrafluoroborate produces two radicals: Q₂H[•] and Q₃CHMe₂[•]. The latter radical is also observed in radiolysis of 1,3-di(*iso*-propyl)imidazolium tetrafluoroborate. When the irradiated sample of 1,3-di(*tert*-butyl)imidazolium tetrafluoroborate is warmed above 125 K, the [•]CMe₃ gradually appears (together with a much weaker signal from Q₂H₂⁺⁺), whereas the signal from Q₂H[•] gradually disappears. This behavior provides evidence for reaction (40). In the gas phase, collisionally activated imidazolium cations lose their aliphatic arms through reaction (38). Reaction (38) requires less activation than reaction (39). For example, for C₂mim⁺, the corresponding energy barriers are 1.17 and 4.4 eV.⁸⁶ For reaction (40), the dissociation energy of the N–CH₃ bond is only 77 meV, even for 1,3-dimethyl-2-imidazolyl, that is, the Q₃R[•] radicals are thermodynamically unstable. The alkyl substitution at C_α further reduces this energy, facilitating reaction (40). Further weakening of the N–R bond can be achieved by replacing the alkyl arm with the alkoxy arm. For 1,3-dimethoxy-2-imidazolyl, reaction (40) is *exergonic* by 1.06 eV, whereas reactions (38) and (39) are endergonic by 1.29 and 2.36 eV, respectively. These estimates suggest the ease of losing the N-methoxy arms. Irradiation of 1,3-dimethoxy-imidazolium hexafluorophosphate and 2-methyl-1,3-dimethoxy-imidazolium bistriflimide yields the formyl and hydroxymethyl radicals. The latter is generated via rearrangement of the leaving MeO[•] radical that can be formed either via reaction (39) or (40). The formation of the formyl radical and the absence of the Q₃⁺ (OCH₂[•]) radical (generated in reaction 5) can be accounted for by energetics: our calculations indicate that the Q₃⁺ (OCH₂[•]) radical would be

unstable,



decaying to yield the formyl radical.⁸⁶

6 CONCLUDING REMARKS

With so many reactive intermediates generated in the “ionization of the ions,” it is inevitable that these react with many solutes in the ILs generating a great variety of secondary radicals. Many of such reactions are common reactions of electrons, holes, and small radicals ($\text{H}\cdot$, $\text{Me}\cdot$) that also occur in many solvents. However, there are also important differences. Because the EDE of the constituent anions tends to be low and the electron affinity of the constituent aromatic cations is relatively high, in such aromatic ILs, electron (and energy) transfer reactions involving these primary species with many solutes are disfavored. A spectacular example of this behavior concerns the trialkylphosphates, $(\text{RO})_3\text{PO}$.⁷⁰ Tributylphosphate (TBP) is the common solvent modifier and the extracting agent in spent nuclear fuel processing. For example, in PUREX (Plutonium-URanium EXtraction) process, 30 wt% TBP in dodecane is used to extract U(VI) and Pu(IV) from the nitric acid raffinate.⁹³ In irradiated alkane solvents, the excess electron rapidly reacts with the TBP, yielding $\text{R}\cdot + (\text{RO})_2\text{PO}_2^-$. This DEA reaction leads to the formation of dibutylphosphates that extract trivalent lanthanide radionuclides into the organic phase, undermining separations selectivity. However, even when 10–40 wt% of trimethylphosphate is added to imidazolium IL, the prompt yield of methyl radicals is low, suggesting that most of the “electrons” react with the constituent cations rather than the solute.⁷⁰ High radiation resistance of another class of common extracting agents, crown ethers, in the ILs has also been demonstrated.⁹⁴ It appears that aromatic IL solvents may exert significant radioprotective effect on many of the solutes and cosolvents used in such nuclear separations.

We hope that this article will stimulate more interest in free radical chemistry, radiation chemistry, photochemistry, and electrochemistry of the new “salt of the Earth”—IL.

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Radical Cation/Anion and Neutral Radicals: A Comparison

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1 INTRODUCTION: RADICAL CATION/ANION AND NEUTRAL RADICALS: A COMPARISON

Over the past several decades, radicals and radical ions have emerged as an important class of reactive species. Recognition of their role as potential intermediates in numerous organic and bio-organic reactions and development of several new synthetic methods based on their chemistry has attracted significant attention. This article explores parallels between radical and the equivalent radical ion reactions; in cases where available data facilitates comparison. Generally, it is shown that the results of one class extrapolate to the other in a useful way. However, as is seen, the investigator should exercise extreme caution when inferring reactivity trends for a radical ion from a radical. A seemingly subtle molecular change such as introduction of charge can have a profound impact on structure, stability, and reactivity of a molecule.

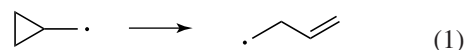
2 CYCLOPROPANE RADICAL CATIONS AND ANIONS

2.1 Cyclopropylcarbinyl $\rightarrow$ Homoallyl Rearrangements

2.1.1 Radical Ion Probes/Clocks Based on the Cyclopropylcarbinyl $\rightarrow$ Homoallyl Rearrangement

Unimolecular rearrangements based on cyclopropane chemistry are useful from a mechanistic

perspective (i.e., as mechanistic probes or radical ion clocks) (see **Radical Kinetics and Clocks**). The mechanistic probe approach is essentially an intramolecular trapping experiment. A structural feature (e.g., a cyclopropyl group) is incorporated into the substrate that, in principle, will lead to a rearrangement uniquely ascribed to a radical or radical ion intermediate. Historically, the use of a cyclopropyl group in such an experiment is predicated on the expectation that the relief of ring strain will drive the rearrangement. The prototypical example of such a process, the cyclopropylcarbinyl $\rightarrow$ homoallyl neutral radical rearrangement (1) is fast ($k \approx 10^8 \text{ s}^{-1}$) and essentially irreversible.¹



The mechanistic probe approach is founded on two critical assumptions: (i) structurally rearranged products arise exclusively from the single-electron transfer (SET) pathway and (ii) the rearrangement is rapid and (preferably) irreversible. Although the kinetics (and mechanism) of unimolecular rearrangements of neutral radicals have been extensively studied, until recently, very little was actually known regarding analogous rearrangement of radical ions. Frequently, it was (and is still) assumed that structural features that lead to facile rearrangement of neutral free radicals would do the same for radical ions.

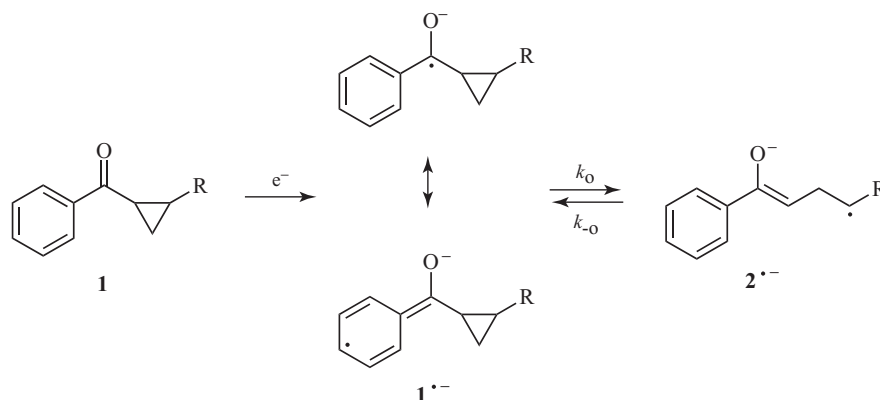
2.1.2 Cyclopropylcarbinyl $\rightarrow$ Homoallyl-Type Rearrangements of Radical Anions Generated from Aromatic Ketones

In 1990, we reported our first results pertaining to the chemistry of radical anions generated from substituted phenyl cyclopropyl ketones (Scheme 1).² For R = alkyl or hydrogen, ring opening of $1^{\bullet-}$ was found to be very slow, and reversible with an equilibrium constant favoring the ring-closed radical anion ($k_o < 10 \text{ s}^{-1}$ and $K_{eq} = k_o/k_{-o} = 10^{-8}$ for R = H).^{2,3} These results suggested that there were two important considerations in the design of radical ion probes based on the cyclopropylcarbinyl $\rightarrow$ homoallyl rearrangement: (i) ring strain (the relief of which favors ring opening) and (ii) resonance energy (which may help or hinder rearrangement, depending on the specific system). Thus for $1^{\bullet-}$ (R = H or alkyl), ring opening is disfavored (kinetically and thermodynamically) because there is a loss of resonance energy associated with ring opening (the ring-closed radical anion is highly delocalized). Placement of radical-stabilizing substituents (R = phenyl or vinyl) on the cyclopropyl group partially compensates for this loss of resonance energy, and ring opening becomes more favorable ($k_o \approx 10^6\text{--}10^7 \text{ s}^{-1}$ for R = CH=CH₂ or Ph).⁴

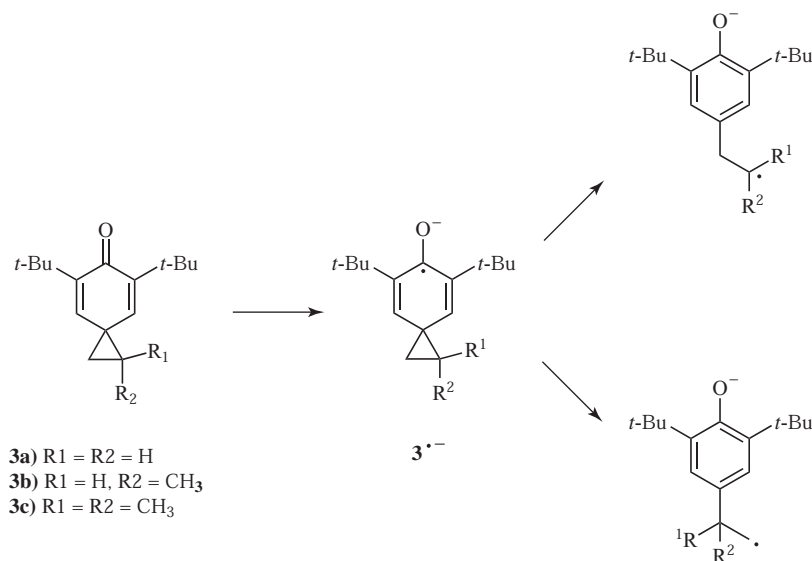
On the basis of this reasoning, spirocyclohexadienones **3** emerged as particularly attractive substrates because ring opening of the corresponding radical ions would be driven by both the relief of cyclopropane ring strain and an increase in resonance energy, because of the formation of

an aromatic ring. Both the direct and indirect (mediated) electrochemistry of **3a-c** were characterized by rate limiting electron transfer (suggesting a rate constant for ring opening $\geq 10^7 \text{ s}^{-1}$ for their corresponding radical anions). From the indirect electrochemistry, rate constants for electron transfer between **3a-c** and a series of aromatic radical anions were measured, and from these results, reduction potentials and reorganization energies were derived using Marcus theory. The value of the symmetry coefficient (α , derived from the direct electrochemistry) and reorganization energy (λ , derived from the Marcus treatment) are consistent with a radical anion which has a discrete lifetime (i.e., electron transfer and ring opening are not concerted).⁵

For the unsymmetrical radical anions, ring opening (Scheme 2) occurs with modest selectivity favoring formation of the more substituted (stable) radical anion (in a 10:1 ratio for $3c^{\bullet-}$ and a 1.2:1 ratio for $3b^{\bullet-}$).⁵ The observed regiochemistry for ring opening is very similar to that observed for the 2,2-dimethylcyclopropylcarbinyl and 1-methylcyclopropylcarbinyl neutral free radicals (where the ratios are 6.7:1 and 1.2:1, respectively).^{1a} These neutral radicals rearrange with rate constants $>10^8 \text{ s}^{-1}$, and it appears likely that rate constants for ring opening of radical anions $3b^{\bullet-}$ and $3c^{\bullet-}$ are of the same order of magnitude. Radical anion $4^{\bullet-}$ ((2)⁶ reproduced by permission of the American Chemical Society) was studied by direct electrochemical techniques. Because of extended conjugation in the ring-closed form (compared to spirocyclohexadienones **3**⁻), the rate constant for

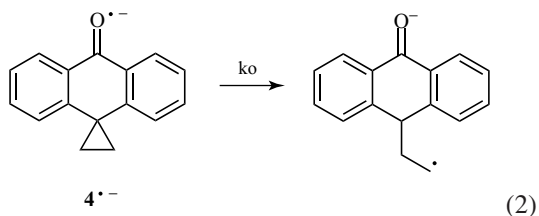


Scheme 1 Phenyl cyclopropyl ketones radical anion ring opening. [Reprinted with permission from Ref. 2. Copyright 1990 American Chemical Society.]



Scheme 2 Unsymmetrical radical anions ring opening.

ring opening of $4^{\bullet-}$ is sufficiently slow that it can be measured directly by cyclic voltammetry (CV). In dimethylformamide (DMF), $k_o = 140 \text{ s}^{-1}$.⁶



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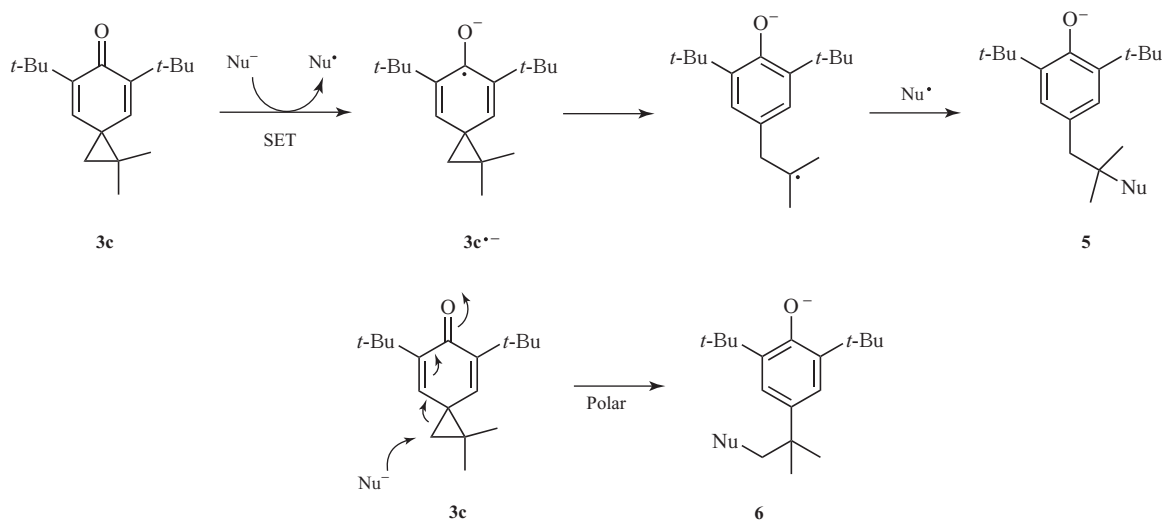
Because of the regiochemistry of radical anion ring opening, spirocyclohexadienone **3c** emerged as a particularly attractive probe for SET because it allows clear experimental distinction between products formed via SET as opposed to a polar pathway (Scheme 3). Ring opening via a polar pathway (essentially an S_N2 reaction) would result in product(s) where the nucleophile was attached to the least-substituted carbon of the cyclopropyl group **6**; an SET process would yield a product where the nucleophile was attached to the more substituted carbon **5**. In this manner, it was shown that Grignard ($RMgX$) and alkyllithium reagents (RLi) react with **3c** mainly via an SET pathway.

The results pertaining to the mechanism for reaction of **3c** with dialkyl lithium cuprates (R_2CuLi) were ambiguous, and could be accounted for by either an SET or a polar pathway. However, one limitation associated with the use of **3c** was discovered.⁷ In protic solvents (PhS^- as nucleophile) reaction of **3c** was found to involve a rare $S_N2(C+)$ mechanism.⁸

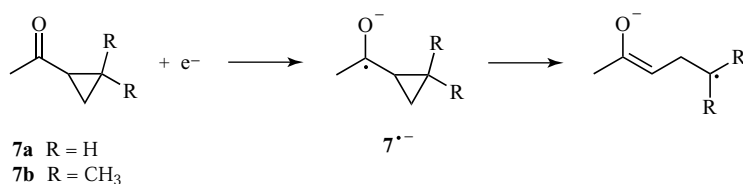
2.1.3 Cyclopropylcarbinyll $\rightarrow$ Homoallyl-Type Rearrangements of Radical Anions Generated from Aliphatic Ketones

Radical anions derived from **7a** and **7b** undergo cyclopropane ring opening, slightly favoring the 3° distonic radical anion in the case of **7b^{•-}** (Scheme 4). Electron transfer was found to be the rate limiting step regardless of whether the reduction was carried out directly (CV) or indirectly (homogeneous redox catalysis) suggesting a rate constant for ring opening $\geq 10^7 \text{ s}^{-1}$. (The value of α derived from the direct electrochemistry suggested these radical ions do have a discrete lifetime).⁹

Because the kinetics of both the direct and mediated reduction of **7a** and **7b** involves rate limiting electron transfer, the rate constant for ring opening could not be determined. However, it was reasoned that the corresponding cyclobutyl derivative would undergo ring opening at a significantly lower rate,

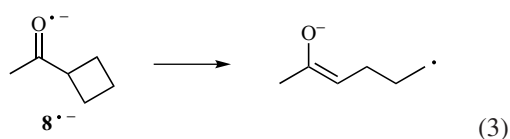


Scheme 3 Cyclopropane ring opening via the polar pathway.



Scheme 4 Ketyl radical anions ring opening. [Reprinted with permission from Ref. 9. Copyright 2002 American Chemical Society.]

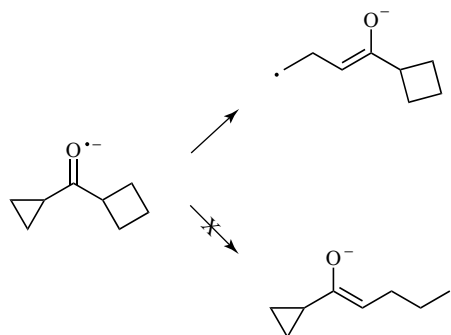
and that ring opening might be the rate limiting step for this system. In fact, the rate constant for ring opening ((3) Reprinted with permission from Ref. 6. Copyright 2005 American Chemical Society.) of $8^{\bullet-}$ ($k = 8 \times 10^3 \text{ s}^{-1}$) was found to be similar to that of the cyclobutylcarbiny (neutral) radical.⁹



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When this cyclobutyl-based rearrangement was used as an intramolecular clock to estimate the rate constant for cyclopropyl ring opening via competition experiments (Scheme 5), only a cyclopropane ring-opened product was detected.⁹

Compound $9^{\bullet-}$ undergoes ring opening according to ((4) Reprinted with permission from Ref. 6.



Scheme 5 Intramolecular competition between cyclopropane and cyclobutane radical anion ring opening. [Reprinted with permission from Ref. 9. Copyright 2002 American Chemical Society.]

Copyright 2005 American Chemical Society.). The exocyclic double bond significantly enhances the rate of ring opening (For $R = \text{phenyl}$, an enhancement $>10^3$ was estimated).⁶ This enhanced rate is likely attributable to the increase in ring

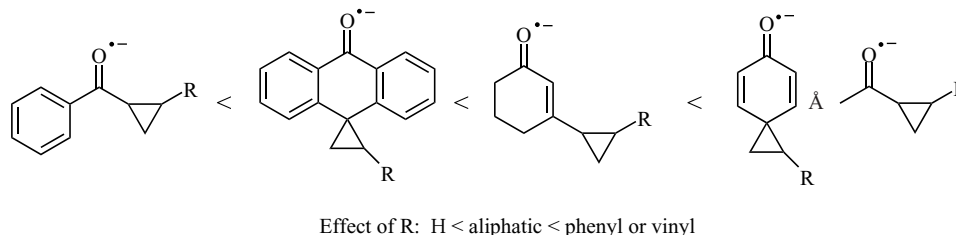
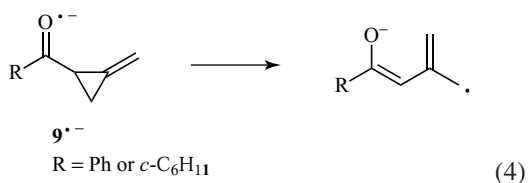


Figure 1 Rates of cyclopropylcarbinyll homoallyl-type rearrangements of ketyl radical anions. [Reprinted with permission from Ref. 6. Copyright 2005 American Chemical Society.]

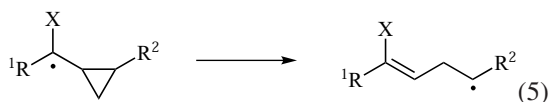
strain resulting from the double bond exocyclic to the cyclopropane ring, rather than to resonance stabilization (the rupturing C–C bond is orthogonal to the π -system of the exocyclic double bond).



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2.1.4 Cyclopropylcarbinyll → Homoallyl-Type Rearrangements: Structure/Reactivity Trends

Sufficient data is now available to allow a comparison between cyclopropylcarbinyll → homoallyl-type rearrangements of neutral radicals and radical anions generated from ketones ((5)⁶ reproduced by permission of the American Chemical Society). There are certain similarities: (i) radical-stabilizing groups at the α -carbon (R¹) decelerate the ring opening process and (ii) radical-stabilizing substituents on the cyclopropyl group (R²) accelerate the reaction. For both types of processes, relief of cyclopropyl ring strain is not the sole mitigating factor associated with the rates of these rearrangements. Resonance energy (spin delocalization) in the ring-closed versus ring-opened form must also be considered.⁶

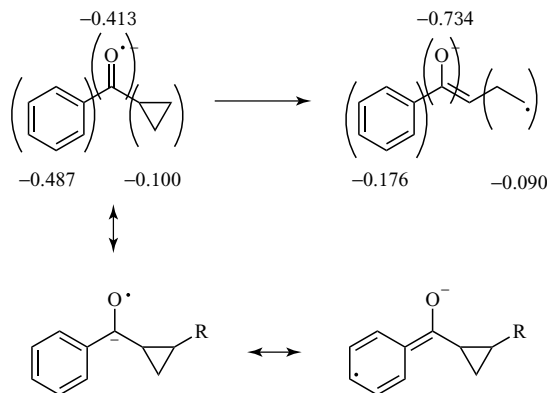


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However, there is an important difference: for radical anions, charge delocalization is at least as important as, and perhaps more important than, spin delocalization (*vide infra*). This interplay between charge and spin delocalization in the ring-closed and ring-opened (distonic) radical anions leads to the reactivity order summarized in Figure 1.⁶

For radical anions generated from aromatic ketones (aromatic ketyls), ring opening of the structurally related neutral (benzylic) radical is much faster. For aliphatic ketones, it is the other way around. Unquestionably, the difference is the ability of the aromatic ring to stabilize the negative charge via resonance (Scheme 6); the numbers refer to Mulliken charges calculated by density functional theory). Clearly, this stabilization of charge is responsible for the low reactivity and thermodynamic stability of the aromatic ketyls.⁹

In contrast, these results show aliphatic ketyls are at least as reactive as (and likely more reactive than) alkyl radicals in β -scission-type processes, despite the fact that the former are



Scheme 6 Aromatic ketyl radical anion with calculated Mulliken charges.

thermodynamically much more stable (by as much as 27 kcal mol⁻¹). Essentially, the O⁻ group, being a potent electron donor, is able to stabilize a radical center. The reason that aliphatic ketyls undergo such rapid rearrangement is that the O⁻ group also stabilizes the double bond in the ring-opened form, possibly to an even greater extent. (An equivalent and indistinguishable argument is that the O⁻ is stabilized by an adjacent radical center in the ring-closed form, and by a double bond in the ring-opened form.) In essence, these systems undergo ring opening at what must be rates comparable to the cyclopropylcarbinyl → homoallyl neutral radical rearrangement because the reactants, products, and transition state are all stabilized by the O⁻ substituent.

Qualitatively and quantitatively, rate constants (k_o) for ring opening of the radical anions can be rationalized on the basis of the thermodynamic stability of the radical anion (which is related to the formal reduction potential of the ketone), the ability of substituents on the cyclopropyl group to stabilize the radical portion of the distonic radical anion (reflected by the C–C bond strength of the cyclopropane), and the stability of the enolate portion of the distonic radical anion (related to the pK_a of the corresponding ketone). A thermodynamic

cycle for estimating the driving force (ΔG°) for ring opening was developed and allowing the nature of the activation/driving force relationship for these rearrangements to be probed. Figure 2 presents a plot of $\log(k_o)$ versus ΔG° for cyclopropylcarbinyl → homoallyl-type rearrangements of both ketyl radical anions and neutral free radicals. Despite the differing structure/reactivity trends discussed above, it is noteworthy that the activation/driving force trends for ring opening of neutral free radicals parallel those of radical anions, although at comparable driving force, ring opening of the radical anions is generally slower.¹⁰

Savéant has developed a theory pertaining to radical anion fragmentations which occur in a stepwise manner (e.g., $R-X + e^- \rightarrow R-X^{\cdot-} \rightarrow R^\cdot + X^-$) that is applicable (6), where $\Delta G^\ddagger_o$ refers to the intrinsic barrier (activation energy at zero driving force) and accounts for the reorganization of solvent and/or counter ion (external reorganization), or changes in the molecule itself (internal reorganization), which are required in order to achieve the transition state; k_B , h , R , and T have their usual meanings.¹¹ When applied to the data in Figure 2, several interesting conclusions emerge. For the radical anions, the intrinsic barrier (12 kcal mol⁻¹) is only slightly higher than that for the neutral free radicals (10 kcal mol⁻¹).

$$\log(k_o) = \log\left(\frac{k_B T}{h}\right) - \frac{\Delta G^\ddagger_o}{2.303RT} \left(1 + \frac{\Delta G^\circ}{4\Delta G^\ddagger_o}\right)^2 \quad (6)$$

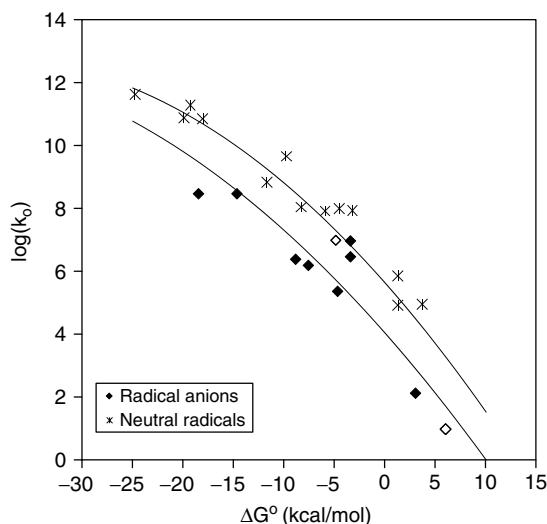
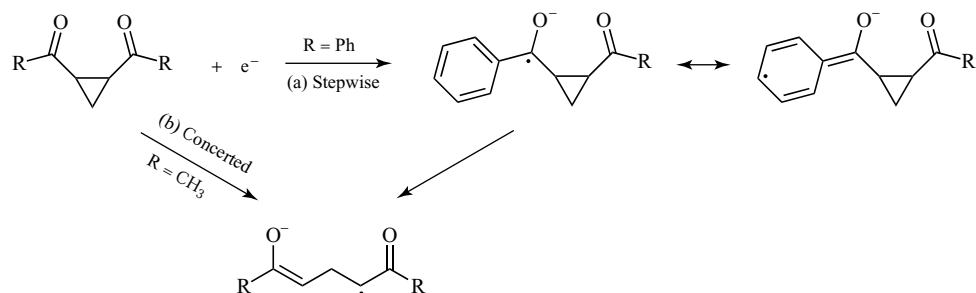


Figure 2 Structure/reactivity relationships for the cyclopropylcarbinyl → homoallyl-type rearrangement of radical anions generated from carbonyl compounds and neutral free radical (unshaded data points are based on estimates of k_o).

Assuming that the bond breaking/making contributions to the intrinsic barrier (i.e., internal reorganization energy) are similar for both classes of paramagnetic intermediates, the small difference in rate is attributable to the contribution of a minor, circa 2 kcal mol⁻¹, solvent reorganization component for the radical anion ring opening. This conclusion makes sense because for these ring openings, the negative charge is closely associated with the electronegative oxygen atom in the ring-closed and ring-opened forms, and a major reorganization of solvent is not needed to stabilize the negative charge in the progression from reactant → transition state → product. In contrast, higher intrinsic barriers (circa 16 kcal mol⁻¹) are found for radical anion fragmentations where the negative charge migrates significantly, for example, $\text{Ph}(\text{C}=\text{O}^{\cdot-})\text{CH}_2\text{X} \rightarrow \text{Ph}(\text{C}=\text{O})\text{CH}_2^\cdot + \text{X}^-$.¹²



Scheme 7 Stepwise and concerted dissociative electron transfer. [Reprinted with permission from Ref. 14. Copyright 1998 American Chemical Society.]

There has been a great deal of interest in the current literature in the mechanistic details of dissociative electron transfer (DET), that is, electron transfer that results in bond cleavage. The radical anion ring openings discussed thus far are examples of this phenomenon, and until recently, were all believed to occur in a stepwise manner (Scheme 7, path a). However, it now appears that certain 1,2-disubstituted cyclopropanes undergo concerted, DET (i.e., electron transfer occurs simultaneously with bond cleavage, path b, Scheme 7). The fact that the process is stepwise when $R = \text{Ph}$ as opposed to concerted when $R = \text{CH}_3$ is readily accounted for by resonance stabilization provided by the phenyl group in the former.¹³

2.2 Cyclopropyl Substituted Radical Cation Ring Openings

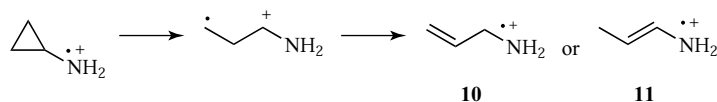
2.2.1 Aliphatic N-Cyclopropylamine Radical Cations: Structure and Mechanism of Cyclopropane Ring Opening

Compared to the chemistry of radical anion and neutral radical analogs, our understanding of reactivity of cyclopropane substituted radical cations is in its infancy. Kinetic data is virtually non-existent for aliphatic amine radical cations.

Theoretical and experimental studies demonstrate cyclopropylamine radical cation undergoes barrierless ring openings in both gas and solution (Freon) phase.¹⁵ The distonic ring-opened radical cation isomerizes via successive 1,2-hydrogen migration (Scheme 8).^{15,16} Ring-opened cyclopropylamine radical cations preferentially form the radical cation of allylamine **10**.

Notably, ring-opening products undergo further dissociative steps to achieve more stable structures in the gas phase, but not in solution. This difference is presumably attributable to stabilizing interactions with solvent.^{14,15a} Cyclopropylamine radical cations pass through a perpendicular transition state while ring opening occurs. Extremely facile ring opening prevents the molecule from rearranging to the bisected conformation before ring opening. Computational analysis of the relative rates of ring opening for the cyclopropoxyl radical, cyclopropylcarbinyl radical, and cyclopropylaminyl radical cation confirmed barrierless radical cation ring opening is most facile, followed by a preference for ring opening of the cyclopropoxyl radical over cyclopropylcarbinyl radical in a ratio of 3.1×10^6 to 1.^{15b}

The unique structural features of alkylcyclopropylamines likely to govern reactivity and stability were highlighted in electron spin resonance (ESR) and



Scheme 8 Ring openings of aliphatic cyclopropylamine radical cation and subsequent 1,2-hydrogen migration. [Reprinted with permission from Ref. 17. Copyright 1997, American Chemical Society.]



Figure 3 Neutral tricyclopropyl amine adopts a perpendicular conformation; structural reorganization on formation of the radical cation yields a bisected conformation.

computational studies by de Meijere and coworkers. In *N,N*-diisopropyl-*N*-cyclopropylamine, the cyclopropyl group adopts a perpendicular geometry and the molecule has C–N–C bond angles of about 113.3° because the cyclopropyl group prefers to accept electron density into its lowest unoccupied molecular orbital (LUMO).¹⁸ In triisopropylamine, replacement of isopropyl groups with cyclopropanes, results in significant increases in the ionization energy for the radical cation. The ionization energy increased from a value of 7.18 eV for triisopropylamine to 8.44 eV for tricyclopropylamine, as determined experimentally. A similar increase from 7.13 to 8.26 eV was determined by computational work.¹⁸ Generally, trialkylamine radical cations prefer planar orientations that facilitate donation of electron density to the electron deficient nitrogen center.¹⁹ Neutral tricyclopropylamine is significantly more pyramidal than the corresponding radical cation. The cyclopropyl groups in tricyclopropylamine radical cations are in a bisected conformation relative to the N's partially filled orbital. A large structural reorganization from the perpendicular conformation of the neutral analog is required to form the radical cation (Figure 3).^{18,19}

Alkyl substituted analogs typically exhibit conformations where the singly occupied N orbital is eclipsed by a H from an adjacent alkyl substituent affording stabilization by delocalizing spin through hyperconjugative interactions (Figure 4).¹⁹ The preference for the bisected conformation in tricyclopropylamine radical cation means that these hyperconjugative interactions do not exist because the H on the cyclopropane is twisted about 90° from the nitrogen center into a nodal plane of the half filled p orbital.¹⁹ (In the bisected conformation, the cyclopropyl group is a potent π -electron donor.)

While there is much to be learned about the chemistry of aliphatic cyclopropylamine radical cations; it is interesting to note that (i) bi and tricyclopropylamines deviate significantly from the planarity characteristic of the corresponding trialkylamines

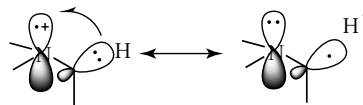


Figure 4 Hyperconjugative stabilization characteristic of aliphatic amine radical cations.

and require structural rotations on formation of the radical cation, (ii) these changes likely accompany alignment of the partially filled orbital on nitrogen with the adjacent π system of the cyclopropane, and (iii) ring opening for cyclopropylamines has a low barrier and products undergo further rearrangement in gas phase. Analogous rearrangements do not occur in solution. Taken as a whole, kinetic data available for ring opening of aliphatic cyclopropylamine radical cations comes from computational work and suggests that ring opening is concerted and extremely rapid.

2.2.2 Application: *N*-Cyclopropyl Ring Opening in Ring Expansions of Arylcyclopropanes

Cyclopropane substituted radical cation ring openings are also useful in synthesis. In nonaromatic *N*-cyclopropyl substituted radical cations, the driving force for ring opening is stability imparted by separation of the radical and cation on different atoms, as well as the relief of ring strain. Blackstock and coworkers exploited this in the study of a series of cyclopropylamines (Figure 5), generating the radical cation of the amines via photoinduced-electron transfer.¹⁷

Efficient ring opening, and product formation, was observed for **12** and **13**, although reaction of **13** was slower.¹⁷ The mechanism of these reactions proceed from the N-centered ring-closed radical cation to the ring-opened product that undergoes a subsequent 1,5-hydrogen atom shift (Scheme 9). Intramolecular hydrogen transfer was confirmed via isotopic labeling studies. Subsequent deactivation of the radical ion pair partner 1,4-dicyanobenzene radical anion (DCB^{•-}) via SET is followed by generation of a ketone product through hydrolysis of the neutral ring-opened amines during work up. With the exception of bicyclic compound **14**, these aminocyclopropane radical precursors are used as

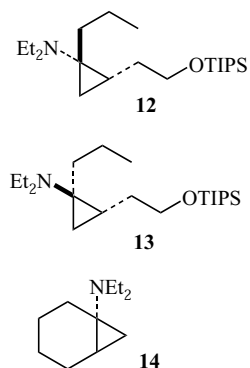


Figure 5 Structures of cyclopropylamines investigated as potential precursors to ketones. TIPS = Triisopropylsilyl.

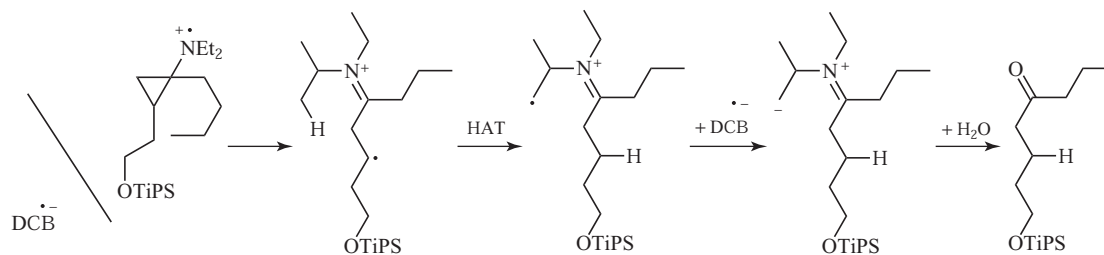
synthetic analogs of enamines, affording high yields of ketones.

2.2.3 Application: Vinyl and Siloxy Substituted Cyclopropyl Ring Opening in Ring Expansions

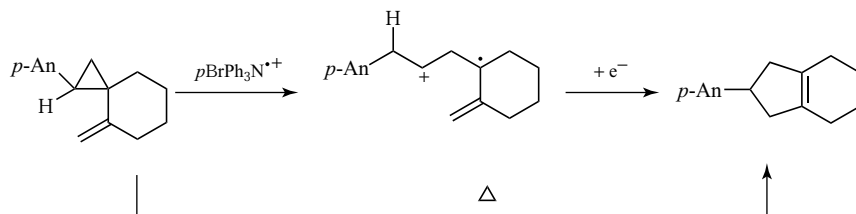
Chemically induced one electron oxidation of vinylcyclopropanes leads to radical cations that rearrange to the corresponding cyclopentene radical

cations; the rate is much greater than the comparable thermally induced vinyl cyclopropane $\rightarrow$ cyclopentene rearrangement.²⁰ Neither *cis*-1-*p*-anisyl-2-vinylcyclopropane nor *trans*-1-*p*-anisyl-2-vinylcyclopropane undergoes ring expansion to 4-*p*-anisylcyclopentene because the *s*-*trans* radical cation formed cannot ring expand. The former undergoes *cis* $\rightarrow$ *trans* isomerization. In contrast, the spiro compound forms the desired cyclopentene product via a mechanism involving ring opening of the spirocyclic vinylcyclopropane radical cation intermediate (Scheme 10). Similar to the *cis* $\rightarrow$ *trans* isomerizations, the rate of rearrangement is enhanced by SET. Half-lives of 10^{12} min compared to ≤ 1 min were observed for the thermal and SET-induced processes, respectively. SET-induced ring expansion of *cis* and *trans* 1-*p*-anisyl-2-methyl-2-prop-1-en-cyclopropane demonstrates that this chemistry is not limited to structurally rigid cyclopropanes, although it is unclear why these compounds ring expand and the *p*-anisyl-vinylcyclopropanes do not.²⁰

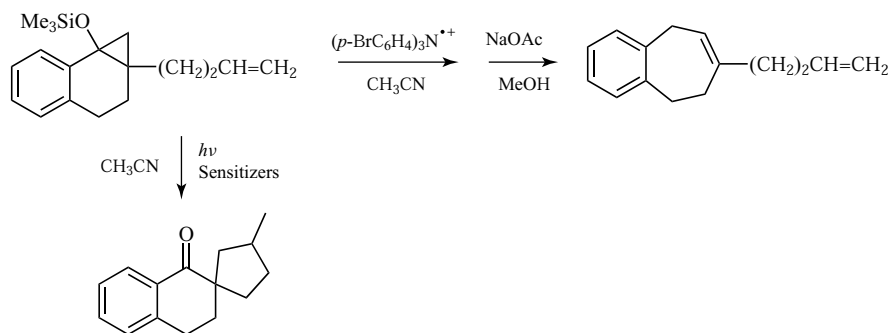
Siloxy cyclopropane radical cations are also key intermediates in synthesis of larger ring systems wherein the radical cation ring opens, without nucleophilic assistance, to a distonic radical cation, and subsequent loss of the silane group forms a β -keto radical.²¹ These β -keto radicals



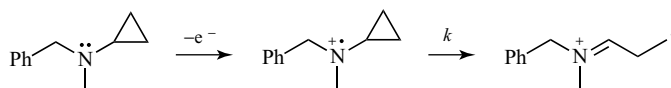
Scheme 9 Ring opening of photo-generated cyclopropylamine radical cation. [Reprinted with permission from Ref. 17. Copyright 1997 American Chemical Society.]



Scheme 10 Ring expansion via ring opening of spirocyclic vinylcyclopropane. [Reproduced with permission from Ref. 20. Copyright 1988 American Chemical Society.]



Scheme 11 Spirocyclic cyclopropane radical cation exhibits regioselectivity during ring opening as determined by mode of radical cations generation. [Reprinted with permission from Ref. 23. Copyright 2007 American Chemical Society.]

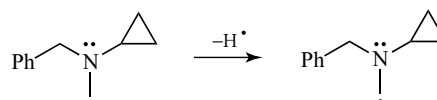


Scheme 12 SET generation of ring opening of *N*-cyclopropylbenzylamine radical cation. The ring-opened form is proposed to inhibit SET enzymes by covalent interaction with a residue in the active site. [Reproduced with permission from Ref. 25. Copyright 2006, American Chemical Society.]

have proven useful in the formation of polycycles through intramolecular addition to π systems. Transition state calculations by Mattay and coworkers on (bicyclo[4.1.0]heptan-1-yloxy)trimethylsilane determined that endocyclic bond cleavage of the cyclopropane ring occurs.²² This result supports experimental work with analogous compounds, by Hasegawa.²³ Further study of the regioselectivity of the cleavage of the bonds in these bicyclic compounds (Scheme 11) revealed that (i) photochemically induced electron transfer and chemically induced oxidation (by tri-bromophenylaminy radical cation) caused ring opening to occur via different pathways, as evidenced by observed products and (ii) the presence of a nucleophile in chemically oxidized systems enhances the ability of the radical cation to undergo desylation thus increasing reaction efficiency.²³ In addition to utility in synthesis, *N*-cyclopropyl substituted radical cations have been controversial and interesting target molecules for use as mechanistic probes and radical clocks.

2.2.4 Application: *N*-Benzyl-*N*-cyclopropylamine Radical Cation Mechanistic Inhibitors in SET Enzymes

In the late 1970s, the SET mechanism was first invoked to explain irreversible inhibition



Scheme 13 With HAT, hydrogen abstraction yields a neutral carbon-centered radical, which is not expected to ring open. [Reproduced with permission from Ref. 25. Copyright 2006, American Chemical Society.]

of *P450s* by *N*-benzyl-*N*-cyclopropylamine substrates.²⁴ The potential of this class of substrates to resolve controversy between the hydrogen atom transfer (HAT) and SET mechanisms (Schemes 12 and 13), for oxidation of tertiary amines by *P450s* and monoamine oxygenases, stimulated significant interest in mechanistic inhibitors containing cyclopropane moieties to probe for SET in enzymes.^{24b,25} The metabolism of *N*-benzyl-*N*-cyclopropylamine and the 1-methyl substituted analog show similar inhibitory behavior toward *P450* suggesting the hydrogen of the cyclopropane is not involved in inhibition; and further decreasing the probability of HAT for benzylcyclopropylamine.²⁶ Consistently low deuterium isotope effects for dealkylation of tertiary amines by *P450* provided further evidence for the SET pathway.^{27,28}

2.2.5 Application: *N*-Cyclopropylaniline Radical Cations as Mechanism-Based Inhibitors in SET Enzymes

Hanzlik and coworkers set out to demonstrate, using horse radish peroxidase (HRP), that mechanism-based inactivation and ring opening of aryl-*N*-cyclopropylamines occur exclusively through the SET pathway.²⁶ Because HRP's oxidation potential (0.75 V) is less than *cP450*'s (1.7–2.0 V); *N*-methyl-*N*-cyclopropylaniline (which is easier to oxidize) was used in lieu of *N*-methyl-*N*-cyclopropylbenzylamine.²⁶ Products arising from ring opening were detected, although the yields suggested the ring opening pathway accounts for less than 25% of *N*-methyl-*N*-cyclopropylaniline consumed in the reaction. The consumption of this substrate also followed a first order decay indicating inactivation of the enzyme is not occurring to an appreciable degree.²⁶ Radiolabeled cyclopropylaniline inhibitors (Figure 6) and radical traps were employed to determine the fate of the cyclopropyl group. In HRP, trapped products were unambiguously ascribed to SET.²⁶ Products derived from HRP oxidation of *N*-methyl-*N*-cyclopropylbenzylamines **15**, **19** suggested a unimolecular rearrangement, as different products are expected from a nucleophile-assisted ring opening.^{24b} In contrast, both *N*-methylaniline **16** and *N,N*-dimethylaniline **17** undergo deprotonation of the *N*-methyl group after SET.²⁶ In *P450* neither inhibition nor ring opening products were observed with *N*-methyl-*N*-cyclopropylanilines **18**.²⁵ Experiments with *P450* and the *N*-benzyl-*N*-cyclopropylamines produced the ring-opened metabolite of the SET pathway in 57% yield!²⁵ Interestingly, analogous investigation of *N*-methyl-*N*-cyclopropylbenzylamine was first order showing no inhibition or

ring- opened product; rather dealkylation to form *N*-cyclopropyl-*N*-benzylamine was observed.²⁵

Key to the viability of aromatic *N*-cyclopropyl substituted amines as mechanistic inhibitors is validation that (i) ring opening is competitive with other modes of decay for the radical cation, such that inhibition due to ring opening occurs with a frequency that can be easily detected relative to normal modes of catalysis and (ii) ring opening and the resultant enzymatic inhibition are irreversible processes.

2.2.6 Cyclopropane Ring Opening in Chemical Systems: *N*-Cyclopropylaniline Radical Cations

A comprehensive understanding of all factors that govern the mechanism, kinetics, and energetics of cyclopropane radical cation reactions, as well as the relative propensity of these oxidized species to decay by one pathway or another, is integral to unlocking their potential as mechanistic inhibitors, radical clocks, and photosensitizers. Recently, our group studied the ring opening of electrochemically generated *N*-methyl-*N*-cyclopropylaniline radical cations, and curiously, ring opening occurred much slower than deprotonation.²⁹ On the basis of the variation of peak potential with sweep rate and concentration, it was concluded that decay of the radical cation is first order (as expected for a ring-opening process). Notably, decay is zero order in CH₃OH, which effectively rules out the nucleophile-assisted pathway for Nu[−] = CH₃OH.²⁹ Indirect electrochemical studies using various substituted ferrocenes were performed, and in all cases, the kinetics were controlled by the chemical step (i.e., cyclopropane ring opening). These two sets of experiments enable both the oxidation potential (+0.528 V vs 0.1 M Ag⁺/Ag) and the rate constant for ring opening

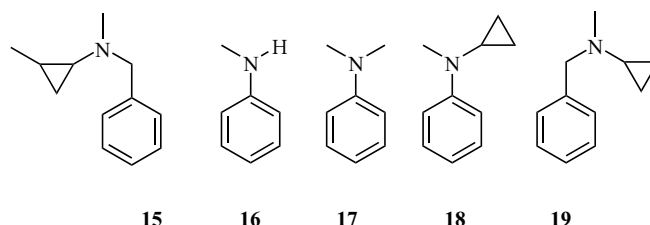
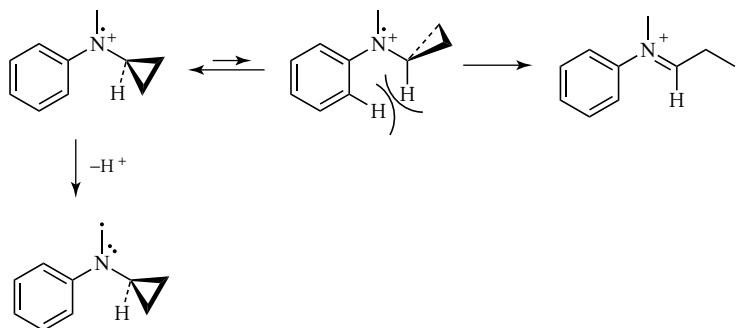


Figure 6 Structures of aryl cyclopropylamines investigated in enzymatic systems.

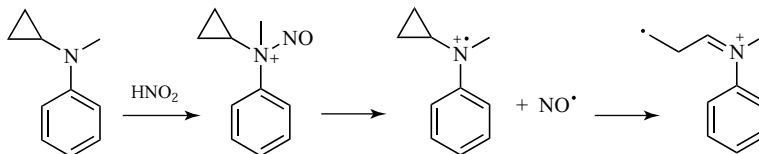
($k_o = 4.1 \times 10^4 \text{ s}^{-1}$) to be resolved.²⁹ Laser flash photolysis (LFP) experiments (direct photoionization at 266 nm) showed that the radical cation of *N*-cyclopropyl-*N*-methylaniline was detected at a λ_{max} of 480 nm, and the lifetime for the radical is not perturbed on introduction of a *N*-cyclopropyl group (in place of an *N*-methyl) suggesting that ring opening occurs on a time scale too long for LFP, meaning that k is less than $1 \times 10^6 \text{ s}^{-1}$.²⁹ Thus, rather than being more easily oxidized, *N*-cyclopropyl-*N*-methylaniline is actually slightly more difficult to oxidize than *N,N*-dimethylaniline ($E_{\text{ox}} = +0.491 \text{ V}$). The sluggish rate of ring opening, and the fact that the cyclopropyl group seems to have exerted little effect on the oxidation potential is easily explained; in *N*-cyclopropyl-*N*-methylaniline radical cation, the perpendicular conformation is lower in energy than the bisected conformation.²⁹ In the perpendicular conformation, overlap between the highest occupied molecular orbital (HOMO) of the cyclopropyl group and adjacent π -system is minimal.²⁹ Thus, the radical cation does not enjoy thermodynamic stabilization afforded by the cyclopropyl group, and is in the wrong conformation for ring opening to occur. This system is of particular interest because *N*-cyclopropyl-*N*-methylaniline and several structurally related derivatives were

used to probe for SET in amine oxidations mediated by *P*450. Information regarding the low rate and unfavorable stereoelectronic factors for ring opening was not available for these studies.^{5, 13–16, 18} On the basis of this new information, it is likely that even if electron transfer were occurring in these systems, the sluggish rate of ring opening would be unable to compete with other processes such as radical cation deprotonation (Scheme 14).

N-Alkyl-*N*-cyclopropylaniline radical cations have been employed as mechanistic probes in nitrosations of aromatic amines where ring opening is an indicator of radical cation intermediates in nitrosation of *N,N*-dialkyl aromatic amines. Nitrosation of *N*-alkyl-*N*-cyclopropylanilines in acidic media (Scheme 15) proceeds through an aminyl radical cation intermediate. This intermediate undergoes regioselective ring opening and reacts further to form *N*-alkyl-*N*-nitroanilines.³⁰ Studies of acidity effects on decomposition pathway revealed the preferential mode of reactivity is de-ethylation (vs de-methylation) when solution pH is above 2.³¹ With addition of base, α -deprotonation emerges, a favored pathway of decay; when the acidity is high, deprotonation is suppressed and *N*-alkyl-*N*-cyclopropylanilines ring opening dominates.



Scheme 14 Ring opening and deprotonation are noncompetitive for *N*-methyl-*N*-cyclopropylaniline radical cations.



Scheme 15 Nitrosation mechanism for *N,N*-dialkylanilines. [Reproduced from Ref. 29. © 2007, Royal Society of Chemistry.]

2.2.7 Cyclopropane Ring Opening in Chemical Systems: Cyclopropylarene Radical Cations

In the past decade, kinetic studies of arylcyclopropane radical cations have emerged shedding light on their reactivity.^{12,23,25–28,32} One very notable feature of cyclopropylaryl compounds is the stability provided by cyclopropanes in the plane of the π system containing the radical.³³ Crystallographic data in addition to molecular mechanics calculations for several aryl cyclopropane radical cations suggests cyclopropanes can act as electron donors when the cyclopropane is in the bisected conformation (Figure 7).

The equilibrium conformation for cyclopropyl naphthyl and phenyl compounds is bisected while the 9-anthryl compounds adopt a perpendicular geometry (Figure 8).³³ The cyclopropylanthracenes are forced into this conformation by unfavorable steric interactions between the cyclopropane and peri-hydrogens on the adjacent anthracene. For the naphthyl and phenyl compounds the preference for the bisected conformation enables interaction of the aryl groups' π system with the sp^2 orbital of the cyclopropyl carbon.³³ When the molecule is strongly electron deficient, as in the case of a radical cation, the p orbital on the aryl carbon adjacent to the cyclopropane is twisted out of conjugation, with

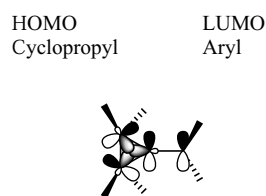


Figure 7 Walsh model for the cyclopropane HOMO in the bisected conformation mixes with the LUMO of the aryl group, also coplanar, allowing it to donate electron density to the conjugated ring. [Reprinted with permission from Ref. 33. Copyright 1990 American Chemical Society.]

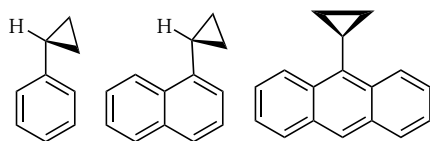
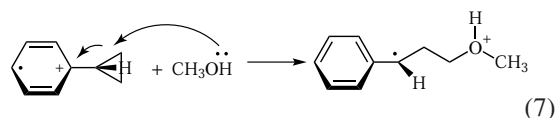


Figure 8 Cyclopropylarenes.

the cyclopropane in the perpendicular conformation, markedly decreasing propensity for ring opening.³³

Dinnocenzo *et al.* demonstrated that ring opening of phenylcyclopropane radical cation occurs via a nucleophile-assisted, overall second-order process as delineated in ((7))³⁴ in part with permission from Ref. 34. Copyright 1997 American Chemical Society).



[In part with permission from Ref. 34. Copyright 1997 American Chemical Society.]

Inversion of configuration was observed in the nucleophile-assisted ring opening of 1-phenyl-2,3-dimethylcyclopropanes, phenylcyclopropane reacting with methanol, isopropanol, *tert*-butanol, pyridine, water, and cyanide ion.^{34,35} Stereoinversion is attributed to positive overlap between the nonbonding orbital of the nucleophile and the σ^* orbital of the radical cation's one electron bond favoring a backside (σ^*) rather than frontside (σ) interaction.^{35,36} Interestingly, the rate constants in Table 1 for substitution on 1,1-diphenylcyclopropane translate to a reactivity ratio 5:3:1, or less, going from primary to tertiary alcohol.^{35a}

Structural distortion inherent to radical cations formed by one electron oxidation leads to an early transition state with a large carbon–nucleophile distance lessening the effect of the nucleophile's steric bulk on kinetics.^{35a} Additionally, the electronic environment of the carbon is significantly more important in determining the site of substitution than in four electron S_N2 reactions.

Table 1 Rate constants for ring opening of phenylcyclopropane radical cation by various nucleophiles at 23 °C.

Nucleophile	k , ($M^{-1}s^{-1}$)
CH_3OH	1.6×10^7
CH_3CH_2OH	1.4×10^7
$(CH_3)_2CHOH$	1.1×10^7
$(CH_3)_3COH$	0.73×10^7

Source: Reproduced from Refs 34 and 35. © 1997, 1990, American Chemical Society.

Table 2 Rate constants for methanol-assisted ring opening for 1,1-diphenyl-2-alkylcyclopropanes at 23 °C in CH₃CN.

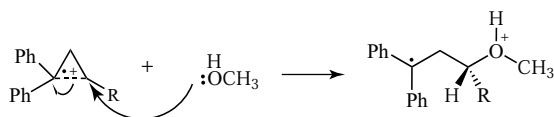
C2 substituent(s)	<i>k</i> (M ⁻¹ s ⁻¹)
CH ₃ , CH ₃	3.2×10^8
CH ₃	1.5×10^8
CH ₃ CH ₂	8.3×10^7
(CH ₃) ₂ CH	3.0×10^7
(CH ₃) ₃ C	4.8×10^6

Source: Reprinted with permission from Ref. 37. Copyright 1993, American Chemical Society.

Rate constants in Table 2 for the reaction of 1,1-diphenyl-2-alkylcyclopropane radical cations present a counter intuitive trend in that reaction kinetics actually increase as the degree of substitution is increased at the site of attack.

The preference for anti-Markovnikov addition of methanol to substituted cyclopropanes was quite accurately predicted to be a result of weakening but not breaking of the C_α–C_β bond by Hixson and coworkers.³⁸ Much later, this supposition was confirmed by computational work that showed the C_α–C_β bond is about 10 kcal mol⁻¹ in the transition. Further, it is noted that displacement preferentially occurs at the more substituted carbon.³⁷ Enhanced stabilization of the positive charge in the transition state on the more substituted carbon primarily drives the reaction to proceed at the more sterically hindered, but more electron rich, carbon on the cyclopropane ring as shown in Scheme 16.³⁷

In the transition state, increased C_α–C_β bond length, a 140° C_α–C_β–OMe bond angle, and a greatly increased localization of positive charge at the β position are predicted by both AM1 and PM3 calculations.^{35b} The latter feature predicts the observed positive ρ value and high degree of correlation between *k* and the Hammett σ⁺ (rather than σ) parameter. *p*-Substituted phenyl groups at C_α stabilize the positive charge decreasing the importance of substitution at the C_β attack site

**Scheme 16** Methanol adds at the more substituted carbon on an alkylsubstituted cyclopropane radical cation. [Reprinted with permission from Ref. 30b. Copyright 2000, American Chemical Society.]

on the cyclopropane effectively, reintroducing the issue of steric bulk at the site of substitution, and leading to an increased barrier to reaction as shown by the rate constant trend in Table 2. Although the structures of neutral cyclopropanes are relatively unresponsive to alkyl substitution, their radical cation counterparts are far more sensitive.

Cyclopropylbenzene and cyclopropylnaphthalene radical cations undergo nucleophile-assisted ring opening,^{35,39} whereas radical cations derived from cyclopropylanthracenes do not undergo ring opening.³⁹ Surprisingly low rate constants for ring opening of cyclopropylnaphthalenes have been observed, on the order of 10 M⁻¹ s⁻¹. The decay occurs via a bimolecular pathway where the barrier to reaction is significantly affected by the magnitude of the positive charge on the cyclopropane in the transition state.⁴⁰ The ring openings of the analogous radical anions are unimolecular processes with rate constants several orders of magnitude larger (10⁶–10⁸ s⁻¹) than those observed for the aforementioned radical cations.⁴¹ Electrochemically generated 9-cyclopropylanthracene and 9-bromo-10-cyclopropylanthracene radical cations show that nucleophilic attack on the aromatic ring occurs, rather than a nucleophile-assisted ring opening, in the presence of methanol.^{40b} While some cyclopropane ring-opened products were observed, in these studies, ring-opened products were shown to arise from reaction of a primary product during work up of the reaction mixture.^{40b}

A thermochemical cycle was used to estimate Δ*G*^o showing nucleophile-induced ring opening is extremely exothermic for all these radical cations (Δ*G*^o = –39, –28, and –20 for Ar = phenyl, α-naphthyl, and 9-anthryl, respectively). These results rule out the explanation that the sluggish rate of ring opening associated with the α-naphthyl and 9-anthryl systems is simply attributable to the enhanced stability of these radical cations. Two major factors were found to contribute to Δ*G*₀ for ring opening: (i) the ability of the aryl group to stabilize the ring-closed radical cation (related to *E*_{Ar⁺/Ar}⁰) and (ii) the ability of the aryl group to stabilize the radical portion of the ring-opened (distonic) radical cation. On this basis, it was suggested that the reason that ring opening is slow for arylcyclopropane radical cations is a late (product-like) transition state, Figure 9, in which the positive charge is localized on the cyclopropyl group and

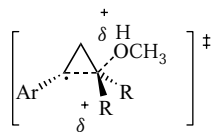


Figure 9 Charge localized transition state for ring opening of cyclopropylarenes. [Reprinted with permission from Ref. 35b. Copyright 1997 American Chemical Society.]

thus, unable to benefit from stabilization offered by the aromatic ring.

The aromatic ring stabilizes the radical portion in the transition state; however, the effect of the aryl group on radical stability is miniscule compared to the effect of the aryl group on the stability of the ring-closed radical cation. (In the case of 9-cyclopropylanthracene radical cation, stereoelectronic factors may also contribute to the high barrier to ring opening; the cyclopropyl group in this system may exist in the perpendicular conformation, which does not meet the stereoelectronic requirements for ring opening.) For a cyclopropane containing compound to act as an effective probe, for a SET mechanism with a radical cation intermediate, ring opening must occur faster than other possible decay processes. In the case of these radical cations the reactions proceed slowly through a product-like transition state with significantly localized charge, which severely limits their reactivity and dominates over the large thermodynamic stabilization that would otherwise suggest these molecules would make attractive substrates for use as mechanistic probes or radical clocks (see **Radical Kinetics and Clocks**).⁴²

B3LYP calculations with a 6-31G(d) basis set suggest the structure of phenylcyclopropane radical cation has a cyclopropane containing two long and one normal length bond in contrast to the one long two normal bond length configuration observed for the alkylsubstituted cyclopropanes in Figure 10.^{35b} Additionally, with alkyl substitution at the β position the bisected conformation

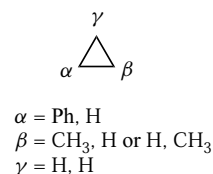


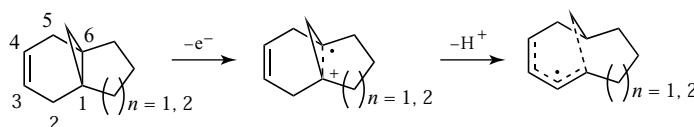
Figure 10 Substituted cyclopropanes studied in computations.

of the phenyl ring (which in the unsubstituted compound overlaps and stabilizes the two C–C σ bonds relatively equally) moves into a conformation with a higher degree of overlap with the longer C_α – C_β bond. Redistribution of charge accompanies these structural changes because the alkyl substituents are capable of stabilizing more of the positive charge associated with the radical cation character.^{35b}

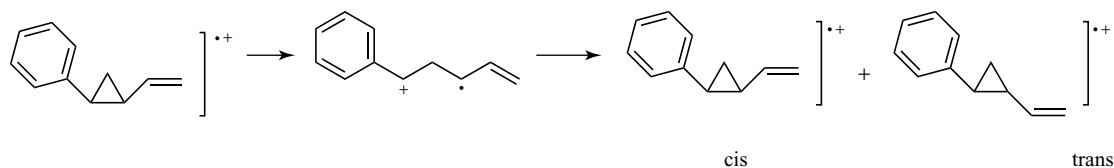
Photochemically generated three-ring-bridged allylcyclopropane radical cations undergo nucleophilic substitution in the presence of base. These substitution products are arrived at through a deprotonation mechanism, Scheme 17.⁴³ Deprotonation products are favored at position 2 because of resonance stabilization afforded by interaction with the neighboring functional groups.⁴³

Like nucleophile-assisted ring openings, the cis–trans isomerization of 1,2-disubstituted cyclopropane radical cations proceed through ring-opened intermediates. These isomerizations proceed by different mechanisms when the initial one electron oxidation to form the ring-closed radical cation is induced photolytically or by a chemical oxidant.⁴⁴ The latter process (Scheme 18) is significantly more facile; the chemical oxidation of 1-phenyl-2-vinyl-cyclopropane by p -BrPh₃N⁺ SbF₆[–] experiences a rate increase of 10^{24} relative to the thermal process.^{44a}

Furthermore, the chemically induced oxidation does not involve the biradical intermediate (Figure 11) implicated in the photochemical reaction, although both reactions do proceed through a ring-opened intermediate.^{44,45} The involvement



Scheme 17 Allyl cyclopropanes deprotonation of the radical cation intermediate at position 2.



Scheme 18 Isomerization proceeds via ring openings of 1,2-disubstituted cyclopropane radical cation. [Reprinted with permission from Ref. 37. Copyright 1993, American Chemical Society.]

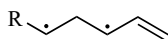


Figure 11 Biradical intermediate characteristic of isomerization of photochemically generated 1,2-disubstituted cyclopropane radical cation.

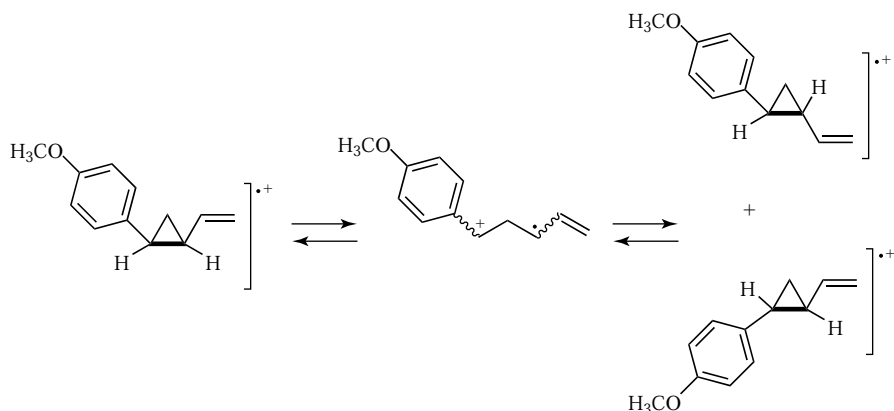
of the biradical intermediate is easily eliminated in chemically induced isomerization as it is exothermic by only $0.7 \text{ kcal mol}^{-1}$ and 32 kcal mol^{-1} are needed to form the biradical (estimated to be equal to the enthalpy of activation for the thermal process).^{44a}

The chemically oxidized cyclopropane isomerizes through a ring-opened distonic radical cation intermediate. The reaction mechanism involves rotation at both stereocenters in a noncorrelated way as shown in Scheme 19. These mechanistic conclusions are supported by isotopic labeling studies that show both possible trans products are formed. NMR analysis of the reactions proved that this is not a pre- or post-reaction equilibrium. Additionally, accelerated isomerization of the chemically generated cyclopropane radical cation results from a

decreased propensity to undergo back electron transfer thus favoring the competing isomerization.^{44a} Additional reactions of chemically and photochemically generated cyclopropane radical cations have been reported to be involved in cycloaddition reactions, although that is outside of the scope of this review as these mechanisms may involve ring intact intermediates.⁴⁶

2.3 Comparison of Trends for Neutral Cation and Anion Radicals of Cyclopropane Substituted Compounds

The use of substituted cyclopropane substituted radicals and radical ions as mechanistic probes hinges largely on our understanding of their reactivity. Some notable parallels can be drawn from comparison of cyclopropane radicals, radical anions, and radical cations ring openings. Alkyl radicals undergo rapid ring openings like their ketyl radical anion analogs. In some cases, the ketyl radical anion ring openings are more facile because the oxygen is



Scheme 19 Chemically oxidized 1-phenyl-2-vinyl-cyclopropane radical cation isomerization through a ring-opened intermediate. Rotation at both stereo centers yield both trans products.^{44a}

a potent electron donor that can very effectively stabilize the ring-opened product and transition state. While similar kinetic data is not available for aliphatic cyclopropyl radical cations, computations show that alkyl substitution can induce conformational changes in order to facilitate interaction and stabilization of charge. Similarly, no experimental kinetic data is available for aliphatic amine radical cations but computations suggest that aliphatic aminyl radical cations ring open extremely rapidly and the ring-closed form may not exist as a discrete species. Moreover, trialkyl amines that adopt planar conformations maximize interactions of substituents with the radical center. Introduction of cyclopropyl groups induces conformational changes placing the cyclopropane in a bisected conformation facilitating ring opening and delocalizing spin through hyperconjugative interactions. In aliphatic radicals, ketyl radical anions, and aliphatic radical cations a substituent's ability to stabilize charge has important thermodynamic implications. In aminyl radical cations and ketyl radical anions charge stabilization is an important kinetic consideration as well. In aliphatic cyclopropylamine radical cations, the ring-closed radical cations prefer a bisected conformation but the ring-closed form may not represent a potential energy minima and ring opening may proceed through a perpendicular transition state. Contrastingly, in aromatic cyclopropane cation radical systems significant evidence exists to suggest specific stereoelectronic requirements; that is, a planar bisected conformation of the ring relative to the adjacent π system is necessary for ring opening to occur. These stereoelectronic constraints along with the enhanced radical cation stability afforded to the ring-closed form by the aryl group lead to a markedly decreased propensity for ring opening of aryl (vs aliphatic) substituted cyclopropanes. These reactions proceed through a late transition state; therefore, spin and charge delocalization in the reactant is not offset by similar stability in the transition state; in the transition state the charge is highly localized. Moreover, the perpendicular conformation of the reactant is more thermodynamically stable than the bisected conformation necessary for ring opening. The phenyl cyclopropyl radical anion ring openings rate constants are similarly depressed and for similar reasons, highlighting the importance of resonance energy in the radical anion process as well. Substitution of electron-donating groups on the cyclopropyl ring stabilizes the radical in the product

causing a several order of magnitude increase in rate constant and again demonstrates the importance of spin delocalization. In all cases (radical anion, radical cation, and neutral radical) relief of ring strain and delocalization of spin can drive ring opening. For both cyclopropane radical cations and radical anions, delocalization of charge also affect reactivity significantly. In the case of the radical cations, stereoelectronic requirements for ring openings, particularly in the aryl cyclopropanes, will dictate whether ring opening is a favorable process.

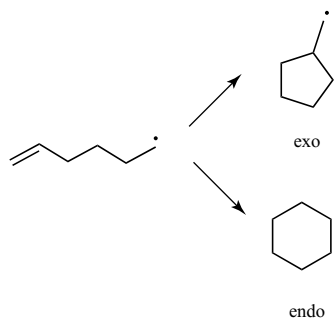
3 Δ -5-HEXENYL RADICAL/RADICAL ION CYCLIZATION

3.1 Δ -5-Hexenyl Radical Cyclizations

The Δ -5-hexenyl radical reaction is the most widely studied radical cyclization mechanism. This is not surprising, as the stereo and regio selectivity of related intramolecular additions make such reactions extremely attractive from a synthetic perspective. Additionally, the Δ -5-hexenyl radical finds use as a radical clock and a mechanistic probe (see **Basic Concepts on Radical Chain Reactions and Radical Kinetics and Clocks**).⁴⁷ This reaction is known to be kinetically controlled for reasons discussed in the preceeding section. While extensive kinetic characterization of the corresponding 5-hexenyl radical anion cyclization has not been performed; product ratio analysis allows parallels between the two processes to be drawn. The next few pages show that the reactions of 5-hexenyl radicals and their corresponding radical anions proceed similarly.

It is well established that the Δ -5-hexenyl radical preferentially undergoes intramolecular addition via the 5-*exo*-trig rather than 6-*endo*-trig pathway to yield the thermodynamically unfavorable product (Scheme 20).⁴⁸ The 6-*endo* product is stabilized relative to the 5-*exo* product because it is a more substituted radical with less ring strain. In spite of thermodynamics; the *exo* product occurs in 98 to 2 percent excess over the *endo* product.⁴⁹

The pathway to the *endo* product proceeds through a boat-like transition state whereas the *exo* cyclization proceeds through a less strained chair-like transition state (Figure 12) that has been shown to be 2.8 or 1.7 kcal mol⁻¹ lower in energy than the *endo* transition state (by calculation and



Scheme 20 Δ -5-Hexenyl radical cyclization.

experiment, respectively).⁴⁵ The chair conformation maximizes orbital overlap, thereby imposing a stereoelectronic demand for exo cyclization.

Table 3 shows the 5-hexenyl cyclization was more facile than cyclization of larger chains and more endo selective. Comparing an alkyne and alkene, addition is more facile for the alkene and more regioselective for the alkyne.

3.1.1 Regioselectivity of Δ -5-Hexenyl Radical Cyclization

Functionalization of the terminal end of the alkene, and the corresponding polarization of the scissile

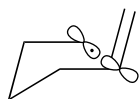


Figure 12 Proposed exo transition state for 5-hexenyl radical cyclization. [Reprinted with permission from Ref. 50. Copyright 2005 American Chemical Society.]

Table 3 Rate constants for formation of both regioisomers for radical cyclizations at 25 °C. Regioselectivity varies as a function of chain length and bond order.⁵¹

Radical	$k_{\text{exo(calc)}} \text{ (s}^{-1}\text{)}$	$k_{\text{endo(calc)}} \text{ (s}^{-1}\text{)}$
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}_2$	2.3×10^5 1.1×10^5	4.1×10^3 5.0×10^2
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}\equiv\text{CH}$	2.8×10^4	$< 6 \times 10^2$
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$	5.2×10^3	8.3×10^2
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2\text{CH}_3$	1.2×10^2	$< 7 \times 10^1$

Table 4 Changes in regioselectivity based on strain energy of the transition state due to substituents on the double bond at 25 °C.⁴⁹

Radical	$\Delta E_{\text{strain exo(calc)}} \text{ (kcal mol}^{-1}\text{)}$	$\Delta E_{\text{strain endo(calc)}} \text{ (kcal mol}^{-1}\text{)}$
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}_2$	6.7	13.5
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$	7.0	10.2
$\cdot\text{H}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$	9.7	9.5

double bond, markedly affects kinetics and the preference for endo or exo cyclization. The 5-hexenyl radical is nucleophilic and polarization of the double bond affects preferential site of addition. The attraction between the nucleophile and the most electrophilic site on the cleavable double bond favors reaction through the more strained transition state structure and forms the thermodynamic product. Stabilizing groups at the exo attachment site introduce a steric effect which makes both regioisomers equally likely (Table 4). The endo selectivity is increased when a methyl group is present at the endo attack site.

Geminal substitution increases k relative to the unsubstituted 5-hexenyl reaction (Table 5). The maximum effect was observed for the 3 position. The rate constant for the 1-substituted compound is lower than those for the other substituted compounds in Table 5 because it involves cyclization of a secondary radical. Conversely, substitution of electron-withdrawing groups at or near the radical site increases radical nucleophilicity and rate constant for cyclization. Donation of electron density to the radical decreases the rate and decreases selectivity. Substitution of a $\text{Si}(\text{CH}_3)_2$ for the two carbon stabilizes the radical to such an extent that it becomes exo selective.

3.1.2 Stereoselectivity of Δ -5-Hexenyl Radical Cyclization

Substitution not only plays a role in regioselectivity but also dictates stereoselectivity for these cyclizations. For 5-hexenyl radicals, substitution at the 1 or 3 position leads to the cis product while

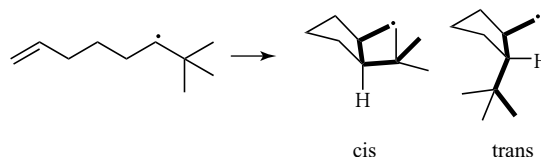
Table 5 Rate constants displaying regioselectivity of 5-hexenyl at 25 °C. Cyclization trends with site of substitution and electron-withdrawing/donating substituents.^{49,51,52}

Radical	Solvent	$k_{\text{exo(expt)}} \text{ (s}^{-1}\text{)}$	$k_{\text{endo(expt)}} \text{ (s}^{-1}\text{)}$
	Hexane	3.5×10^5	6.0×10^3
	None	3.6×10^{6a}	$<1 \times 10^{5a}$
	None	5.1×10^{6a}	$<1 \times 10^{5a}$
	None	3.2×10^6	$<1 \times 10^{5a}$
	Benzene	8.5×10^6	$<1 \times 10^5$
	Benzene	7.4×10^4	5.0×10^3
	Benzene	8.7×10^2	1.8×10^3

^a Calculated.⁵¹

substitution at the 2 or 4 position favors the trans product (Figure 13). Generally, substituents in the 2, 3, or 4 position prefer a chair-like transition state placing bulky substituents in a pseudoequatorial position. Moreover, selectivity increases with geminal disubstitution at the 3 position.⁵⁰ Rate data for cyclization of various methyl substituted 5-hexenyl radicals is presented in Table 6. Placing substituents in an axial position is disfavored by destabilization imparted by Van der Waals interactions, bending, and torsional strain in the transition state. Methyl substitution at the radical center leads to increased stereoselectivity. Similar substitution near the cissile alkene bond enhances production of the trans product. Interestingly, the strain energy of the transition state, assuming a chair conformation for both the stereoisomers, overestimates the cis contribution. The experimental partitioning ratio for the cis and trans products is in good agreement with computational work where the trans isomer proceeds through a boat-like transition state.

Rate data for cyclization of alkenylaryl compounds (Table 7) showed the rate constants for these reactions to be three to four orders of magnitude greater than for the corresponding alkenyl reactions.

**Figure 13** Isomeric products for cyclization of 1-*t*-butyl-5-hexenyl radical cyclization.

These aryl radicals are subject to lesser torsional strain and less energy is required to form the new bond. The aromatic radicals are isolated in an orbital adjacent to the π system. The corresponding ether exhibits an order of magnitude increase in rate constant. Substitution of the electrophilic double bond for the aryl ether causes a moderate decrease in the cyclization rate constant relative to the unsubstituted double bond.

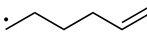
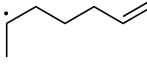
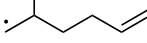
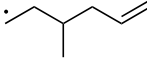
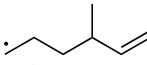
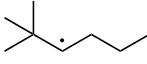
In 1-methyl-5-hexenyl radical cyclization, the cis product is obtained because stabilizing torsional interactions between the methyl and C6 outweigh the strain imposed by bending. For many years, replacement of the methyl with a more sterically bulky group, such as *t*-butyl, was believed to introduce unfavorable Van der Waal interactions that would dominate torsional and bending effects and calculations suggested subsequent cyclization would preferentially form the trans product (Figure 13). On reinvestigation, Curran and others were able to show that both experiment and higher level computational analysis evidenced a preference for the cis product.⁵⁰

Comparing molecular mechanics and quantum mechanical calculations it was noted that only the latter computation accurately predicts the cis product preference, thus providing a basis for the assertion that both steric and electronic factors contribute to determination of product stereochemistry.⁵⁰ It has been noted in competition experiments that yields are affected by alkyl substitution of the cissile bond; with more cyclized product forming when the 5-hexenyl radical is more highly substituted.

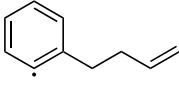
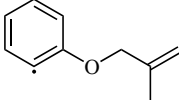
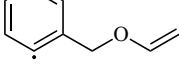
3.1.3 Solvent Effects on Δ -5-Hexenyl Radical Cyclization

In some cases, as solvent polarity is increased the cis isomer becomes more predominant; notably, this is not the case for all hexenyl radical cyclizations

Table 6 Effects of substitution on stereoselectivity of 5-hexenyl radical cyclizations at 25 °C.

Radical	Solvent	k_{cis}^a	k_{trans}^a	k_{overall}^a	cis : trans _(calc)	cis : trans _(expt)
 52–55	Hexane	—	—	2.3×10^5	—	—
	Cyclopropane	—	—	1.1×10^5	—	—
	Cyclohexane	—	—	1.0×10^5	—	—
	Isopentane	—	—	1.0×10^5	—	—
 49,56	Benzene or Hexane	1.1×10^4	4.2×10^4	1.5×10^5	66:34	67:33
 49		2.4×10^5	4.5×10^5	6.9×10^5	40:60	36:64
 49,56		7.0×10^5	2.4×10^5	9.4×10^5	63:37	71:29
 49,56		7.5×10^4	3.6×10^5	4.4×10^5	19:81	17:83
 57		2.8×10^4	8.7×10^4	11×10^4	—	—

^aRate constants given in (s⁻¹).**Table 7** Aryl 5-hexenyl radical cyclization rate constants at 25 °C.⁴⁹

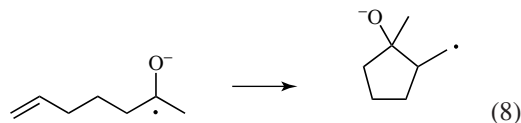
Radical aromatic	$k_{\text{exo(expt)}} \text{ (s}^{-1}\text{)}$	$k_{\text{endo(expt)}} \text{ (s}^{-1}\text{)}$
	3.1×10^8	$<6 \times 10^6$
	1.7×10^9	3.6×10^7
	5.3×10^9	$<5 \times 10^7$

in Table 8. The stereoselectivity of the cyclization of the 2,2-dimethyloct-en-3-yl radical exhibits a moderate dependence on solvent polarity. Similar trends have been observed for the hept-6-en-2-yl and the 1,1,1-trifluorohept-6-en-2-yl radical. The proportion of cis isomer increases with increasing solvent dipole moment, results being likely indicative of a polar transition state.⁵⁷

3.2 6-Hepten-1-one Radical Anion Cyclizations

Similar 6-hepten-1-one radical anion cyclizations ((8) reproduced from Ref. 66. Copyright 1989,

American Chemical Society) have been investigated for their potential use in synthesis of cyclic molecules as well as intramolecular radical clocks; not unlike their neutral radical analogs.⁶⁷

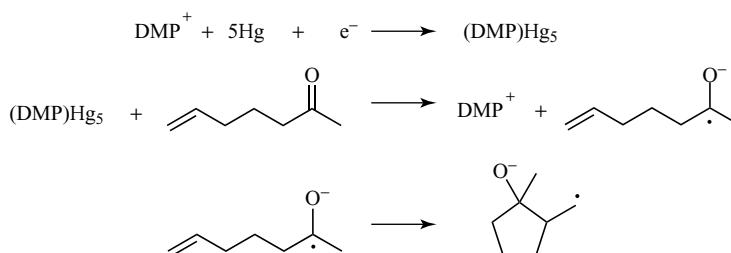


[Reproduced from Ref. 66. © 1989, American Chemical Society.]

The dimethylpyrrolidinium (DMP) mediated reduction of substituted 6-hepten-1-ones shows these radical anions undergo regioselective cyclization to form the exo product, similar to the neutral radical analog. The analogous direct reductions of 6-hepten-1-ones form straight chain alcohols, not the cyclized alcohols characteristic of the mediated process. These products are thought to form because, at the oxidation potential of the direct reduction, the radical anion can undergo subsequent reduction to the dianion. The dianions of these ketones do not prefer the cyclization pathway.⁶⁶ Heterogeneously catalyzed reduction of *o*-(3-butenyl)fluorobenzene exhibits regioselectivity similar to that observed for the aforementioned ketones.⁴⁷ The initial steps of the

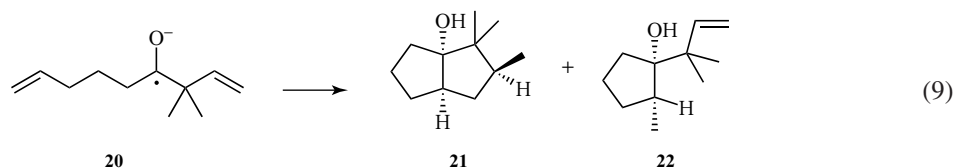
Table 8 Stereoselectivity of 5-hexenyl radical cyclizations in solvents of varying polarity at 25 °C.⁵⁸

Radical	Value	Benzene/hexane	1,2-Dimethoxyethane	1-Propanol
	[cis/trans]	0.95	0.93	0.94
	[cis/trans]	1.13	1.86	1.70
	[cis/trans]	0.57	0.57	0.57
	[cis/trans]	3.1	4.4	5.9

**Scheme 21** DMP mediated reduction and subsequent cyclization of 6-hepten-2-ones. [Reprinted with permission from Ref. 68. Copyright 1988 American Chemical Society.]

synthesis of cyclic molecules by DMP mediated reduction of ketones are shown in Scheme 21.⁶⁷

from Ref. 47. Copyright 1989 American Chemical Society.)



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3.2.1 Regio/Stereoselectivity of 6-Hepten-1-one Radical Anion Cyclizations

These radical ion cyclizations are known to be endo selective, reminiscent of a 5-hexenyl radical cyclization. The primary product of the radical ion reaction for analog **20** is **21**, which is expected to result through nucleophilic attack on the less sterically crowded face of the molecule.⁶⁷ Two isomeric radicals result; the trans radical leads to the minor product **22** because of an inability to undergo further cyclization ((9) reproduced with permission

Other ketones **23–26**, shown in Figure 14 are also reduced by DMP to yield radical anions exhibiting similar regio- and stereospecificity in cyclization.⁶⁷

Swartz and coworkers astutely noted that the plot of product yield as a function of molar equivalents of electrons consumed exhibits a linear relationship with a slope on the same order of magnitude as the previously reported rate constant for the corresponding cyclizations for both hexenyl and hexynyl radicals.⁶⁸ Moreover, **26** shows a retardation in rate constant of about an

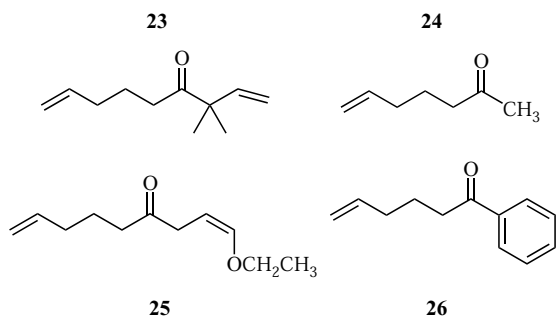


Figure 14 Structures of ketones known to undergo mediated reduction and subsequent cyclization.

order of magnitude, as indicated by the analogous plot; this result is cogent as cyclization onto an arene would be expected to be subject to a rate decrease.

The reductive cyclization by DMP is highly stereoselective.⁶⁸ The homogeneously catalyzed reduction of 6-hepten-2-one has been shown to be sensitive to the concentration of water while the heterogeneous process is not. The heterogeneous process is extremely stereoselective, so even if it was subject to an analogous effect it would be difficult to discern an increase in stereoselectivity that was statistically significant. Unlike the heterogeneous process the ratio of cis to trans product formed for the homogeneously catalyzed reduction can be increased by changing the concentration of water or catalyst or by using a different redox catalyst all together.

A similar mechanism is invoked to explain the homogeneously and heterogeneously catalyzed processes. The two mechanisms are differentiated by the reversibility of the cyclization step in the homogeneously catalyzed system. The observation of an appreciable amount of the thermodynamically favored product in the homogeneously catalyzed reaction results from differences in how the catalysts function.⁶⁶ The insoluble heterogeneous catalysis complex will form the kinetic product at the electrode surface by extremely rapid subsequent irreversible reduction of the cyclized product.⁶⁶ Contrastingly, in the homogeneous system, the proportion of the product going to the kinetic product will be proportional to the concentration of catalyst in solution.⁶⁶

3.3 Stereo- and Regiochemical Trends for Δ -5-Hexenyl Radicals and Radical Anions

Comparatively, the radical anion and radical processes exhibit similar regio- and stereoselectivity in cyclization. Generally, both reactions undergo exo ring closure and preferentially form the cis product. Of course, substituent effects and electronic effects lead to exceptions in both cases. Little kinetic data exist for the radical anion process but it has been proposed that the two processes occur through a similar step in their mechanisms, cyclization through the neutral radical center. Swartz suggests that the radical anion process is expected to occur with similar rate constants to Beckwith's measured ones for 5-hexenyl cyclizations. For the radical anion reactions the catalyst used is known to be a factor that could potentially allow for selective production of the thermodynamic product. For the neutral radical, the most favored transition state resembles the cyclohexane chair conformation, maximizes overlap between the singly occupied orbital containing the radical and the π^* orbital of the atom being attacked, and minimizes ring strain in the transition state. Steric factors have been shown to play some role in both processes with steric demands and the placement of bulky groups in the transition state modulating stereochemistry of the products and kinetics of the cyclization. In some 5-hexenyl radical cyclizations, increasing solvent polarity increases the preference for the cis product, although this is not true for all 5-hexenyl radical cyclizations. In light of the available evidence, it is reasonable to conclude that the neutral radical and the radical ion cyclization may proceed through similar transition states. This may indicate that, unlike the previously discussed cyclopropane ring openings, charge delocalization in the transition state is not a primary factor in determining reactivity. Similar to the cyclopropanes, this may result from the stabilization afforded by the oxygen on the ketyl radical anions. Of course, these suppositions are simply those without further investigation of the radical anion reactions. Understanding the nature of the transition state for these intramolecular additions as well as determination of important kinetic parameters has facilitated their use in stereo- and regioselective synthesis of cyclic compounds. Moreover, knowledge of the kinetic parameters for these reactions can aid in determination of useful kinetic parameters for other interesting reactions by acting

as intramolecular radical clocks. One class of reactions where radical clocks like these are useful is in atom and group transfer reactions (see **Halogen and Chalcogen Transfer Chemistry**). The forthcoming section addresses a particularly interesting class of atom transfers, namely, deprotonation and hydrogen transfer reactions.

4 MECHANISMS OF HAT

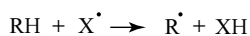
4.1 Modes of HAT

The most common, and seemingly simple, atom transfer reaction involving radicals is hydrogen transfer (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**). The equivalent process for a radical cation is deprotonation. HAT reactions are an extremely interesting class of radical reactions, finding widespread importance in both synthesis and biology.

Classical HAT is characterized by the simultaneous removal of a proton and one electron from the breaking bond. As of late, several authors report evidence suggesting alternative routes for HAT involving radicals and radical ions such as sequential proton loss electron transfer (SPLET), electron transfer followed by proton transfer (ET/PT), and proton-coupled electron transfer (PCET).⁶⁹ Classical concerted HAT proceeds via direct transfer of a hydrogen atom between molecules via a three-electron transition state as shown in Scheme 22.

4.1.1 Classic HAT

Many HAT reactions including the reaction of the *N*-hydroxylphthalimide radical (PINO[•]) with toluene and several other aliphatic and aromatic hydrocarbons proceed via classical HAT.⁷⁰ Since proton and electron transfer occur in a single molecular motion via a three-electron transition state, neither will individually affect the rate of



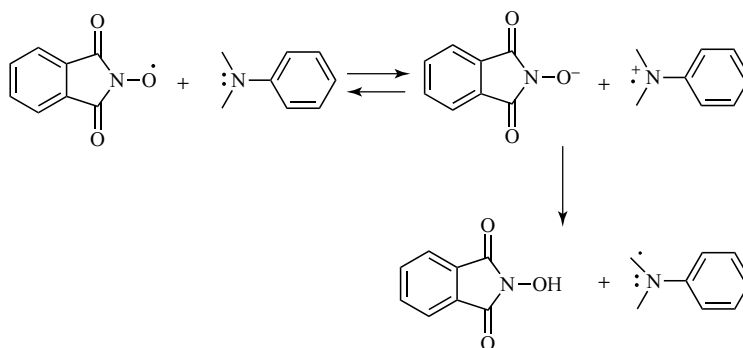
Scheme 22 Concerted hydrogen transfer.

reaction. Instead, the rate is directly related to relative difference in the strength between the breaking and forming of the bond. The relationship between reaction kinetics and bond dissociation energy is quantified by the Evans Polyani Principle; a nice example of this is the HAT from hydrocarbons to phthalimide *N*-oxyl radical (PINO[•]) in acetic acid.^{70,71} For this process, a reasonably linear correlation is noted with an α value of about 0.38 denoting a slightly exothermic process.⁷¹ The Evans Polyani Equation is not well suited to represent the relationship between kinetics and thermodynamics of reactions when factors such as stereoelectronic effects, steric effects, and polar effects influence enthalpy since these variables are not considered in the corresponding equation.⁷² One example where stereoelectronic factors significantly impact kinetics is in the reactions of the 1-hydroxy-benzotriazole radical (BTNO[•]) with cyclic and acyclic alkylarenes. Bond scission is more facile in the former case as a result of hyperconjugative interactions between the breaking C–H bond and the aromatic system; these interactions weaken the C–H bond.⁷³

4.1.2 Electron Transfer Followed by Proton Transfer

One sequential alternative to classical HAT is the electron transfer followed by proton transfer mechanism. Studies of the reaction of several para-substituted dimethylanilines with PINO[•] indicate sequential electron transfer, proton transfer is a probable mechanism for HAT as shown in Scheme 23.^{69e}

Baciocchi asserts differences in isotope effects observed for dideuteromethyl and monodeuteromethyl *N,N*-dimethyl anilines suggest that electron transfer and proton transfer are not concerted. The intermolecular isotope effects observed for the former compounds were smaller than those observed for the corresponding monodeuteromethyl amines. Kinetic isotope effect (KIE) studies showed large primary isotope effects for monodeuteromethyl amines with electron-withdrawing para substituents.^{69e} In addition, the overall rate is also highly dependent on the electron-donating ability of the substituent. Furthermore, the intramolecular KIEs are larger than the intermolecular ones, suggesting that

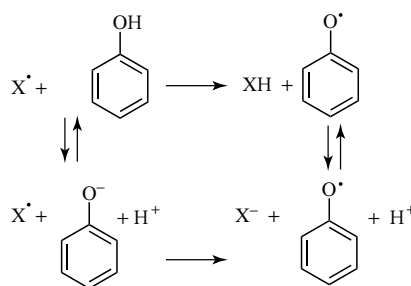


Scheme 23 ET/PT mechanism for the reaction of PINO radical with *N,N*-dimethylanilines. [Reprinted with permission from Ref. 74. Copyright 2005 American Chemical Society.]

removal of the hydrogen atom is not necessarily the rate determining step. These observations suggest electron transfer is followed by proton transfer. Electron transfer was shown to be rate limiting for substrates having electron-donating substituents; whereas proton transfer could affect the rate for electron-withdrawing substituents. Insomuch as electron-donating substituents on a particular compound should correspond to a more favorable and consequently exothermic process, the rate of reverse electron transfer is expected to be significantly less than the favored deprotonation.^{69e} The magnitude of intramolecular deuterium isotope effect results from the decay route of the electron transfer product, either back electron transfer or deprotonation. For strongly electron-donating substituents, no intramolecular isotope effects were observed, further supporting a rate limiting electron transfer. Contrastingly, for electron-withdrawing substituents, back electron transfer is expected to proceed faster as these substituents pull electron density from the radical cation making it less able to stabilize the electron deficiency of the nitrogen.^{69e} In studying these particular compounds, it is noted that significant intermolecular isotope effects emerge alluding to the significance of proton transfer in the rate of these reactions.^{69e} A similar mechanism was observed in the reaction of benzotriazole *N*-oxyl radical reactions with para-substituted *N,N*-dimethylanilines.⁷⁴ In contrast to this sequential process, previous studies by Espenson of deprotonation on phenols and several hydrocarbons suggest concerted HAT mechanisms with PINO^{70,71,75}

4.1.3 Sequential Proton Loss Electron Transfer

A second sequential mechanism proposed for HAT is SPLET. The SPLET mechanism was first proposed by Ingold and coworkers to explain a solvent induced effect on rate of deprotonation of phenols by 2,2-diphenyl-1-picrylhydrazyl radical (dpph').⁷⁶ In studying the kinetics of these reactions, the authors observed a drastic increase in rate constant for hydrogen abstraction from phenols by dpph' in solvents with the ability to hydrogen bond to the phenol.⁷⁷ Moreover, studies in alkane solvents showed decreased rate constants, *vide infra*.^{76a} One would expect that hydrogen bonding of the phenolic hydrogen would result in a stabilized reactant, and as a result, the rate constant of the simple HAT would be expected to decrease. These counterintuitive results can be rationalized on the basis of a faster HAT proceeding via SPLET as shown in Scheme 24 (see also **Antioxidants in Chemistry and Biology**).



Scheme 24 SPLET mechanism for phenol with a neutral radical.

The SPLET mechanism is shown in contrast to HAT for the reaction of phenol with a radical. SPLET is facilitated by the ionization of phenol followed by proton loss and then electron transfer to yield a phenoxyl radical and a neutral species. SPLET reactions proceed much faster than HAT when favorable, and are favored by solvents that promote ionization of the phenol as shown in Scheme 24.^{76c} In polar, hydrogen bond accepting solvents, reaction rates are faster as hydrogen bonding favors protonation of the solvent and simultaneous ionization of the phenol. Studies by Ingold consistently show no change in the ratio of rate constants for deprotonation by a given radical in two different solvents when comparing reactions involving several phenols and several radicals of varying reactivity.⁶⁹ This result provides further affirmation that the radical and its reactivity are not the limiting factor in SPLET mechanisms. In acidic media when SPLET is not favored (because ArOH remains protonated), PCET emerges in some cases as an alternative route to simple HAT.^{69e}

4.1.4 Proton-Coupled Electron Transfer

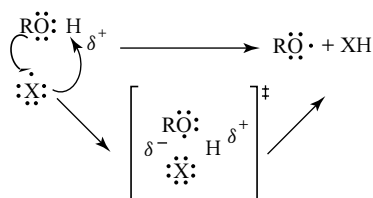
PCET is characterized by transfer of a proton coupled to the transfer of a nonbonded electron; it is important to note that for this mechanism, the proton and electron are transferred from different orbitals in a single step. PCET was first proposed by Mayer in theoretical investigation comparing the abstraction of hydrogen from toluene and phenol by their deprotonated radical counterparts and is shown in Scheme 25.⁷⁸

Studies of deprotonation by $\text{dpph}^\bullet$ from phenol displayed a much greater rate constant than the reaction with toluene.⁶⁹ The enhanced rate of

H-abstraction from phenol is because phenol has a nonbonding electron pair, and can react via PCET, while toluene does not and can only react via classical H-abstraction.⁶⁹ Interestingly, in nonpolar solvents reactions between $\text{dpph}^\bullet$ and phenols are believed to proceed through a product-like transition state and computations evidence the contribution of both HAT and PCET to the overall reaction mechanism.⁷⁹ For the reactions of $\text{dpph}^\bullet$ and *N,N*-dimethylanilines, a PCET mechanism is supported, rather than a sequential mechanism, by the observation of primary isotope effects.⁸⁰ During PCET, electron transfer occurs simultaneously with transfer of a proton between pairs of electrons on both reactants.⁷⁶ While both mechanisms involve the transfer of a proton and an electron, the difference between PCET and SPLET or ET/PT is that the first is concerted, while the last two are stepwise.⁶⁹ Mayer suggests that stepwise processes do not necessarily proceed through intermediates with a lower energy than that of concerted PCET. The increase in energy required to move both a proton and electron in concert (as opposed to just the electron as in an ET/PT) is often more than compensated for by the reduction in solvation energy displayed by the concerted process. In addition to the intrinsic barrier to reaction, the Gibbs free energy of PCET is consistently lower and the mechanism is thermodynamically favored over a stepwise process.⁸¹

4.1.5 Role of Hydrogen Bonding in Determining Mode of HAT

In the analysis of self decomposition reactions, phenol exhibited severely increased rates of reaction with the phenoxyl radical, relative to the carbon centered benzyl radical reaction with toluene. It has been suggested that the rate of hydrogen abstraction from phenol by phenoxyl radical was greater because hydrogen bonding between reactants created a short-lived intermediate complex.⁸² It should be noted that researchers suggest that hydrogen bonding between the two phenolic reactants does lend stability to the reactants and, in effect, decreases the reactivity of these species although this stabilization is offset by the closer proximity and enhanced accessibility of the two reacting species to each other.^{76,82} The increase in rate for the phenol reaction is attributed to the increased accessibility of the oxygen resulting from the smaller



Scheme 25 PCET mechanism for the reaction of a neutral radical with an alcohol. [Reprinted with permission from Ref. 63. Copyright 1991 American Chemical Society.]

radius of the oxygen in the phenol relative to the carbon being deprotonated on toluene.⁷⁶ In addition, Ingold highlights another well known consequence of a narrow reaction barrier, the increased probability of tunneling.^{69a} Proton tunneling in this case results from the closeness of the hydrogen bonded reacting molecules. The SPLET mechanism occurs so readily with phenols that, to observe the PCET pathway, ionization must be prevented by performing the reaction in the presence of acetic acid or another readily ionizable solvent. Favoring ionization of the solvent over the phenol disfavors the SPLET pathway (see also **Antioxidants in Chemistry and Biology**).⁷⁶

4.2 Radical Cation Deprotonations

4.2.1 Radical Cation Deprotonation: Thermodynamics

Radical cations, because of their electron deficient nature, are not likely to participate in HAT; instead, they undergo the analogous radical ion fragmentation, proton transfer. Factors that influence proton transfer are also significant for sequential HAT. In sequential HAT, radical ion intermediates undergo deprotonation as an elementary step of the overall HAT.

In deprotonations, in addition to the alkalinity of the base and strength of the breaking bond, the acidity of the radical is a factor that may significantly impact kinetics. Acidities for selected aromatic hydrocarbons, phenols, and amines are displayed in Table 9. The pK_a s estimated using thermodynamic cycles show solution phase acidity is drastically decreased relative to the gas phase acidity; ionization is less favored because energy is required to solvate solution phase ions.⁸³ Analogous results would be expected for all radical cations as a result of the increased electrophilicity of a cation relative to a neutral radical. A comparison of phenol in both DMSO and H₂O can be made; data suggests that in the less polar protic solvent the phenol is more acidic. These highly acidic compounds are known to react in HAT processes via either SPLET or PCET.

The predominate mechanism of HAT is largely dependent on reaction conditions and the ability of the phenol to ionize, as reflected by its pK_a . As radical cations are very acidic relative to their

Table 9 Acidities for selected radical cations and their neutral analogs.

Compound	pK_a	pK_a^{*+}	Proton affinity
C ₆ H ₆	—	—	147 ± 1 ^{59c}
C ₆ H ₅ CH ₃	43 ^{60a}	−20 ^{60a}	191 ^{60b} 139 ± 1 ^{59c} 200 ^{60b}
C ₆ H ₅ OH	9.99 ^{46(a) d} 18.3 ^{60a}	−2.0 ^{61e} −8.1 ^{60a}	
C ₆ H ₄ (OH) ₂	9.85 ^{46(a) d}	−0.75 ^{61e}	
C ₆ H ₅ NH ₂	30.6 ⁶²	6.4 ^{62f}	
C ₆ H ₅ NHCH ₃	29.5 ⁶²	4.2 ^{62f}	
C ₆ H ₅ N(CH ₃) ₂	—	9 ^{63f} 18.8 ^{64(a) g}	
(C ₆ H ₅) ₂ N	—	3.6 ^{65d}	
(CH ₃ CH ₂) ₂ N	—	5.3 ^{65d}	

^a DMSO.

^b Gas phase proton affinity.

^c Gas phase proton affinity.

^d H₂O.

^e Gas phase proton affinity, error ±5%.

^f CH₃CN.

^g CH₃CN/0.5M H₂O.

Table 10 pK_a s of aromatic amine radical cations.

Aromatic amine	pK_a^{*+} CH ₃ CN ⁶³	pK_a^{*+} 0.5 M·H ₂ O/ CH ₃ CN ^{64a}
C ₆ H ₅ N(Me) ₂	9	18.8
<i>p</i> -MeOC ₆ H ₄ N(Me) ₂	13	23.2
<i>p</i> -MeC ₆ H ₄ N(Me) ₂	12	19.5
<i>p</i> -ClC ₆ H ₄ N(Me) ₂	9	16.6
<i>p</i> -CF ₃ C ₆ H ₄ N(Me) ₂	—	14.6

neutral counterparts, electron transfer might be a good mechanism for catalysis especially when a C–H bond is broken during the reaction because a highly ionizable radical cation favors the subsequent deprotonation step. In Table 10, pK_a s calculated for several anilines and their corresponding radical cations are presented.

These compounds are of interest as a result of their structural similarity to several substrates for SET enzymes. In fact, until recently *N*-cyclopropyl-*N*-methylanilines were thought to be attractive mechanistic probes for mechanism of catalysis for these enzymes, vide supra. As expected, the radical cations are extremely acidic relative to the neutral bases. On average, for substituted anilines the radical cation is more than 20 orders of magnitude more acidic than the neutral counterpart! The large difference between the pK_a of the anilines and their radical cations

displays this increased acidity; analogous results would be expected for all radical cations as a result of the increased electrophilicity of a cation relative to a neutral radical. It is this increased acidity that puts forth PCET as a mechanism for catalysis involving these substrates in SET enzymes. The authors use this evidence to assert the idea that this decreased acidity decreases the possibility that HAT from the parent compound will proceed via a route involving deprotonation of a radical cation intermediate.⁶⁵ Notably, in the table above the acidity of the radical cation is increased relative to the neutral compound, although, the radical cations are not very acidic. Although values were not available for the pK_a s of the neutral dimethylanilines discussed below, these values are expected to exhibit alkalinity similar to that of other aromatic amines to a normal aliphatic C-H bond. In Table 10, pK_a values for several dimethylaniline radical cations are shown in CH_3CN and 0.5 M H_2O in CH_3CN . Table 10 presents the acidities of several dimethylaniline radical cations; the pK_a refers to the acidity of a C-H bond and not of a quaternary protonated amine; this point is further clarified by Scheme 24 showing the acid and its conjugate base. Moreover, the acidities of the aniline radical cations are greater than those of the corresponding dimethylaniline radical cations. From the values in Table 10, some general structure-acidity relationships are apparent. Values for pK_a s, calculated by Bordwell and Dinnocenzo, for both sets of compounds show similar trends, in that as the electron-donating ability of the substituent decreases, the pK_a increases, indicating the most electron-withdrawing para substituents are the most acidic. This result is cogent because as electron-donating ability decreases the positive charge localized on the nitrogen attached to (or adjacent to) the protic hydrogen in anilines (and dimethylanilines) also decreases. Again, as noted for the anilines, the dimethylaniline radical cations are not extremely acidic as might be expected. Although pK_a s were not provided for tertiary aliphatic amine radical cations, a study by Nelsen *et al.* states that several acidities calculated via a thermodynamic cycle show that the trialkyl amine radical cations exhibit average pK_a s of 15, suggesting tertiary alkyl amines radical cations are also not as acidic as might be expected.⁶⁵ These species do exhibit drastically lowered C-H bond dissociation energies in the radical cation, which

Table 11 pK_a s of some aliphatic amine radical cations.⁶⁵

Aliphatic amines	$pK_a^{*+} \text{H}_2\text{O}$
Diphenylamine	3.6 ± 0.2
Diethylamine	5.3 ± 0.5
Dimethylamine	6.8 ± 0.5
Piperidine	5.8 ± 0.5
Pyrrolidine	5.5 ± 0.5

is attributed to orbital mixing between the C-H bond and the nitrogen's p orbital containing the unpaired electron.⁶⁵ The authors further note that the stability of the resultant carbon centered neutral radical is high due to resonance in support of the conclusion that acidity of the radical cation is not a primary factor in deprotonation. Griller noted in the study of deprotonation of alkyl radical cations by their parent compound that the amines were not basic enough to cause facile deprotonation to occur. Other studies of tertiary alkyl amine radical cations indicate stronger bases could significantly increase rates.⁸⁴ Nelsen poignantly asserts that a probable reason for this is that weaker bases do not deactivate the radical cation by deprotonation at a rate competitive with other means of decay.⁶⁵ In Table 11, strictly for comparison, the experimentally determined aqueous pK_a s of several secondary aliphatic amine radical cations are shown, displaying weakly acidic behavior, although more acidic than values calculated for their tertiary counterparts.

What is more, as the degree of substitution increases, the acidity of the amine decreases because alkyl substituents donate electron density to the nitrogen disfavoring deprotonation and a further increase in electron density on the nitrogen adjacent to the α carbon attached to the protic hydrogen.

4.2.2 Radical Cation Deprotonation: Kinetics

The kinetics of deprotonation of radical cations are dependent on several factors discussed above such as bond strength and pK_a of the radical cation; the strength of the base can also impact kinetics. For radical cations that have a low thermodynamic acidity, deprotonation may occur on a time scale slow enough that other routes of decay are plausible.^{65,85} Further convoluting kinetic analysis is difficulty distinguishing the rate constant

for radical cation deprotonation from that of other steps such as preceding electron transfer to generate the radical cation.⁶⁵ As dynamics of deprotonation has long been a topic of interest, there is a vast amount of literature pertaining to the topic.

Rate constants for deprotonation of dimethylaniline radical cations by acetate and pyridine have been determined previously by electrochemical and photochemical means.⁶⁴ Parker noted decay of the *N,N*-dimethylaniline radical cations by dimerization without base present, likewise noting this occurrence even for para substituted derivatives.^{64b} In the presence of base, facile deprotonation of these radical cations is observed and attributed to the positive charge on the nitrogen being relatively close to the α carbon deprotonated by the base.^{64b} Hammett and Bronsted analysis was performed for reactions with both bases. Hammett and Bronsted plots display linear free energy relationships of acidity of the radical cation with the nature of substituents, and base strength with rate constant for deprotonation.⁸⁶ The acetate deprotonation proceeds with a rate constant several orders of magnitude greater than that of the corresponding reaction with pyridine as shown in Table 12.^{64b}

Reactions of both bases with *para*-substituted *N,N*-dimethylanilines in acetonitrile show sensitivity to substituents effects giving linear Hammett

plots displaying the relationship between rate constant and $\sigma+$ yielding ρ values of 1.7 and 3.5 for acetate and pyridine, respectively.⁶⁴ Although these reactions are affected by the nature of the substituent, it should be noted that the magnitude of this effect decreases for the more energetically favorable, and consequently faster deprotonation by acetate. Bronsted analysis was also performed and α values were determined to be 0.24 and 0.51 for acetate and pyridine, respectively.^{64b} Because the α value is a measure of transition state location, a low value of α suggests an early transition state, consistent with acetate being more reactive.^{64b} Also, this explains the lower ρ value because acetate is more reactive; the rate is less sensitive to the nature of the substituent. Building on these observations and evidence from previous studies of radical cation kinetics, the authors suggest the mechanism for proton transfer shown in Scheme 26.

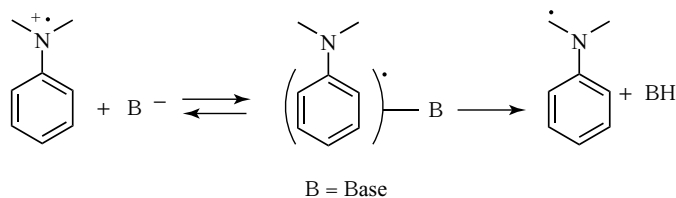
This mechanism is characterized by a fast reversible formation of an adduct followed by rate determining proton transfer as the complex breaks apart.^{63,64} Parker uses this mechanism to also account for observed experimental results for proton transfers involving several arene radical cations, and these studies provide further support for a mechanism involving adduct formation.^{63,87}

Later, photochemical analysis by Dinnocenzo of the acetate deprotonations of several substituted *N,N*-dimethylaniline radical cations revealed similar trends in rate constants for the *para* substituted compounds as previously noted by Parker although the magnitudes of the photochemically acquired rate constants were greater in all cases than those attained electrochemically. Differences are to be expected as ionic strength was maintained with different electrolytes and in the latter experiments a different solvent system was employed. The second-order rate constants for the reaction of several substituted dimethylaniline cations with acetate in 0.5 M H₂O in CH₃CN are shown in Table 13.^{64a}

Table 12 Rate constants of the reactions of *p*-substituted *N,N*-dimethylaniline radical cations with acetate and pyridine at 25 °C in CH₃CN with 0.5 M *n*-Bu₄CIO₄.

Substituent	k_{pyridine} (M ⁻¹ s ⁻¹)	k_{acetate} (M ⁻¹ s ⁻¹)
CH ₃ O	0.94	3.5×10^6
Cl	1.0×10^3	6.2×10^8
CN	2.5×10^5	1.0×10^9
NO ₂	1.4×10^5	3.0×10^9

Source: Reprinted with permission from Ref. 63. Copyright 1991, American Chemical Society.



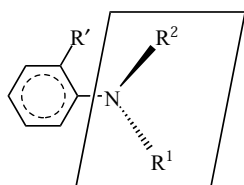
Scheme 26 Mechanism of proton transfer from *N,N*-dimethylaniline radical cations.

Table 13 Rate constants for deprotonation of substituted *N,N*-dimethylaniline at room temperature in 0.5 M H₂O in CH₃CN with 0.5 M *n*-BuClO₄.⁶⁴

Substituent		<i>k</i> (M ⁻¹ s ⁻¹)
Para	OCH ₃	1.1 × 10 ⁷
	CH ₃	4.1 × 10 ⁷
	H	1.2 × 10 ⁸
	Cl	1.7 × 10 ⁸
	CF ₃	1.4 × 10 ⁸
Ortho	CH ₃	2.4 × 10 ⁸
	<i>t</i> -Bu	4.9 × 10 ⁹
	CH ₃ , CH ₃	3.6 × 10 ⁹

In the Dinnocenzo experiments, 0.5 M H₂O in acetonitrile in lieu of neat acetonitrile was the solvent used in an effort to maintain polarity as, in these studies, it was observed that the rate of deprotonation was significantly affected by ionic strength and polarity.^{64a} Small primary deuterium kinetic isotope effects were noted in kinetic studies of *N,N*-dimethylanilines with deuterated α carbons suggesting that the barrier to reaction is governed by the C–H bond breaking and an early transition state.^{64a} This corresponds well to the low α value observed by Parker, Bronsted relationship noted previously by Parker further confirming an early transition state. Dinnocenzo performed Bronsted analysis; an α value of 0.23 was observed, providing further support for the reactant like transition state.^{64a} In addition, the effect of electron-donating ability showed similar trends to those observed by Parker. Notably, the effect of ortho substituents is an increase in acidity of the amine.^{64a} This occurs for steric reasons as the nitrogen twists, consequently breaking up the conjugation with the aromatic ring, and concentrating electron density on the nitrogen as shown in Figure 15.^{64a}

This supposition was confirmed via density functional theory calculations that displayed a

**Figure 15** Ortho substituents increase amine acidity by twisting α -carbon out of the plane of the aromatic ring.

rotation of the nitrogen in the ortho substituted compounds.^{64a} Dinnocenzo further suggests this localization may lend an increased acidity to the analogous radical cation as charge and spin will also be localized in close proximity to the protic hydrogen supporting a more facile deprotonation.^{64a}

4.3 Comparing Mechanisms: HAT and Deprotonation

When proton and electron transfer occur in concert, whether it be involving a single hydrogen atom or a proton and an electron in a near by orbital, the reaction is typically more facile than a stepwise HAT because the solvation cost for involving deprotonation (and ions) outweighs the increase in reaction barrier for both processes to occur in a single step. Also, these processes have been shown to be more thermodynamically favorable than their sequential counterparts.⁸¹ The Evans–Polyani relationship is a great linear free energy relationship to describe simple concerted hydrogen transfer reactions; although many reactions, especially sequential HAT processes, are effected by complicating stereoelectronic or polar effects making this type of data treatment ineffective and necessitating investigation of kinetic dependence on other structural features such as thermodynamic acidity of the molecule undergoing HAT.

Generally, attempts to differentiate between deprotonation and HAT require careful and innovative experimental strategies. In sequential HAT mechanisms where deprotonation is the rate limiting step, it is impossible to elucidate the actual mechanism in some cases. In these cases, the elementary step with the greatest barrier is deprotonation. Therefore, factors governing deprotonation control the reaction, thereby making sequential HAT and deprotonation indistinguishable. This ambiguity is not limited to differentiating between sequential processes and deprotonation; concerted HAT and deprotonation can also be extremely difficult to discriminate as the transition states for a concerted HAT and deprotonation process are isoelectronic. Similar to the rearrangements discussed in the preceeding sections, the radical process (HAT) is intimately related to the radical ion process (deprotonation). In all cases transition state similarities predict similar kinetic trends and

often thermodynamic parameters that predict how specific structural features influence reactivity will trend similarly with kinetics for both the radical and radical ion processes. This is a lucky and important observation for many of us who study radical ion processes making assumptions that these charged species will behave similarly to their neutral analogs.

5 CONCLUSIONS

In the preceeding pages, a relatively comprehensive comparison of some radical and radical ion processes is presented. Two classes of radical reactions are discussed, rearrangements and atom transfers. In the context of atom transfer, routes leading to hydrogen transfer for neutral radicals are compared to the complementary radical ion process, deprotonation. Many sequential hydrogen transfer reactions involve deprotonation as an elementary step in their mechanism. What is more, concerted hydrogen transfer and deprotonation proceed through isoelectronic transition states, often leading to difficulties in discriminating the processes experimentally. Both classes of unimolecular rearrangements discussed, cyclopropyl ring openings and Δ -5-hexenyl cyclizations, have been utilized in synthesis and as radical clocks. Many trends observed for the well characterized Δ -5-hexenyl radical cyclizations extrapolate accurately to predicting the regio- and stereoselectivity of the lesser known radical anion siblings. Likewise, there is much to be gleaned about radical ion reactivity from the extensive work on cyclopropylcarbinyl $\rightarrow$ homoallyl rearrangements. The role of torsional strain, ring strain, and the stereo-electronic requirements for ring opening show both marked similarities as well as notable differences comparing the reactivity of radicals, radical anions, and radical cations of cyclopropyl substituted compounds. These particular reactions stand out from the others discussed because there is a rather complete data set for both radicals and radical anions. The cyclopropyl rearrangements provide an excellent example of how similar factors may influence radicals and their complimentary radical ions reactions while also clearly demonstrating the need for caution when extrapolating reactivity trends as the relative importance of factors influencing reactivity may change significantly with the introduction of charge. The similarities observed in the reactions

discussed herein are not fortuitous but rather indicative of similar activation or driving force trends for the complementary processes. Prudently used, these reactivity relationships are an excellent predictive tool when studying the radical ion analog of a previously characterized radical process.

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Atmospheric Radical Chemistry

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1 INTRODUCTION

The atmosphere is a complex photochemical reactor. A vast majority of the chemical transformations that take place in the atmosphere involve reactions of free radicals that are generated by photodissociation of closed-shell precursors. The four chemical species N_2 , O_2 , H_2O , and Ar, account for more than 99.9% of the gas-phase molecules in the atmosphere.¹ We will see below that two of these major atmospheric components, namely, O_2 and H_2O , do play a significant role in atmospheric chemistry. However, a vast majority of the gas-phase chemistry of interest for understanding major environmental issues such as climate change, urban air quality, stratospheric ozone depletion, as well as the ability of the atmosphere to cleanse itself of pollutants, is driven by reactions of trace components that have mixing ratios (i.e., mole fractions) ranging from less than 1 part per trillion up to a few parts per million.

Because the atmosphere is an oxidizing environment, atmospheric chemistry can be viewed as low-temperature combustion. However, the radical chain reactions that ultimately produce oxidized species such as CO_2 occur rather slowly under atmospheric conditions. Biological processes contribute to fairly rapid rates of injection of chemically reduced species such as methane (CH_4) into the atmosphere, and such species are present at much higher levels than chemical equilibrium considerations would suggest. For example, the atmospheric mixing ratio of CH_4 , which is 1.7 ppmv

(parts per million by volume), is more than 100 orders of magnitude greater than would be expected if the combustion reactants and products CH_4 , O_2 , H_2O , and CO_2 were present at equilibrium concentrations. As a result, a description of the chemistry of the atmosphere requires the application of chemical kinetics. Rate coefficients for a multitude of free-radical reactions are necessary input parameters into photochemical models that are used to interpret field observations and make predictions about the future state of the atmosphere. Both NASA (National Aeronautics and Space Administration) and IUPAC (International Union of Pure and Applied Chemistry) sponsor panels that critically review the literature and recommend kinetic parameters for use in modeling atmospheric chemistry. The most recent comprehensive NASA panel evaluation appeared in 2006,² with an updated version scheduled to appear in early 2011;³ the NASA evaluations appear as Jet Propulsion Laboratory (JPL) publications and are available to the public on a dedicated web site.^{2,3} The most up-to-date IUPAC evaluations have been published as a series of papers in the journal *Atmospheric Chemistry and Physics* that have appeared over the 2004–2010 time period.^{4–8} Data sheets for individual reactions are also available at www.iupac-kinetics.ch.cam.ac.uk.

1.1 The Atmospheric Condensed Phase

Condensed-phase processes play a significant role in atmospheric chemistry. At any instant in time, clouds are found above approximately 60% of the

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earth's surface.⁹ The liquid water content of clouds is typically in the range 0.1–0.3 g of H₂O per cubic meter, which corresponds to a volume mixing ratio of liquid water (volume of H₂O(l)/volume of air) in the range $(1-3) \times 10^{-7}$.⁹ Many atmospheric trace gases are highly soluble in water and such species can be taken up into cloud water and undergo chemical transformation in the aqueous phase. Uptake into cloud water and subsequent removal from the atmosphere by rain is an important pathway for removing some soluble pollutants from the atmosphere. However, most clouds evaporate rather than produce rain. When a cloud evaporates, some chemical substances are returned to the gas phase but often in a chemically more oxidized form than upon initial uptake into the aqueous phase. Since oxidized substances are typically less volatile than their reduced precursors, cloud evaporation often does not result in complete return to the gas phase of all mass that entered the droplet by uptake from the gas phase: that is, “cloud processing” of atmospheric particles (see below) represents a mechanism for particle growth.

In addition to cloud droplets, particles represent another form of condensed-phase material in the atmosphere. There is currently enormous interest in anthropogenic (i.e., resulting from human activity) atmospheric particles because of their health effects and their climate impacts, which result from their role in scattering and absorbing atmospheric radiation (direct effect) as well as their role in altering cloud properties (indirect effect).^{1,9,10} It is worth pointing out that cloud droplets cannot form by condensation of pure water vapor, but instead must grow from particles that have the correct thermodynamic properties to act as cloud condensation nuclei.⁹ In addition to their importance in health effects and climate, particles provide a medium on (or in) which some chemical transformations can occur that would not occur in the gas phase. One important example of this behavior that will be discussed in a later section of this article is the role of polar stratospheric cloud (PSC) particles in creation of the Antarctic ozone hole.

1.2 Vertical Layers in the Atmosphere

Approximately 99.9% of the mass of the atmosphere is contained in the lowest 50 km of altitude and

this altitude regime is divided into two distinct layers, the troposphere and the stratosphere.^{1,9–11} This article will focus on radical chemistry in these layers. Some of the basic characteristics of the troposphere and stratosphere are summarized below. References for individual statements are not given since the characteristics summarized below are discussed in atmospheric chemistry textbooks.^{1,9–11}

The troposphere is the lowest layer of the atmosphere. It extends from the earth's surface to an altitude that varies from about 8 km at polar latitudes to about 15 km in the tropics. Approximately 85% of the atmospheric mass is contained in the troposphere. The primary energy source in the troposphere is radiative heating from the earth's surface. As a result, temperature drops with increasing altitude, and rapid vertical mixing by convection can occur. Solar radiation at wavelengths shorter than 290 nm is absorbed at altitudes above the top of the tropopause (the boundary between the troposphere and stratosphere), so all photochemistry in the troposphere is initiated by photons with $\lambda > 290$ nm. The average temperature at the earth's surface is currently estimated to be 288 K, while the average temperature at the tropopause is approximately 210 K. The troposphere can be further divided into two vertical layers, the planetary boundary layer and the free troposphere. The planetary boundary layer tops out during daytime hours at altitudes that vary from about 1–3 km depending on the amount of solar heating of the surface. After sunset, the surface cools radiatively more rapidly than the overlying atmosphere, leading to the creation of a temperature inversion and a low boundary layer top at night. Pollutants emitted into the boundary layer at the surface are mixed into the free troposphere on a timescale of a day or two, and vertical mixing to the tropopause occurs, on average, on a timescale of 1 month. In strong thunderstorms, chemical species can be transported from the boundary layer top to the tropopause in only a few hours. The general circulation pattern in the troposphere is such that nonreactive chemical species that are emitted into the atmosphere at mid-latitudes in the Northern Hemisphere are transported to the tropics or to polar latitudes on a timescale of 1–2 months and to the Southern Hemisphere on a timescale of about 1 year. The competition between transport and chemical loss results in a strong correlation between a pollutant chemical's lifetime and its distribution in the troposphere; less reactive species tend to be uniformly distributed,

whereas more reactive species tend to be found only in the vicinity of sources.

The stratosphere extends from the tropopause to an altitude of approximately 50 km. The primary energy source in the stratosphere is absorption of solar radiation by O_2 and O_3 ; ozone (O_3) is produced by the association reaction of atomic oxygen, which is the product of O_2 photodissociation, with O_2 . In the stratosphere, temperature increases with increasing altitude from about 210 K at the tropopause to about 270 K at the stratopause (the boundary between the stratosphere and the overlying mesosphere). Approximately 90% of atmospheric ozone (O_3) resides in the stratosphere, and this ozone, in combination with O_2 , prevents radiation at wavelengths shorter than 290 nm from penetrating to the earth's surface where it would have harmful effects on the biosphere. Hence, the focus in stratospheric chemistry is on understanding how anthropogenic activity impacts the ozone levels. Because temperature increases with increasing altitude, the stratosphere is very stable toward vertical mixing. Furthermore, the tropopause defines the location of a substantial meteorological barrier to vertical transport. The characteristic time for transport from the troposphere to the stratosphere is estimated to be 7.4 years. Hence, only reasonably long-lived tropospheric species have a significant probability of being transported to the stratosphere. For this reason, the chemistry of the stratosphere is much simpler than that of the troposphere. Atmospheric pressure in the stratosphere varies from about 100 Torr at the tropopause to about 0.1 Torr at the stratopause. The lower pressure in the stratosphere compared to the troposphere results in much more varied chemistry for atomic oxygen in the stratosphere than in the troposphere, where essentially every ground-state oxygen atom produced combines with O_2 to generate O_3 . We will see in Section 2 on stratospheric radical chemistry that atomic oxygen plays a central role in a number of catalytic cycles that can destroy ozone.

1.3 Radical Families in Atmospheric Chemistry

In our discussion of atmospheric radical chemistry, it will be useful to define families of reactive species (all but one of which are radicals). The families of primary interest are $O_x \equiv O + O_3$,

$NO_x \equiv NO + NO_2$, $HO_x \equiv OH + HO_2$, $ClO_x \equiv Cl + ClO$, and $BrO_x \equiv Br + BrO$. Later in this article, we will sometimes write HO_2 (hydroperoxyl radical) as HOO. The NO_3 radical is sometimes included in the NO_x family, and the H atom is sometimes included in the HO_x family. We will also have occasion to discuss the chemistry of I atoms and IO radicals, which together make up the IO_x family. The usefulness of defining radical families is based on the fact that, in the atmosphere, the family members are interconverted much more rapidly than the family is either produced or destroyed. Hence, steady-state kinetics can often be employed to evaluate concentration ratios of family members under conditions where it is inappropriate to invoke steady-state kinetics to evaluate the total concentration of all family members.

Except where necessary for clarity, in the text we write chemical formulae for radicals without using dots to designate the site of the unpaired electron. The notation we use is that customarily employed in the atmospheric chemistry literature. As a helpful guide to nonexperts, we include dots in the figures, where most of the common atmospheric radicals appear. No dot appears on the NO_3 radical in Figure 2 because the three oxygen atoms share the unpaired electron density.

1.4 Rates of Photochemical Reactions in the Atmosphere

In atmospheric chemistry models, it is often necessary to evaluate the rate of occurrence of a photochemical reaction. For this purpose, a first-order photochemical rate coefficient (often referred to as a J -value in the atmospheric chemistry literature) can be defined as follows:¹

$$J_X = \int \sigma_X(\lambda) \Phi_X(\lambda) I(\lambda) d\lambda$$

In the above equation, J_X is the first-order rate coefficient for photochemical destruction of X, $\sigma_X(\lambda)$ is the wavelength-dependent cross section for X, $\Phi_X(\lambda)$ is the wavelength-dependent quantum yield for photochemical destruction of X, and $I(\lambda)$ is the actinic flux distribution function which represents a measure of the number of photons of wavelength between λ and $\lambda + d\lambda$ crossing a unit horizontal surface from any direction per unit time.

The J -values can sometimes not only be determined from *in situ* atmospheric measurements, but can also be calculated using the evaluated absorption cross sections and quantum yields^{2–8} in conjunction with tabulated actinic flux distributions.¹⁰ By choosing the appropriate values for $\Phi_X(\lambda)$, one can define a J -value for photochemical destruction of X, photo-excitation of X, or production of a particular photoproduct from X.

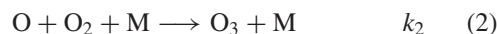
2 RADICAL CHEMISTRY IN THE STRATOSPHERE

In the late 1800s, Hartley identified ozone as the chemical species responsible for the 290-nm cut-off of solar radiation penetrating into the lower atmosphere¹²; hence, the strong ozone absorption feature centered at $\lambda \sim 255$ nm is known as the *Hartley band*. The first accurate spectroscopic measurement of the ground-level ozone mixing ratio was reported by Strutt in 1918,¹³ and reliable measurements of the ozone column, that is, the total number of ozone molecules in a column of unit cross-sectional area extending from ground level to the top of the atmosphere, became available during the 1920s.^{14,15} The combined results of the ground-level ozone measurements and the ozone column measurements implied that there must be an altitude regime where ozone mixing ratios are significantly higher than they are at the earth's surface. A photochemical model capable of predicting the presence of an "ozone layer" was proposed by Chapman in 1928.¹⁶

In this section on stratospheric radical chemistry, we will first describe the mechanism proposed by Chapman and compare its predictions with observations. We will find that the observed ozone levels can be accounted for only if radical-catalyzed destruction of odd-oxygen is incorporated into the overall chemical mechanism. Details of the radical-catalyzed odd-oxygen destruction chemistry are discussed. The Antarctic ozone hole was discovered during the 1980s,¹⁷ which stimulated field and laboratory work that led to the realization that heterogeneous (i.e., multiphase) chemistry plays an important role in controlling stratospheric ozone levels.¹⁸ New radical chemistry that is driven by the occurrence of heterogeneous reactions is described.

2.1 The Chapman Mechanism

The photochemical mechanism proposed by Chapman contained five elementary steps; one of these steps, that is, the recombination of two oxygen atoms to form O₂, is now known to be unimportant under stratospheric conditions. The four reactions that have stood the test of time are the following:



The species M in reaction (2) is any third body collision partner; in the atmosphere, M is mostly N₂ and O₂. Under stratospheric conditions, reactions (2) and (3), which are the reactions that interconvert the members of the O_x family, occur much more rapidly than reactions (1) and (4), which are the reactions that produce and destroy odd-oxygen (O_x). Reaction (2) is found to be in its low-pressure termolecular limit under all conditions that exist in the atmosphere,² so its rate is proportional to P^2 (P = pressure). Since pressure decreases approximately exponentially with altitude,¹ the rate of reaction (2) falls off dramatically with increasing altitude. On the other hand, the rate of reaction (3) increases with increasing altitude because the ultraviolet radiation that is most effective at photolyzing O₃ is attenuated via O₃ absorption as it passes downward through the stratosphere. It is clear that, on the basis of the above considerations, the Chapman mechanism predicts that the ratio [O]/[O₃] should increase dramatically as a function of altitude and this is, indeed, observed to be the case.^{1,11} A quantitative kinetic analysis of the Chapman mechanism under low latitude conditions that uses up-to-date values for J_1 , k_2 , J_3 , and k_4 yields a [O₃] versus altitude dependence that reproduces the observed dependence reasonably well; the altitude of maximum [O₃] is predicted to be ~ 28 km by the kinetic analysis and is observed to be ~ 24 km.¹

It is worth pointing out that photodissociation of O₂ and O₃ produces both ground-state ³P and electronically excited ¹D oxygen atoms. Electronically excited oxygen atoms are much more reactive than ground-state oxygen atoms and, as we will discuss later in this article, O(¹D) plays a crucial role

in the production of atmospheric HO_x , NO_x , and ClO_x radicals; it is also an important initiator of the degradation of numerous long-lived atmospheric constituents. However, under stratospheric conditions, a vast majority of $\text{O}(^1\text{D})$ atoms are deactivated to $\text{O}(^3\text{P})$ via quenching by N_2 and O_2 . Hence, for purposes of analyzing the Chapman mechanism, it is not necessary to distinguish between the two types of oxygen atoms.

It took nearly 50 years following the publication of the Chapman mechanism before the rate coefficient k_4 was quantified over the stratospheric temperature regime.^{19–22} Once k_4 was known quantitatively, it became possible to compare the observed ozone concentrations with those predicted on the basis of the Chapman mechanism and also to compare the O_x production rate from (1) with the O_x loss rate from (4); since globally averaged stratospheric O_3 levels are not changing significantly as a function of time, the overall production and loss rates of O_x must be approximately equal. Odd-oxygen concentrations predicted from a steady-state analysis based on the Chapman mechanism are larger than the observed concentrations by more than a factor of two.¹ Furthermore, a careful analysis of odd-oxygen chemical production, chemical loss, and transport rates shows that loss of O_x via the combination of (4) and downward transport to the troposphere occurs at a rate that is only about 20% of the production rate from (1).²³ The implication of the above findings

is that there must be additional chemical sinks for stratospheric odd-oxygen. Furthermore, since stratospheric odd-oxygen is present in large excess over any species that could destroy it via chemical reaction, it appears that the additional chemical sinks must be *catalytic* in nature. We examine pathways for radical-catalyzed destruction of stratospheric odd-oxygen in the next section.

2.2 Radical Catalysis of Odd-Oxygen Destruction

Bates and Nicolet suggested that HO_x radicals can catalyze stratospheric odd-oxygen destruction in 1950, more than 20 years before it was firmly established that catalytic pathways must be important.²⁴ During the early 1970s, a number of benchmark papers appeared showing that NO_x ,^{25–29} ClO_x ,^{29–32} and BrO_x ³³ radicals were also likely to be important catalysts for odd-oxygen destruction. The early work of Crutzen, Molina, and Rowland was influential in the award of the 1995 Nobel Prize in Chemistry to these three atmospheric chemists.^{25,26,31}

Key chemical pathways in the gas-phase stratospheric chemistry of HO_x , NO_x , ClO_x , and BrO_x radicals are summarized in Figures 1–4. The figures show significant radical source reactions, significant catalytic cycles, significant null cycles, and the key reactions governing the formation and destruction of

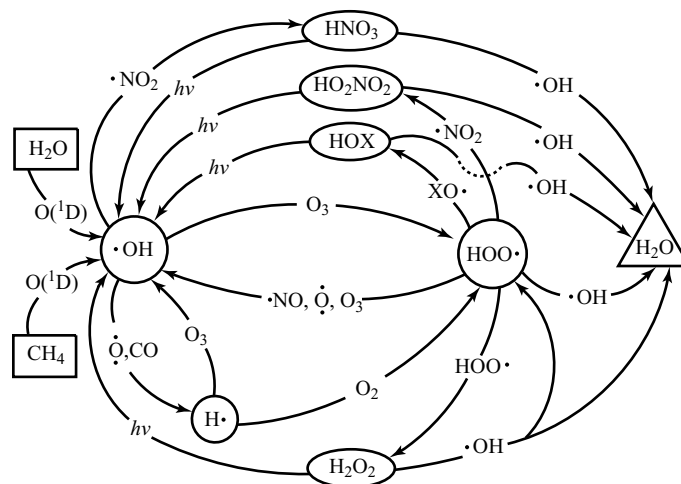


Figure 1 Schematic overview of the gas-phase stratospheric chemistry of HO_x radicals ($X=\text{Cl}, \text{Br}$). [Adapted (with modifications) from Ref. 158.]

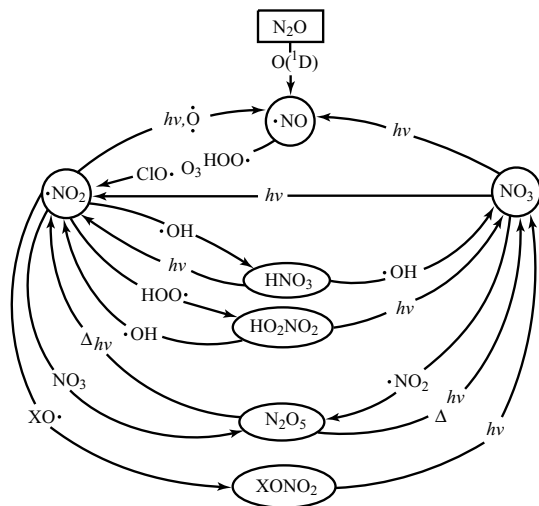


Figure 2 Schematic overview of the gas-phase stratospheric chemistry of NO_x radicals ($X = \text{Cl}, \text{Br}$). [Adapted (with modifications) from Ref. 158.]

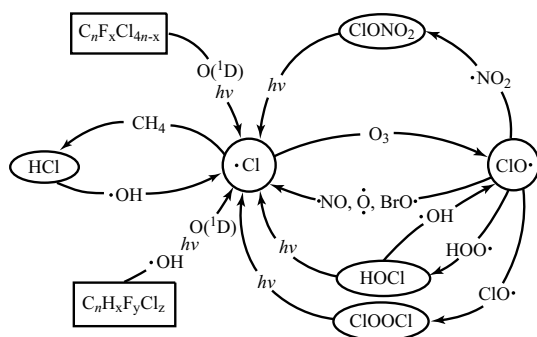


Figure 3 Schematic overview of the gas-phase stratospheric chemistry of ClO_x radicals. [Adapted (with modifications) from Ref. 158.]

reservoir species. The figures are coded with source compounds shown in rectangular boxes, reactive radicals shown in circular boxes, reservoir species shown in elliptical boxes, and one gas-phase sink species (H_2O , a sink for HO_x radicals) shown in a triangular box. Catalytic cycles are discussed in detail in this section. Null cycles and the chemistry of reservoir species are discussed in the next section.

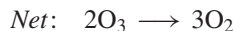
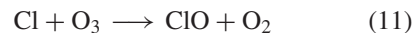
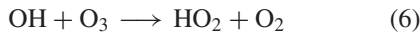
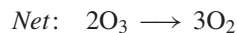
To complete a catalytic cycle, member 1 of a radical family must be converted to member 2 via a reaction that destroys ozone, and member 2 must be cycled back to member 1 without re-forming ozone. The net reaction of the cycle

must be the conversion of odd-oxygen to O_2 . Under stratospheric conditions, the net reactions for the most important catalytic cycles are either reaction (4) or (5):



It is worth noting that, while the uncatalyzed $\text{O} + \text{O}_3$ reaction (4) occurs at a significant rate in the stratosphere, the uncatalyzed $\text{O}_3 + \text{O}_3$ reaction (5) is negligibly slow. As discussed in Section 2.1, the ratio $[\text{O}]/[\text{O}_3]$ increases dramatically with increasing altitude. As a result, catalytic cycles where the net is (4) tend to be most important in the middle and upper stratosphere whereas those where the net is (5) tend to be most important in the lower stratosphere.

Numerous catalytic cycles can be identified upon examination of Figures 1–4. Those that are thought to be most important in controlling stratospheric ozone levels are written out below. Each elementary step is shown, and the step that is rate-limiting under typical stratospheric conditions is written in ***bold italics***. In the atmospheric chemistry literature, it is customary to identify a cycle by specifying the reactants in the rate-limiting step. For example, the first catalytic cycle shown below is often referred to as the $\text{O} + \text{HO}_2$ cycle; we will use this approach to identify cycles. Note that in Figures 1–4 and in the reactions written out below, $\text{O} \equiv \text{O}(^3\text{P})$, the ground state oxygen atom.



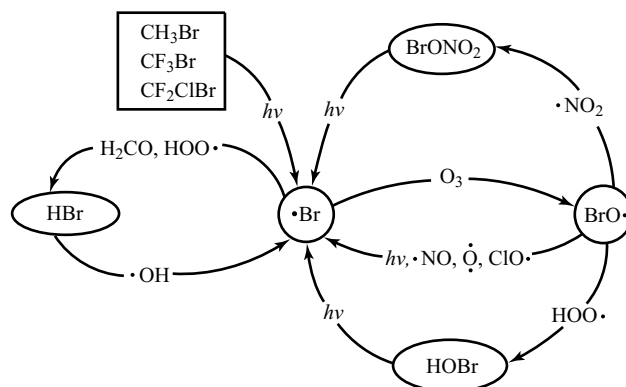
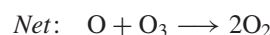
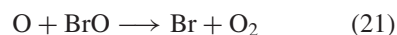
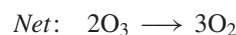
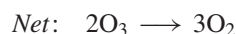
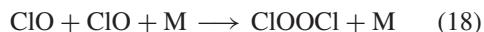
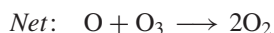
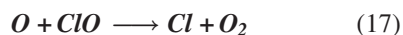
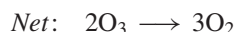
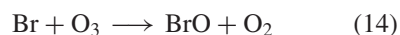


Figure 4 Schematic overview of the gas-phase stratospheric chemistry of BrO_x radicals.

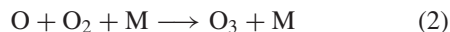
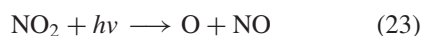


By the early 1980s, laboratory studies of key reactions (see above) in combination with results from field observations of the O_3 column made it possible to assess the potential for observed stratospheric ozone levels to be accounted for by including catalytic pathways for ozone destruction along with Chapman chemistry in model simulations.³⁴ It was concluded that the observed ozone columns could readily be accounted for by incorporating HO_x catalysis, NO_x catalysis, or ClO_x catalysis either separately or in combination. However, the effects of the different radical families were found to be nonadditive, with the nonlinear behavior appearing to result primarily from the coupling between NO_x chemistry and the chemistries of other families. As we discuss in the next section, the presence of NO_x radicals reduces the efficiency with which other radical families can destroy ozone because NO_x participates in null cycles that compete with catalytic cycles, and because NO_x participates in the formation of reservoir species that tie up HO_x , ClO_x , and (to a lesser extent) BrO_x radicals in relatively unreactive forms, thus inhibiting their ability to destroy ozone.

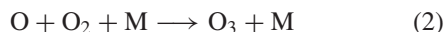
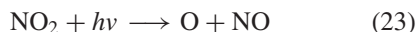
2.3 Null Cycles and Reservoir Formation

To complete a null cycle, member 1 of a radical family must be converted to member 2 via a reaction that destroys ozone, and member 2 must be cycled

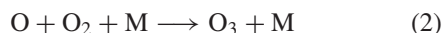
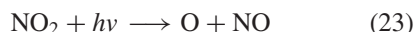
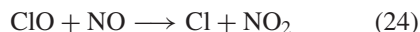
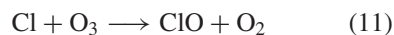
back to member 1 via a pathway that re-forms ozone. The net reaction of the cycle must be no change. Important null cycles are written out below with each elementary step shown.



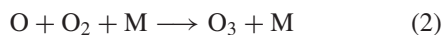
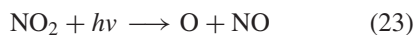
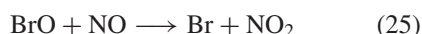
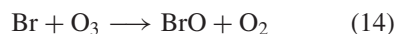
Net: Nothing



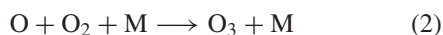
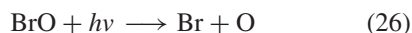
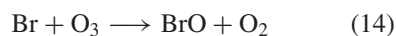
Net: Nothing



Net: Nothing



Net: Nothing



Net: Nothing

Null cycles compete with catalytic cycles, thereby reducing the rate of catalytic ozone loss. Model calculations that evaluate stratospheric ozone levels are very sensitive to the choice of rate coefficients for reactions (22) and (24), even though the primary role of these reactions is their involvement in “net nothing” cycles.

Another group of gas-phase reactions that impact stratospheric ozone levels are reactions that interconvert radicals and reservoirs. A reservoir species is one that serves as a holding tank for reactive radicals, tying them up in a less reactive form. We distinguish *reservoirs* from *sinks* by their ultimate fate. Reservoirs are converted back to reactive radicals, whereas sink species are lost from the stratosphere without being converted back to reactive radicals. The partitioning of reactive species between radicals and reservoirs strongly influences the effectiveness of a radical family as a catalyst for ozone destruction. All species shown in elliptical boxes in Figures 1–4 are reservoir species; the key reactions that convert radicals to reservoirs and reservoirs back to radicals are shown in these figures.

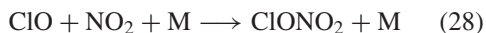
Three of the five null cycles specified above involve the interaction of NO_x radicals with other radical families. In addition, formation of the key reservoir species nitric acid (HNO_3 or HONO_2), peroxyxynitric acid (HNO_4 , HO_2NO_2 , or HOONO_2), chlorine nitrate (ClNO_3 or ClONO_2), and bromine nitrate (BrNO_3 or BrONO_2) also involve interaction of NO_x radicals with other radical families. The effect of the occurrence of both the family-coupling null cycles and the family-coupling reservoir reactions is reduction in the effectiveness of XO_x ($\text{X}=\text{H}$, Cl , or Br) as a catalyst for ozone destruction. For this reason, the dependence of the overall ozone removal rate on $[\text{NO}_x]$ is highly nonlinear over the range of $[\text{NO}_x]$ that can be present in the stratosphere. When NO_x levels are low, the ozone removal rate decreases with increasing $[\text{NO}_x]$ because of the effect of increasing NO_x on HO_x , ClO_x , and BrO_x catalysis. However, when NO_x levels get high enough, the $\text{O} + \text{NO}_2$ catalytic cycle becomes the dominant mechanism for ozone destruction and the ozone removal rate increases with increasing NO_x .³⁵

2.4 Effectiveness of FO_x , ClO_x , BrO_x , and IO_x as Catalysts for Ozone Destruction

The halogen radical families ClO_x and BrO_x have played a prominent role in our discussion of gas-phase stratospheric radical chemistry, whereas the radical families FO_x and IO_x have not. It is interesting at this point to examine the differences between the gas-phase chemistries of the different halogen radicals.

The production rate of F atoms in the stratosphere is rather low because only very high energy radiation is capable of releasing F atoms from organic fluorine compounds via photolysis. Furthermore, a significant fraction of the F atoms that are formed react by abstracting hydrogen from CH₄ or H₂O to produce HF. Unlike other HX species (X = Cl, Br, I), HF does not react with OH to re-form the F atom. Hence, HF is not a reservoir species; it is a sink species. For this reason, FO_x radicals are of negligible importance as a catalyst for ozone destruction.

The production rate of ClO_x radicals via photodissociation of chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), reactions of CFCs and HCFCs with O(¹D), and reactions of HCFCs with OH is significant. Once formed, ClO_x radicals are converted to reservoir species efficiently. The most important reservoir-forming reactions are the following:



Under conditions where gas-phase chemistry is dominant, the partitioning of reactive chlorine at steady state is typically about 10% ClO_x radicals and 90% reservoirs in the upper stratosphere and about 2–3% ClO_x radicals and 97–98% reservoirs in the lower stratosphere.¹⁸ We will see in the next section that heterogeneous (i.e., multiphase) chemistry can change the picture significantly. However, in parts of the stratosphere that are not heavily impacted by heterogeneous chemistry, chlorine is only moderately effective as a catalyst for ozone destruction because its partitioning is primarily to reservoirs.

Because absorption spectra of organic bromine compounds are red-shifted from those of the analogous organic chlorine compounds, the bromine source compounds CH₃Br, CF₃Br, and CF₂ClBr release Br atoms by photodissociation very efficiently in the lower stratosphere where O₃ levels are high. Formation of the HBr reservoir does not occur nearly as rapidly as the formation of the HCl reservoir because reactions of Br with CH₄ and H₂ are endothermic and do not occur at significant rates in the stratosphere. Furthermore, the rate coefficient for the OH + HBr reaction, which converts HBr to Br, is considerably larger than that for the OH + HCl reaction, which converts HCl to Cl (a factor of 14 at 300 K, increasing to a factor of

33 at 200 K).² Hence, while HCl is a key reservoir for ClO_x radicals, HBr is of only minor importance as a reservoir for BrO_x radicals. The rates of formation of the XONO₂ reservoir species (X=Cl, Br) are very similar, but the rate of conversion of BrONO₂ to BrO_x by photolysis is significantly higher than that of ClONO₂ to ClO_x by photolysis (again because the BrONO₂ absorption spectrum is red-shifted relative to the ClONO₂ absorption spectrum).² In regions of the lower stratosphere not heavily impacted by heterogeneous chemistry, differences in the rates of formation and loss of key reservoirs result in a much higher fraction of reactive bromine (about 50%) being present as radicals compared to the fraction of reactive chlorine present as radicals (2–3%, see above). As a result, bromine is much more effective than chlorine *on a per atom basis* as a catalyst for the destruction of stratospheric ozone. However, the total chlorine levels in the stratosphere are currently a factor of 160 larger than total bromine levels, so chlorine contributes more than bromine to ozone depletion.³⁶

If iodine were present at significant levels in the stratosphere, it would be a potent catalyst for ozone destruction because reactive iodine would be partitioned almost entirely into IO_x radicals. However, the absorption spectra of organic iodine source compounds are sufficiently red-shifted compared to those of the analogous bromine and chlorine compounds, so that the iodine compounds photodissociate efficiently in the troposphere; their tropospheric lifetimes are typically a few days. Hence, the iodine source compounds do not reach the stratosphere in significant quantity and iodine is thought to be unimportant as a catalyst for stratospheric ozone destruction.

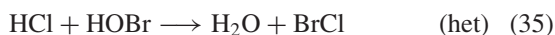
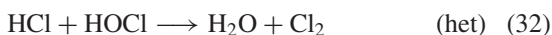
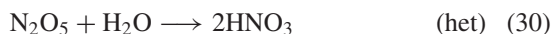
2.5 Role of Heterogeneous Chemistry in Stratospheric Ozone Depletion

The first paper reporting the observation of the Antarctic ozone hole appeared in 1985.¹⁷ Measurements of ozone vertical profiles at the South Pole during the late 1980s and early 1990s showed that ozone mixing ratios were typically normal in late August, showing peak O₃ partial pressures of about 15 mPa at altitudes between 15 and 20 km.¹ However, by mid-October, O₃ levels over the South Pole at altitudes of 10–20 km dropped to near zero.¹ Examination of the time series of observed

average October O₃ vertical profiles at the South Pole showed that the massive depletion of O₃ at lower stratospheric altitudes was not observed in the late 1960s, but evolved over a 15-year period between 1970 and 1985.^{18,37}

The typical air circulation pattern that exists in the wintertime Antarctic lower stratosphere is such that the polar air mass is isolated; that is, it mixes only very slowly with air from lower latitudes.¹ Hence, any chemical changes that occur in this isolated “polar vortex” are not diluted. In addition, temperatures are so low (~190 K) that PSC particles, which are composed of water, nitric acid, and sulfuric acid, form.^{1,18}

During the late 1980s, large field programs were organized to develop an understanding of the Antarctic ozone hole. The key data that helped to establish the cause of the ozone hole involved observations of reactive chlorine species, most notably ClO.^{38–40} Inside the lower stratosphere polar vortex, springtime ClO mixing ratios were found to reach 1 ppbv (parts per billion by volume), more than 100 times greater than the mixing ratio predicted by photochemical models employing only gas-phase chemistry (Sections 2.1–2.4 above).^{18,38–40} A possible mechanism for generation of large levels of ClO involves production of ClO_x photolytic precursors via reactions on (or in) PSC particles, and laboratory studies carried out during the late 1980s and early 1990s demonstrated the occurrence at atmospherically relevant rates of a number of such *heterogeneous* reactions:^{18,41–52}



The homogeneous gas-phase versions of reactions (29)–(35) are all extremely slow and do not play a significant role in atmospheric chemistry. The above

heterogeneous reactions convert ClO_x and BrO_x reservoirs to photochemically labile Cl₂ and BrCl which are released to the gas phase and build up in concentration during the long, dark polar winter. When the sun comes up in the polar spring, Cl₂ and BrCl are rapidly photolyzed to produce large quantities of ClO_x and BrO_x radicals. Furthermore, NO_x radicals are depleted from the gas phase because the HNO₃ that participates in PSC formation as well as the HNO₃ product of reactions (29)–(31), (33), and (34) largely remains in the condensed phase as NO₃[−]. Hence, the rates of null cycles and reservoir-forming reactions of NO_x are very slow, and ClO_x radical mixing ratios reach extremely high levels; levels of BrO_x radicals are also somewhat higher than under “unperturbed” stratospheric conditions. Under Antarctic lower stratosphere springtime conditions, the ClOOCl + *hν* catalytic cycle, that is, reactions (11), (18), and (19), which is unimportant in the unperturbed stratosphere, becomes dominant. The ClOOCl + *hν* cycle accounts for about 80% of odd-oxygen destruction under ozone hole conditions, with most of the remaining 20% attributable to the ClO + BrO cycle, that is, reactions (11), (14), and (20).^{1,18}

The ClO dimer, which is formed via the ClO + ClO association reaction (18), is a key intermediate in polar stratospheric chemistry. The most stable isomer of Cl₂O₂ is thought to be ClClO₂.⁵³ However, the dominant product of the ClO self-reaction has been shown to be ClOOCl,⁵⁴ and this isomer is thought to be the only one of importance in atmospheric chemistry. The strength of the ClO–OCl bond is only 76 ± 3 kJ mol^{−1},^{2,53} so ClOOCl is thermally stable only at the low temperatures typical of the polar vortex. If ClOOCl photodissociated via rupture of the weak O–O bond, then its formation and photolysis would complete a null cycle and ozone loss would not occur. However, careful laboratory studies have shown that the dominant photodissociation channel produces Cl + ClOO, although small yields of ClO are observed at λ > 300 nm.^{55–59} The Cl–OO bond is so weak (~20 kJ mol^{−1}) that this species fragments almost instantaneously to Cl + O₂.^{3,60}

Because reaction (19) is the rate-limiting step in the catalytic cycle that dominates springtime polar ozone destruction, it is not surprising to find that model simulations identify uncertainty in the rate of this reaction, which arises primarily from uncertainties in ClOOCl absorption cross sections

at $300\text{ nm} < \lambda < 450\text{ nm}$ (the important wavelength range for atmospheric photolysis), as the single largest chemical uncertainty limiting quantitative modeling of polar ozone depletion.⁶¹ The relevant cross sections are difficult to measure because they are relatively small (particularly at $\lambda > 350\text{ nm}$) and because it is difficult to prepare ClOOCl samples that are free of absorbing impurities. The absorption cross sections recommended in the 2006 NASA panel evaluation² represent an average of results from two studies that lead to photodissociation rate coefficients (i.e., J -values) that differ by a factor of 2.6.^{62,63} The largest set of measured cross sections⁶² appear to be the most consistent with ClO and ClOOCl levels observed in field studies.⁶⁴ In 2007, Pope *et al.* published a careful experimental study where a novel approach to minimize interferences from impurity absorptions was employed;⁶⁵ the results of this study suggest that the ClOOCl photolysis rate is a factor of 6.2 slower than the 2006 NASA panel recommendation and about an order of magnitude too slow to be consistent with field observations assuming that the chemical mechanism used to interpret the field observations is correct. The Pope *et al.* paper has stimulated significant recent work on the ClOOCl absorption spectrum in a number of leading laboratories around the world.^{59,66–71} It now appears that the majority of new laboratory results predict a relatively large photolysis rate coefficient that is consistent with field observations as interpreted using presently understood chemistry. In their study, Pope *et al.* assumed that a long-wavelength feature in the measured absorption spectrum resulted from Cl₂ impurity and used the known wavelength dependence of the Cl₂ absorption spectrum in conjunction with a least squares fitting procedure to correct the spectrum. Results presented by von Hobe *et al.*⁶⁷ suggest that the long-wavelength spectral feature observed by Pope *et al.* is actually a weak ClOOCl band, so Pope *et al.* probably overcorrected for impurity absorption.

The research conducted to understand the Antarctic ozone hole demonstrated the importance of heterogeneous chemistry involving PSCs. The lower stratosphere contains large amounts of sulfate aerosol over wide regions of latitude,⁷² and the potential role of heterogeneous chemistry at mid-latitudes was investigated extensively during the late 1980s and in the 1990s. An excellent review of our understanding is presented by Solomon.¹⁸

While many of the heterogeneous reactions (29)–(35) appear to play a role in mid-latitude stratospheric chemistry, perhaps the single most important reaction is N₂O₅ hydrolysis (reaction 30); this reaction causes significant reduction in NO_x levels in the lower stratosphere, thereby reducing the importance of the O + NO₂ catalytic cycle and, by reducing competition from null cycles and also reducing the formation rate of NO_x-containing reservoirs, increasing the efficiency of HO_x, ClO_x, and BrO_x catalytic cycles. McElroy *et al.* have modeled lower stratosphere mid-latitude chemistry using (i) a gas-phase-only chemical mechanism and (ii) the same gas-phase mechanism with N₂O₅ hydrolysis in aerosol particles added.⁷³ The gas-phase-only model predicts that the O + NO₂ catalytic cycle dominates ozone destruction at all altitudes between 18 and 30 km, accounting for about 70% of ozone loss independent of altitude. When N₂O₅ hydrolysis is added to the model, the fraction of ozone loss attributable to the O + NO₂ catalytic cycle drops from about 70% at 30 km to about 13% at 18 km and the HO₂ + O₃ catalytic cycle becomes the single most important ozone loss process at altitudes below 23 km, accounting for about 75% of ozone loss at 18 km.⁷³ Model calculations by Lary,⁷⁴ which employ a more complete chemical mechanism than the one employed by McElroy *et al.*, also suggest the importance of the HO₂ + O₃ catalytic cycle in the lower stratosphere, as does data from the SPADE (Stratospheric Photochemistry, Aerosols, and Dynamics Expedition) field campaign where a complete suite of key radical intermediates was measured.³⁵

3 RADICAL CHEMISTRY IN THE TROPOSPHERE

Understanding radical chemistry in the troposphere is crucial for developing a predictive understanding of key societal issues including the ability of the atmosphere to cleanse itself of pollutants, urban air quality, and climate change. Tropospheric radical chemistry also affects stratospheric ozone because the amounts of many ClO_x and BrO_x source compounds that reach the stratosphere are limited by their rates of destruction in the troposphere. Whereas all stratospheric chemistry can be understood in terms of a few hundred elementary

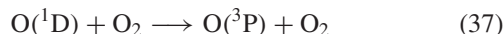
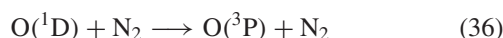
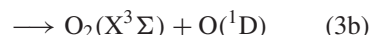
reactions, tropospheric chemistry is much more complex, primarily because of the presence in the troposphere of an enormous variety of organic compounds, most of which are too short-lived to be transported to the stratosphere. As a result, understanding all of tropospheric radical chemistry at the elementary reaction level represents a goal that is virtually impossible to achieve.

In this section, we focus first on a discussion of the key species that initiate the atmospheric degradation of organic and inorganic trace species. We then move on to a description of the basic chain reaction chemistry of the coupled $\text{O}_3/\text{OH}/\text{NO}_x/\text{CH}_4$ system that, to a large degree, controls the oxidizing capacity of the troposphere, that is, the ability of the troposphere to cleanse itself of pollutants. Finally, we provide examples of the complexity that results from the presence of C_2 and larger organic compounds by examining the oxidation mechanisms of ethane and isoprene which is the single most important organic compound emitted into the atmosphere by the terrestrial biosphere. One topic of enormous current interest that we mention in the context of isoprene oxidation and condensed-phase oxidation processes but do not discuss in detail is the role of radical chemistry in the generation of secondary organic aerosol (SOA). A detailed review article entitled "The formation, properties and impact of SOA: Current and emerging issues" is a good source of additional information about SOA for interested readers.⁷⁵

3.1 The Importance of HO_x Radicals in Tropospheric Chemistry

We saw in the previous section that ozone is the single most important chemical species in stratospheric chemistry. Similarly, the hydroxyl radical (OH) is widely considered to be the key species in tropospheric chemistry. The hydroxyl radical is often referred to as the *atmospheric cleansing agent* because reaction with OH initiates the tropospheric degradation of numerous organic and inorganic pollutants. The O–H bonds in water are stronger than most C–H bonds in organic molecules, and OH readily abstracts hydrogen from a majority of both organic and inorganic molecules where the abstraction reaction is energetically favorable. Hydroxyl radicals also add to unsaturated organics and react with most radicals and some closed-shell species

by addition, addition/elimination, or oxygen transfer pathways. The importance of OH as a tropospheric oxidant was first recognized in the early 1970s when model calculations were carried out demonstrating that photolysis of ozone at wavelengths long enough to penetrate into the troposphere could lead to OH production at daytime steady-state levels of around 10^6 molecules cm^{-3} via the following mechanism:^{76,77}

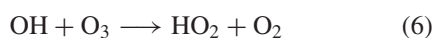
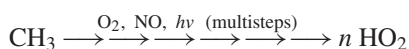
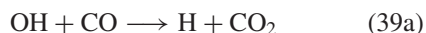


Production of $\text{O}(^1\text{D})$ from O_3 in the troposphere occurs following absorption of radiation within the approximate wavelength range of 300–340 nm. The weak spin-forbidden channel (3b), which has been demonstrated only recently,⁷⁸ is significant because it occurs at longer wavelengths than the spin-allowed channel (3a) and the solar actinic flux increases significantly with increasing wavelength over the wavelength range of interest. The relevant O_3 absorption cross sections and quantum yields for quantitatively evaluating the $\text{O}(^1\text{D})$ production rate are well established.^{3,79} Rate coefficients for reactions (36)–(38) are also well-established; reaction (38) occurs on essentially every encounter between $\text{O}(^1\text{D})$ and H_2O , and $k_{38} \sim 5 k_{37} \sim 6 k_{36}$.^{3,4} Applying the steady-state approximation to the short-lived intermediate $\text{O}(^1\text{D})$ leads to the following expression for the OH production rate, P_{OH} :

$$P_{\text{OH}} = 2k_{38}(J_{3a} + J_{3b})[\text{H}_2\text{O}][\text{O}_3]/(k_{36}[\text{N}_2] + k_{37}[\text{O}_2] + k_{38}[\text{H}_2\text{O}])$$

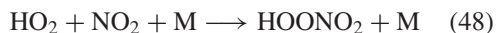
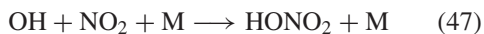
As in our discussion of stratospheric radical chemistry, it is useful to consider the HO_x ($\equiv \text{OH} + \text{HO}_2$) radical family in our discussion of tropospheric chemistry since these two radicals interconvert much more rapidly than they are produced (predominantly via reaction (38) as described above) or destroyed. The most important HO_x radical interconversion reactions are thought to be the

following:^{1,80}



The CH_3 product of reaction (42) is converted to HO_2 via a sequence of reactions, which is discussed in detail in Section 3.3, where it will be emphasized that the reactions of OH with CO and CH_4 , reactions (39) [(39a) + (39b)] and (42), are two of the most important reactions in all of tropospheric chemistry because they are not only the dominant tropospheric loss processes for CO and CH_4 , respectively, but they are also the two most important tropospheric removal pathways for OH. Under typical tropospheric conditions, a steady-state condition is rapidly established by the above interconversion reactions where HO_2 concentrations exceed OH concentrations by 1–2 orders of magnitude.^{81,82}

Loss of HO_x radicals in the troposphere occurs primarily via the following radical–radical reactions:



Reaction (47) plays a significantly different role in tropospheric chemistry than it does in stratospheric

chemistry. Nitric acid (HONO_2) is a reservoir species under most stratospheric conditions, although it becomes more of a sink species in the presence of PSCs. In the troposphere, nitric acid is a sink species since it is removed by (essentially irreversible) heterogeneous processes on a timescale that is short compared to the timescales for photolysis or reaction with OH.

As mentioned above, photochemical models that consider the OH production and loss processes described above predict daytime OH concentrations of about $10^6 \text{ molecules cm}^{-3}$. Major efforts to measure OH in the atmosphere began in the 1970s, but it was not until around 1990 that unequivocal direct measurements of OH were accomplished. Two of the most successful techniques for fast response measurements of OH are laser-induced fluorescence, which directly detects the OH molecule,⁸³ and chemical ionization mass spectrometry, which detects isotopically labeled H_2SO_4 formed by titrating OH with isotopically labeled SO_2 in the presence of O_2 and H_2O .⁸⁴ In addition, CH_3CCl_3 (1,1,1 trichloroethane, methyl chloroform) has been used as a chemical tracer to deduce the average tropospheric OH concentration.^{85–87} Methyl chloroform has no natural sources; it enters the atmosphere only as a result of industrial activity and, with the exception of a small ocean sink that can be quantitatively accounted for, its only tropospheric loss mechanism is reaction with OH. The temperature-dependent kinetics of the $\text{OH} + \text{CH}_3\text{CCl}_3$ reaction are well established.³ Since methyl chloroform is long-lived in the troposphere, it is uniformly distributed. Hence, gas chromatographic measurements at remote sites can be employed in conjunction with sophisticated models that make use of knowledge about sources and sinks to deduce the average tropospheric OH concentration. The result is very close to the value $1 \times 10^6 \text{ molecule cm}^{-3}$ originally predicted in the 1970s.^{76,77,85–87}

Methyl chloroform is sufficiently long-lived that a significant fraction of it is transported to the stratosphere where it can be a significant anthropogenic source of ozone-destroying chlorine. As a result, methyl chloroform is one of the chemical species that has been phased out of industrial production according to the Montreal protocol, an agreement between industrialized nations to protect the stratospheric ozone layer through elimination of the use of chlorine- and bromine-compounds with long enough

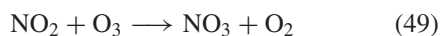
lifetimes to be transported to the stratosphere.^{10,88} Levels of methyl chloroform in the troposphere are dropping rapidly and will become too low to measure in the near future. Hence, the search is on for a replacement tracer that can be used to monitor the time evolution of the average tropospheric OH concentration.

3.2 Other Important Tropospheric Oxidants

Although OH is the single most important oxidant in tropospheric chemistry, many other species also play a role in initiating the degradation of both naturally occurring chemical species and anthropogenic pollutants. In this section, we identify and briefly discuss the chemistry of the most important oxidation initiators other than OH.

3.2.1 Nitrate Radical (NO_3)

The primary source of NO_3 radicals in the atmosphere is the reaction of NO_2 radicals with ozone.



Reaction (49) is relatively slow ($k_{49} = 3.2 \times 10^{-17} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$ at 298 K),³ occurring on a timescale of several hours under typical tropospheric conditions. The NO_3 radical absorbs strongly throughout the visible region of the spectrum, and photodissociation quantum yields are high at all wavelengths shorter than 600 nm.³ Hence, the characteristic time for destruction of NO_3 by photolysis under daytime atmospheric conditions is only a few seconds and, as a result, NO_3 is of little importance in daytime atmospheric chemistry. However, NO_3 production via reaction (49) does not require sunlight, and NO_3 is thought to play a key role as a nighttime tropospheric oxidant. At night, loss of NO_3 occurs via reversible conversion to N_2O_5 coupled with loss of N_2O_5 via its heterogeneous hydrolysis reaction:



Although NO_3 is less reactive than OH, its nighttime concentrations can significantly exceed daytime

OH concentrations, particularly in dry, polluted environments like Southern California where NO_x levels are high and the hydrolysis sink reaction (30) is slow. The nitrate radical reacts rapidly with NO_x radicals, substituted alkenes, and organic sulfides, and it undergoes relatively slow hydrogen transfer reactions with organic compounds possessing relatively weak C–H bonds such as aldehydes and tertiary alkanes. Two extensive reviews covering the reaction kinetics, reaction mechanisms, spectroscopy, and atmospheric impact of the nitrate radical are available in the literature.^{89,90}

3.2.2 Ozone

We have seen above that ozone plays key roles as a source of HO_x radicals and in the interconversion of XO_x radicals ($\text{X} = \text{H}, \text{N}, \text{Cl}, \text{Br}, \text{I}$). In the troposphere, ozone also reacts via addition/elimination pathways with unsaturated organic compounds, and reaction with ozone is the single most important tropospheric degradation pathway for some alkenes.⁹¹ Over the last two decades, it has become clear that ozone reactions with alkenes produce OH radicals.^{92,93} It is now thought that ozone/alkene reactions represent a significant source of HO_x radicals under daytime conditions in some environments and a dominant source of HO_x radicals at night.⁹² The mechanism of an important example, the reaction of ozone with isoprene ($\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$), is discussed in Section 3.4.

3.2.3 Halogen Radicals

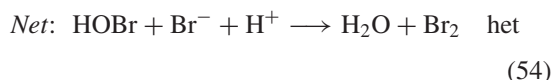
The chemistry of ClO_x radicals in the troposphere differs from that in the stratosphere in two important ways: (i) the source compounds that photolyze to generate Cl atoms in the stratosphere are stable toward photolysis by radiation that penetrates into the troposphere; (ii) whereas in the stratosphere nearly all Cl atoms that are produced react with ozone, in the troposphere most Cl atoms are destroyed by reaction with organics. As a result, ClO_x radicals are largely ineffective at catalyzing ozone destruction in the troposphere. However, chlorine atoms react rapidly with saturated organics by hydrogen abstraction and also react rapidly with

unsaturated organics by addition. Rate coefficients for Cl + organic reactions are typically quite large, often exceeding the corresponding OH + organic rate coefficient by an order of magnitude or more.^{3,5} Hence, if sources are large enough to maintain Cl concentrations greater than ~1% of the OH concentration, then Cl would be an important tropospheric oxidant for many organics. There now exists strong evidence that Cl concentrations can approach 10^5 atoms cm^{-3} at both polar- and mid-latitudes in the marine boundary layer (MBL)^{94–96} where sea-salt aerosol particles provide a large source of Cl^- that can be converted into gas-phase, photochemically labile chlorine species such as Cl_2 , ClNO , or ClNO_2 by heterogeneous reactions occurring either in the bulk or on the surface of aqueous particles.^{97–100} Gas-phase reactants that have been shown to undergo heterogeneous reactions that lead to production of gas-phase Cl atoms include OH, ClONO_2 , N_2O_5 , NO_2 , and HNO_3 .^{97–100} Significant levels of $\text{ClNO}_2(\text{g})$ have recently been observed in Colorado: that is, far removed from the availability of sea-salt aerosol.¹⁰¹ In addition to the heterogeneous chemistry discussed above, some Cl can be generated via purely gas-phase chemistry. Some HCl product of Cl hydrogen abstraction reactions reacts with OH to regenerate Cl atoms (the remaining HCl is removed by uptake into aqueous droplets). Also, while only a small fraction of Cl reacts with O_3 to generate ClO (reaction 11), that Cl is recycled either directly via the $\text{ClO} + \text{NO}$ reaction (24) or indirectly via photolysis of HOCl (reaction 10) that is formed as a product of the $\text{ClO} + \text{HO}_2$ reaction (9). Over the last decade, it seems that the more we have learned about tropospheric chlorine chemistry, the more important Cl has appeared to become as a tropospheric oxidant.

Similar to the situation with chlorine, the source compounds that photolyze to generate Br atoms in the stratosphere are, for the most part, stable toward photolysis by radiation that penetrates into the troposphere. However, unlike chlorine, atomic bromine does not react rapidly with most organic compounds by hydrogen abstraction because only the weakest C–H bonds are weaker than the H–Br bond. Like chlorine, atomic bromine can react with unsaturated organics by addition to form a bromoalkyl radical. However, the C–Br bond in a given bromoalkyl radical is much weaker than the C–Cl bond in the corresponding chloroalkyl radical. The C–Br bond

strength in $^{\bullet}\text{CH}_2\text{CH}_2\text{Br}$ is only 29 kJ mol^{-1} .^{102,103} Substitution of electron-withdrawing groups for the H atoms in $^{\bullet}\text{CH}_2\text{CH}_2\text{Br}$ reduces the C–Br bond strength, while substitution of electron-donating groups has the opposite effect. Conjugated dialkenes such as 1,3-butadiene and isoprene form particularly strongly bound bromine adduct radicals; the most stable Br–isoprene adduct radical has a C–Br bond strength of 70 kJ mol^{-1} .¹⁰⁴ The “effective rate coefficients” for Br + olefin reactions under tropospheric conditions depend on the addition rate coefficient and on the competition between unimolecular decomposition and O_2 addition for consumption of the Br–olefin radical adduct. These effective rate coefficients can have complex dependences on temperature, pressure, and $[\text{O}_2]$, but appear to become quite fast under conditions where the O_2 reaction dominates the competition for removal of the Br–olefin radical adduct.¹⁰⁵

Because Br atoms are less reactive with organics than Cl atoms, Br atoms can participate in catalytic cycles that destroy ozone. The most important catalytic cycle under typical tropospheric conditions is the $\text{BrO} + \text{HO}_2$ cycle, that is, reactions (6) and (12)–(14). As in the case of chlorine, heterogeneous reactions are required to maintain significant levels of BrO_x radicals. During the late 1980s, field observations in the Arctic observed a correlation between extreme springtime sea-level ozone depletion events and high levels of bromine in filter samples containing collected particulate matter.¹⁰⁶ It is now thought that the following heterogeneous reaction scheme involving HOBr that is generated via reaction (12) and taken up into the condensed phase can occur on cold, briny surfaces to produce Br_2 , which escapes to the gas phase and is readily photolyzed to generate Br atoms.^{100,107}



The sequence of reactions (51)–(53) is sometimes referred to as the *bromine explosion*. It results in very high BrO_x levels which, in turn, allow the following catalytic cycle to make a significant contribution to ozone depletion:



The BrO self-reaction actually occurs via two different channels, one as written above and the other to form $\text{Br}_2 + \text{O}_2$. However, Br_2 photodissociates rapidly under tropospheric conditions, so for understanding the role of reaction (55) in tropospheric chemistry it can be assumed to proceed entirely as written above.

In addition to its role in polar boundary layer ozone depletion events and as an oxidant for some unsaturated organics (see above), atomic bromine is thought to be the dominant tropospheric sink species for elemental mercury.^{108,109} Also, BrO radicals are thought to play an important role as a sink species for dimethylsulfide (DMS, CH_3SCH_3),¹¹⁰ emission of which from the oceans is the largest natural source of sulfur to the atmosphere.¹¹¹

A major difference between the tropospheric chemistry of iodine and that of other halogens is that organic iodine compounds can be photodissociated by relatively long-wavelength radiation that is transmitted through the ozone layer to the earth's surface. As a result, catalytic destruction of ozone by iodine can occur without the requirement for generation of photochemically labile IO_x precursors by heterogeneous chemistry (although such production undoubtedly does occur to some extent). A summary of our current understanding of gas-phase tropospheric iodine chemistry is shown in Figure 5. Several catalytic cycles can readily be identified via which IO_x radicals can destroy ozone. The rate-limiting steps in these cycles are the reactions of IO with HO_2 , NO_2 , BrO, IO, and DMS. As discussed above when considering tropospheric HO_x chemistry, the $\text{IO} + \text{HO}_2$ reaction (43) also is of importance because of its impact on the HO_2/OH concentration ratio in some parts of the troposphere. The IO self-reaction is considerably faster than the BrO or ClO self-reactions and occurs via four different channels:³

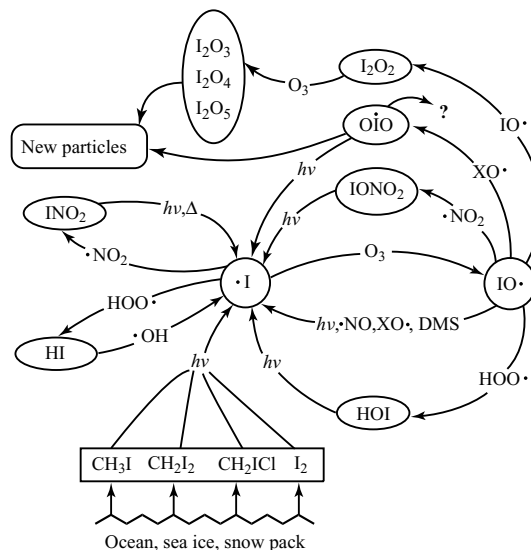
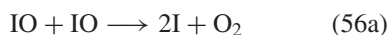


Figure 5 Schematic overview of gas-phase tropospheric iodine chemistry ($X = \text{Br}, \text{I}$). [Adapted (with modifications) from Refs 100 and 159.]

Since I_2 photolyzes rapidly under tropospheric conditions, the production of IO via the reaction of atomic iodine with O_3 coupled with IO loss via reactions (56a), (56b), or (56c) constitutes a catalytic cycle for ozone destruction. The role of reaction (56c) in ozone destruction depends on the fate of OIO, which is currently controversial. The species OIO has a strong absorption band in the 480–650-nm wavelength range. Crowley and coworkers report that quantum yields for production of oxygen atoms and iodine atoms from OIO photolysis are very small.^{112,113} On the other hand, Plane and coworkers report that iodine atoms are formed with unit quantum yield.¹¹⁴ The addition product of the IO self-reaction, namely, I_2O_2 , has been suggested as a precursor to new particles whose formation is correlated with the presence of high levels of iodine, particularly in coastal environments at low tide, that is, under conditions where microalgae are exposed to the atmosphere.^{115–118}

In summary, although IO_x radicals are largely unimportant as direct initiators of the oxidation of tropospheric trace gases, they do have an important indirect effect through their impact on ozone levels. The reaction of IO radicals with DMS does occur with a significant rate coefficient,³ and may represent a non-negligible sink for DMS in some coastal marine environments. In addition, the

role of iodine in new particle formation is a topic of great current interest.

3.2.4 Aqueous-Phase Oxidants

An overview of the atmospheric condensed phase was presented in Section 1.1. Potentially important atmospheric aqueous-phase oxidants include ozone, peroxides, and transition-metal ions, as well as a number of radical species including OH, HO₂, O₂^{•−}, SO_x^{•−} ($x = 3-5$), X₂^{•−} (X = Cl, Br), and NO₃. Aqueous-phase oxidation can be an important atmospheric loss process for chemical species that are highly soluble in water. Herrmann and coworkers have reviewed the state of knowledge of the kinetics of aqueous-phase radical reactions of atmospheric interest,^{119,120} and have also developed aqueous-phase reaction mechanisms for use in modeling atmospheric chemistry.^{121,122}

Perhaps the most important aqueous-phase chemical transformation in atmospheric chemistry is the oxidation of S(IV) to S(VI). The gas-phase reaction of OH with SO₂, which is the rate-limiting step in formation of H₂SO₄(g), an important precursor to new particles in both the troposphere and stratosphere,^{1,9,10} is relatively slow, occurring on a timescale of several weeks. Under most tropospheric conditions, SO₂ is removed from the gas phase primarily by uptake into aqueous droplets and subsequent aqueous-phase oxidation. The dominant aqueous-phase oxidants for S(IV) are thought to be H₂O₂ at relatively low pH and O₃ at relatively high pH.⁹ The OH radical is also thought to make a significant contribution to S(IV) oxidation in the aqueous phase via its reactions with HSO₃^{•−}, SO₃^{2•−}, and deprotonated forms of HOCH₂SO₃H (hydroxy methane sulfonic acid, HMSA) which is formed via aqueous-phase addition of S(IV) to dissolved formaldehyde.^{9,123} In relatively polluted environments, a significant fraction of S(IV) can exist as HMSA, which is relatively stable toward reaction with H₂O₂ and O₃ but reacts rapidly with OH.^{9,123,124} Aqueous-phase reaction with radicals is also thought to be important in the atmospheric transformation chemistry of the DMS oxidation products dimethyl sulfoxide (CH₃S(O)CH₃, DMSO), methane sulfinic acid (CH₃S(O)OH, MSIA), dimethyl sulfone (CH₃SO₂CH₃), and methane sulfonic acid (CH₃SO₂OH, MSA).¹²⁴⁻¹²⁸

Finally, we note that there is currently a great deal of interest in establishing the role that aqueous-phase radical chemistry plays in the formation of SOA.^{75,129}

3.3 The OH-Initiated Chain Oxidation of CO and CH₄

In this section, we discuss the single most important aspect of tropospheric radical chemistry, namely, the chain reactions that maintain the troposphere's ability to cleanse itself of pollutants. As mentioned in Section 3.1, it has been known since the 1970s that the OH radical is the key oxidant in the troposphere and that the two most important sink reactions for OH under a majority of tropospheric conditions are its reactions with CO and methane (CH₄).^{76,77,130} In units of cm³ molecule^{−1} s^{−1}, the currently recommended rate coefficient for the OH + CO reaction is $k_{39} = 1.3 \times 10^{-13} [1 + 0.6P(\text{bar})] \exp(0/T)$, while the currently recommended rate coefficient for the OH + CH₄ reaction is $k_{42} = 2.2 \times 10^{-12} \exp[-1740/T(\text{K})]$.^{3,5} Reaction (39) is the dominant atmospheric loss mechanism for CO, and reaction (42) is the dominant atmospheric loss mechanism for CH₄.¹ Methane is sufficiently long-lived that it is uniformly distributed throughout the troposphere with a mixing ratio of 1.7 ppmv (parts per million by volume). The OH + CO rate coefficient is significantly larger than the OH + CH₄ rate coefficient and, as a result, the tropospheric lifetime of CO is considerably shorter than that of CH₄. Hence, CO is not as uniformly distributed in the troposphere as CH₄. In particular, CO levels are significantly higher in the Northern Hemisphere than in the Southern Hemisphere because combustion sources of CO are found primarily at mid-latitudes in the Northern Hemisphere. Tropospheric mixing ratios of CO are typically more than an order of magnitude smaller than that of CH₄. Assuming a CO mixing ratio of 0.1 ppmv suggests the following lifetimes for OH toward loss by reaction with CO and CH₄ at $T = 298 \text{ K}$: 1.9 s for loss by reaction with CO and 3.4 s for loss by reaction with CH₄.

At the time when OH was first identified as the key tropospheric oxidant and ozone was identified as the photolytic precursor for OH,^{76,77} it was the generally held belief that the dominant source of ozone in the troposphere is transport down from

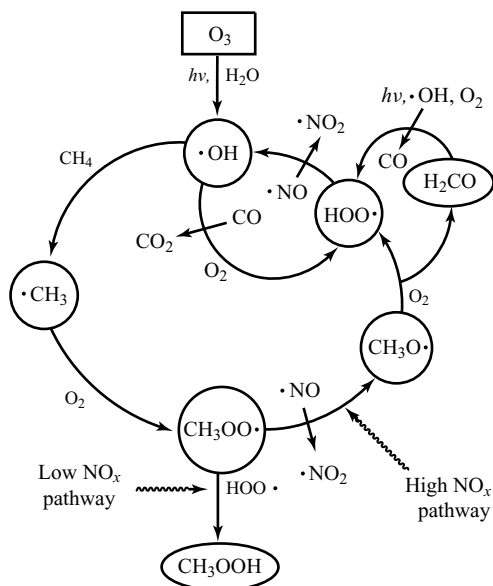


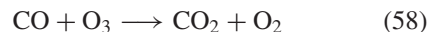
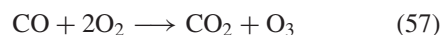
Figure 6 Schematic diagram showing the mechanism for the OH-initiated chain oxidations of carbon monoxide and methane with emphasis on “high- NO_x ” conditions.

the stratosphere. Making such an assumption and using updated estimates for (i) the rate of transport of ozone downward through the tropopause and (ii) the rates of emission of CO and CH_4 into the troposphere leads to the conclusion that, in the absence of additional sources, OH would be titrated, thus allowing pollutants that are removed primarily via reaction with OH (including CO and CH_4) to reach high levels with catastrophic environmental implications.¹ The reason why this doomsday scenario does not actually happen is that OH reactions with CO and CH_4 initiate chain reaction chemistry that, in a majority of tropospheric environments, produces more O_3 and OH than are destroyed in the initiation process. The chain oxidations of CO and CH_4 are summarized schematically in Figure 6, and are discussed in detail below. While extremely important, this chemistry is now well understood and is covered in detail in atmospheric chemistry textbooks.^{1,9–11} Hence, many statements are made below without providing references.

3.3.1 Oxidation of Carbon Monoxide

Oxidation of CO to CO_2 in the troposphere occurs via reactions (39)–(41). The CO_2 coproduct HO_2

reacts predominantly with NO (reaction 22) and O_3 (reaction 8) under a majority of tropospheric conditions. Reactions (8) and (22) both regenerate OH to propagate the chain reaction, but the impact of CO oxidation on ozone levels depends critically on which of the two reactions predominates. If reaction (22) is the dominant pathway for conversion of HO_2 to OH, the OH coproduct is NO_2 whose dominant loss pathway is photolysis to produce ground-state oxygen atoms which combine with O_2 to generate ozone (reaction 23 followed by reaction 2). At this point, it is worth noting that the mechanism (23) followed by (2) is the dominant pathway for photochemical production of ozone in the troposphere. Whenever the oxidation of a tropospheric trace species results in NO_2 production, ozone is generated via NO_2 photodissociation. In the limiting scenario where all HO_2 reacts with NO, the net reaction describing CO oxidation, that is, the sum of reactions (39a), (39b), (40), (41), (22), (23), and (2) is reaction (57), whereas in the limiting scenario where all HO_2 reacts with O_3 , the net reaction describing CO oxidation is the sum of reactions (39a), (39b), (40), (41), and (8), that is, reaction (58).



Under “high- NO_x ” conditions, CO oxidation results in ozone production (reaction 57) whereas under “low- NO_x ” conditions, CO oxidation results in ozone destruction (reaction 58).

On the basis of currently recommended rate coefficients,^{3,4} the ratio k_{22}/k_8 varies from 4300 at 300 K to 15 000 at 200 K. At 280 K, a reasonable estimate for the average temperature at which the OH + CO reaction occurs in the troposphere, $k_{22}/k_8 = 5200$. Assuming a typical ozone mixing ratio of 40 ppbv, the approximate NO mixing ratio at which the rates of reactions (57) and (58) are equal is 8 pptv (parts per trillion by volume), a level that is exceeded in all but the most pristine regions of the troposphere. In virtually all terrestrial environments of the Northern Hemisphere, oxidation of CO results in ozone production.

3.3.2 Oxidation of Methane

Methane oxidation in the troposphere is initiated by the hydrogen abstraction reaction with OH, reaction

(42). Atomic chlorine also abstracts hydrogen from methane (reaction 27) at a rate that may compete with the OH reaction under MBL conditions. All methyl radicals produced from reactions (42) and (27) react with O₂ on a sub-microsecond timescale to produce methylperoxy radicals, CH₃O₂.

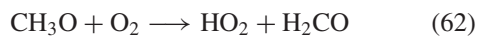


The tropospheric chemistry of CH₃O₂ is similar to that of HO₂ with one important exception. Whereas the HO₂ + O₃ reaction dominates HO₂ removal under low-NO_x conditions, the CH₃O₂ reaction with O₃ is too slow to be important in the troposphere.³ Instead, CH₃O₂ reacts with other peroxy radicals (predominantly HO₂) under low-NO_x conditions, and the competition for removal of CH₃O₂ is between reactions (60) and (61).



For reasons discussed in Section 3.3.1, the occurrence of reaction (60) results in ozone production. At 280 K, a reasonable estimate for the average temperature at which the OH + CH₄ reaction occurs in the troposphere, $k_{60}/k_{61} = 1.4$.³ Daytime levels of HO₂ in the troposphere are somewhat variable but, as discussed in Section 3.1, 2 pptv is a reasonable estimate for the HO₂ mixing ratio, suggesting that reaction (60) becomes the dominant CH₃O₂ removal pathway when the NO mixing ratio exceeds 10 pptv.

Under tropospheric conditions, the carbon-containing products of reactions (60) and (61), namely, methoxy radical (CH₃O) and methyl hydroperoxide (CH₃OOH), undergo the following reactions:



Reaction (62) occurs on a millisecond timescale under tropospheric conditions and completely dominates the removal of CH₃O. Methyl hydroperoxide is removed by photolysis and OH reaction at

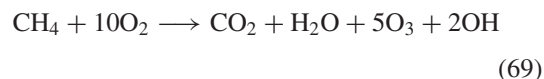
competitive rates; its typical lifetime is around 1 day. Methyl hydroperoxide is less soluble in water than hydrogen peroxide, and uptake into the aqueous phase is a relatively minor loss process.

Examination of the mechanism of reactions (59)–(65) shows that formaldehyde (H₂CO) is formed with unit yield from methane oxidation. Ignoring a relatively minor aqueous-phase sink, formaldehyde is lost primarily by the following processes:



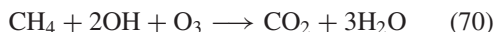
The H atom product of reaction (68b) is converted to HO₂ via reaction (40) on a sub-microsecond timescale, while the H₂ product of reaction (68b) has a tropospheric lifetime of about 5 years toward loss by reaction with OH.³ The radical channel (68b) for formaldehyde photolysis is favored at shorter wavelengths (300–320 nm), while the molecular channel (68a) is favored at longer wavelengths (320–350 nm).³ Under typical daytime conditions, the formaldehyde lifetime is a few hours and $k_{68a} \sim 2k_{68b} \sim 4k_{66}$. Formaldehyde degradation produces CO with unit yield and also results in the production of some HO_x radicals.

To get a picture of how methane oxidation affects the troposphere's ability to cleanse itself of pollutants, it is useful to examine two limiting scenarios that bracket the actual behavior. In limiting scenario 1, we assume "high-NO_x" conditions, that is, all CH₃O₂ and HO₂ radicals are assumed to react with NO via reactions (60) and (22), and we also assume that formaldehyde degradation occurs entirely via the radical-producing photolysis channel (68b); this scenario maximizes the production of O₃ and HO_x radicals from methane oxidation. Summing all the relevant reactions gives the following balanced chemical equation for oxidation of methane to CO₂:



In limiting scenario 2, we assume low-NO_x conditions, that is, all CH₃O₂ reacts with HO₂ via reaction

(61) and all HO_2 reacts with O_3 via reaction (8), and we also assume that all CH_3OOH reacts with OH via reaction (63b) and all formaldehyde reacts with OH via reaction (66); this scenario results in loss of O_3 and HO_x radicals via methane oxidation. Summing all the relevant reactions gives the following balanced chemical equation for oxidation of methane to CO_2 :



3.3.3 The Bottom Line

We generally think of NO as an unwanted pollutant that is emitted into the atmosphere in large quantities from combustion sources. However, the above discussion of CO and methane oxidation shows that maintenance of the atmosphere's ability to cleanse itself of pollutants depends critically on the availability of enough NO (tens of pptv) to make reactions (22) and (60) the most important removal mechanisms for HO_2 and CH_3O_2 radicals, respectively. The currently accepted ozone budget is much different from the budget that was accepted several decades ago. It is now believed that $83 \pm 10\%$ of tropospheric ozone is produced photochemically *in situ* while only $17 \pm 10\%$ is transported down from the stratosphere.¹ The oxidizing capacity of the troposphere will evolve in the future as levels of CO , CH_4 , and NO_x change.

3.4 Tropospheric Oxidation of Organics with Two or More Carbon Atoms

The radical chemistry involved in the tropospheric oxidation of organic molecules becomes progressively more complex as the number of carbon atoms in the organic increases. The complexity arises because (i) the number of different peroxy radicals ($\text{ROO}^\bullet$) that can be formed increases as the size of the organic increases and (ii) the number of loss pathways for each alkoxy radical ($\text{RO}^\bullet$) increases as the number of carbons in $\text{RO}^\bullet$ increases. Page and time limitations prevent us from covering organic oxidation mechanisms with the level of detail that would be desirable. For more information, interested readers are referred to an extensive review by Atkinson.¹³¹ In this section, we discuss

the oxidation of two important examples, ethane and isoprene, the single most important biogenic hydrocarbon in tropospheric chemistry.

3.4.1 Oxidation of Ethane and the Role of PAN in Tropospheric Chemistry

A schematic diagram summarizing the tropospheric oxidation of ethane is shown in Figure 7. Similar to methane, oxidation of ethane is initiated by hydrogen abstraction reactions with OH and Cl , with OH the dominant oxidant. Conversion of the ethyl radical ($\text{CH}_2\text{CH}_3^\bullet$) to ethoxy ($\text{CH}_3\text{CH}_2\text{O}^\bullet$) follows an analogous path to that described in Section 3.3.2 for conversion of methyl to methoxy. Unlike $\text{CH}_3\text{O}^\bullet$, which reacts exclusively with O_2 under tropospheric conditions, $\text{CH}_3\text{CH}_2\text{O}^\bullet$ is removed competitively by reaction with O_2 and C–C bond fission. The bond fission reaction produces $\text{H}_2\text{CO} + \text{CH}_3^\bullet$, both of which are further oxidized as discussed in Section 3.3.2. The $\text{CH}_3\text{CH}_2\text{O}^\bullet + \text{O}_2$ reaction produces acetaldehyde (CH_3CHO). Acetaldehyde photolyzes more slowly and reacts with OH more rapidly than formaldehyde, so OH reaction, which occurs almost exclusively via abstraction of the weakly bound aldehydic hydrogen, dominates acetaldehyde removal. The $\text{OH} + \text{acetaldehyde}$ reaction produces $\text{CH}_3\text{CO}^\bullet$, which, like all carbon-centered radicals, rapidly adds O_2 to produce acetylperoxy radical $\text{CH}_3\text{C}(\text{O})\text{OO}^\bullet$. Like all peroxy radicals, acetylperoxy reacts primarily with NO and/or HO_2 .

Whereas CH_3O_2 and $\text{CH}_3\text{CH}_2\text{O}_2$ reactions with NO_2 are relatively unimportant in tropospheric chemistry because the nitrates formed decompose rapidly, the organic nitrate formed from acetylperoxy + NO_2 is relatively stable; this organic nitrate is known as *peroxyacetyl nitrate* and is commonly referred to as *PAN* by atmospheric chemists. In the troposphere, *PAN* exists in equilibrium with acetylperoxy radicals and NO_2 , and the acetylperoxy + NO reaction represents the dominant *PAN* loss process. Both $\text{PAN} + \text{OH}$ and *PAN* photolysis are very slow under tropospheric conditions. If *PAN* is formed in or transported to a relatively low-temperature tropospheric environment, it becomes stable and can be transported over long distances, and then release NO_x when it finds its way into a warmer environment.

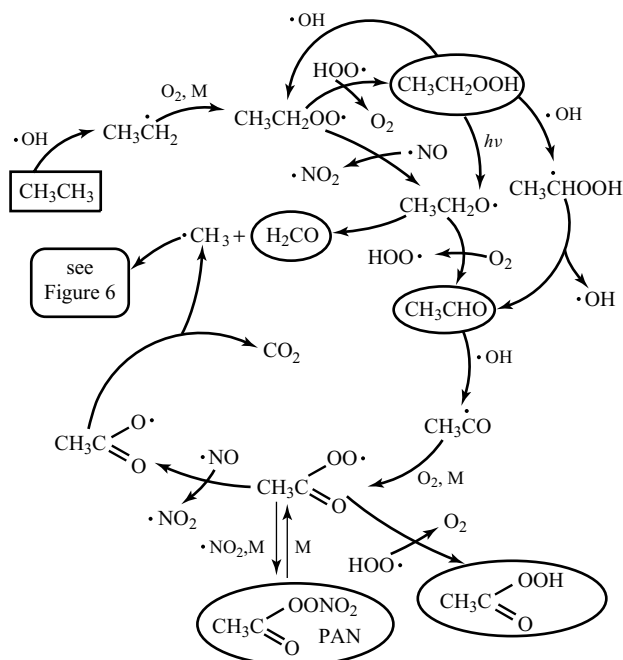


Figure 7 Schematic diagram showing mechanisms for tropospheric ethane oxidation and PAN formation.

Most tropospheric NO_x is anthropogenic in origin; the two largest sources are fossil fuel combustion and biomass burning.¹ The tropospheric lifetime of NO_x is around 1 day, so NO_x does not live long enough to be transported over long distances from source regions. It is generally thought that PAN plays a key role in transporting NO_x to remote regions of the troposphere, thereby helping to maintain the oxidizing capacity of these remote regions.¹ PAN or substituted PANs with the general formula RC(O)OONO_2 can be formed as products of the tropospheric oxidation of numerous organics; as long-lived reservoirs for NO_x radicals, these compounds play an important role in tropospheric chemistry.

3.4.2 Oxidation of Isoprene

Isoprene (2-methyl-1,3-butadiene, $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}=\text{CH}_2$) is produced and emitted into the atmosphere in large quantity by deciduous plants.¹³² The isoprene flux into the atmosphere is larger than that of any hydrocarbon other than methane,¹³³ and isoprene is much more reactive than methane.^{3,5}

At 298 K, rate coefficients for isoprene reactions with OH , NO_3 , O_3 , and Cl (in units of $10^{-13} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$) are 1000, 7.3, 0.00013, and 4100, respectively.³ All reactions proceed by addition pathways, although the Cl reaction also has a minor hydrogen abstraction channel.³ Under typical tropospheric conditions, reaction with OH dominates isoprene removal during daytime.¹³⁴ At night, NO_3 dominates isoprene removal in polluted environments, but O_3 dominates in unpolluted environments.^{134,135} Nighttime NO_3 can be competitive with daytime OH as an isoprene oxidant in polluted environments.^{134,135} Chlorine atoms may be a significant isoprene oxidant in some marine environments.¹³⁴ Product studies carried out under high- NO_x conditions in air, as summarized in a 2003 review,¹³⁴ suggest the following yields of stable first-generation products from the OH -initiated oxidation of isoprene: H_2CO , 0.60 ± 0.07 ; methyl vinyl ketone ($\text{CH}_3\text{C(O)CH}=\text{CH}_2$, MVK), 0.33 ± 0.07 ; methacrolein ($\text{CH}_2=\text{C}(\text{CH}_3)\text{CHO}$, MACR), 0.23 ± 0.06 ; organic nitrates, 0.09 ± 0.05 ; 3-methylfuran, 0.04 ± 0.02 . Under low- NO_x conditions, the OH -initiated oxidation of isoprene in air produces as first-generation products the two hydroxy hydroperoxides $\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}(\text{OOH})$

CH_2OH and $\text{HOCH}_2\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{OOH}$ with a combined yield in excess of 0.7.¹³⁶ For the O_3 + isoprene reaction in the presence of an OH scavenger (needed for reasons discussed below), the yields are H_2CO , 0.90; MVK, 0.16 ± 0.02 ; and MACR, 0.40 ± 0.04 .¹³⁴ Organic nitrates are the major observed products of the NO_3 + isoprene reaction, although small amounts of H_2CO , MVK, and MACR are also produced.¹³⁴

In a number of recent field studies carried out in forested regions where isoprene emissions are high, the measured OH concentrations were found to significantly exceed those expected on the basis of model simulations that employed chemical mechanisms as they were known in 2007.^{137–140} The search for an explanation for the discrepancy between models and measurements has led to major experimental and theoretical efforts to obtain an improved understanding of the isoprene oxidation mechanism.^{136, 141–153} In particular, it has been recognized that the discrepancy between models and measurements would be alleviated if the OH-initiated oxidation of isoprene were found to result in significant regeneration of OH radicals. Production of OH from isoprene oxidation has important implications for atmospheric chemistry in low- NO_x regions with high levels of vegetation such as, for example, the Amazon basin, since this would provide a mechanism for maintaining the oxidizing capacity of the atmosphere even in the absence of net photochemical production of ozone.

Addition of OH to isoprene can occur at any of the four carbons on the 1,3-butadiene backbone. It is well established that addition at the outer carbons is favored, with more than 60% of the initial addition occurring at the 1-position and about 30% occurring at the 4-position.^{141, 143, 154} Theoretical calculations suggest that 1-OH addition produces cis and trans conformers with equal probability whereas 4-OH addition produces 70% cis conformer.¹⁴³ The products of OH addition at the 1- and 4-positions are allyl-resonance-stabilized and, as a result, six different peroxy radicals can be generated by addition of O_2 to the four initially formed adduct radicals.¹⁴⁴ Hydrogen abstraction from the methyl group (not believed to be important for OH + isoprene but significant for Cl + isoprene) leads to formation of a seventh peroxy radical. In order to reproduce OH levels observed in the field experiments cited above,^{137–140} which for the most part explored “low- NO_x ” environments, the peroxy

radicals formed from OH addition to isoprene in the presence of O_2 would have to undergo subsequent reactions that generated OH with a yield of around 0.5. Conventional wisdom, which suggests that the peroxy radicals are consumed primarily via bimolecular reactions with HO_2 and (to a lesser extent) organic peroxy radicals under low- NO_x conditions, seems incapable of rationalizing such a large yield of recycled OH.¹⁴³

Peeters and collaborators have recently reported theoretical studies where unimolecular pathways for isoprene peroxy radical transformations are identified that lead to significant OH generation.^{143, 144, 152, 153} Detailed chemical schemes for oxidation of the 1-OH and 4-OH conformers are presented in two of their papers,^{143, 152} and are not reproduced here. However, their main findings are summarized below:

Under tropospheric conditions, the peroxy radicals have lifetimes of only tenths of a second toward thermal decomposition. The conditions of most laboratory studies are such that peroxy radicals probably undergo bimolecular reaction on a timescale that is short compared to the thermal dissociation time, but in the atmosphere the peroxy radicals have lifetimes of tens of minutes and, therefore, are in thermal equilibrium with the OH-isoprene adduct radicals, rapidly cycling between the two. This allows the bulk of the radical pool to be funneled through the most reactive channels, which are predicted to be 1,6 hydrogen shifts in Z- δ -OH-peroxy radicals to form the hydroxy hydroperoxy radicals $^{\bullet}\text{CH}(\text{OH})\text{C}(\text{CH}_3)=\text{CHCH}_2\text{OOH}$ and $^{\bullet}\text{CH}(\text{OH})\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2\text{OOH}$; these radicals rapidly react with O_2 to form HO_2 + hydroperoxy aldehydes that can rapidly photodissociate to generate OH. In addition, the radicals 1-OH-2-OO'-isoprene and 4-OH-3-OO'-isoprene are predicted to undergo 1,5 hydrogen shifts to generate OH + H_2CO + a second carbonyl compound (MVK or MACR); the net yield of OH via this pathway is estimated to be in the range 0.01–0.1.

The findings of Peeters and collaborators provide a plausible explanation for the large yields of recycled OH when isoprene is oxidized in the troposphere under low- NO_x conditions. Of course, their findings must be considered somewhat speculative until they are verified experimentally. The first step toward experimental verification of the theoretical findings has already been reported.¹⁴⁴

In addition to its role in maintaining the oxidizing capacity of the atmosphere under low- NO_x conditions, isoprene is also of considerable current interest because of its role in SOA formation. Seinfeld and collaborators have made major recent contributions toward understanding the role of isoprene in SOA formation.^{136,145,150,151,155} One key recent finding that impacts both SOA formation and OH recycling is the observation that, under low- NO_x conditions, dihydroxy epoxides are produced from secondary oxidation of the hydroxy hydroperoxides, and the dihydroxy epoxide coproducts are OH radicals.¹³⁶ The dihydroxy epoxides are quite soluble in water and are rapidly oxidized in the aqueous phase to form nonvolatile products; in this manner they contribute to SOA formation.¹⁵⁰ Similarly, MPAN ($\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(\text{O})\text{OONO}_2$), a second-generation isoprene oxidation product under high- NO_x conditions that is formed via oxidation of MACR, has been identified as a key precursor to SOA formation in high- NO_x environments.¹⁵⁰

As discussed briefly above, the reaction of O_3 with isoprene is a key source of OH radicals at night in low- NO_x environments and during daytime in both low- NO_x and high- NO_x environments. A tutorial review of the gas-phase ozonolysis of alkenes has been recently published by Johnson and Marston,¹⁵⁶ and a high-quality experimental study of OH and HO_2 production from O_3 + isoprene has been recently reported by Malkin *et al.*, who find OH and HO_2 to be produced with essentially equal yields of 0.26 ± 0.03 .¹⁵⁷ The O_3 + isoprene reaction proceeds via addition of ozone across one of the double bonds to form a primary ozonide (a five-member ring structure containing the two carbon atoms that made up the double bond and the three oxygen atoms). Each of the two primary ozonides that can be formed from O_3 + isoprene decomposes by O–O bond fission to form two different pairs of Criegee biradical intermediate (CI) + carbonyl products. Hence, for O_3 + isoprene, four sets of products are generated via decomposition of primary ozonides: $\cdot\text{CH}_2\text{OO}\cdot + \text{CH}_2=\text{C}(\text{CH}_3)\text{CHO}$, $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}\cdot\text{HOO}\cdot + \text{H}_2\text{CO}$, $\cdot\text{CH}_2\text{OO}\cdot + \text{CH}_2=\text{CHC}(\text{O})\text{CH}_3$, and $\text{CH}_2=\text{CHC}\cdot(\text{CH}_3)\text{OO}\cdot + \text{H}_2\text{CO}$. The CIs are formed hot, and stabilization competes with unimolecular decay of the hot CIs under tropospheric conditions. The stabilized biradicals can survive long enough to undergo bimolecular reactions.¹⁵⁶ Production of HO_x radicals is thought

to occur via unimolecular decay of hot CIs, but the detailed pathways remain rather uncertain.^{156,157}

4 CONCLUSION

The atmosphere is a complex photochemical reactor where a vast majority of the chemical transformations involve reactions of reactive free radicals that are generated by solar photolysis of stable precursors. This article has focused on radical chemistry in the lowest 50 km of the atmosphere, an altitude regime that contains about 99.9% of the atmospheric mass. The altitude regime of interest is divided into two layers, the lower altitude troposphere and the higher altitude stratosphere.

The stratosphere contains 90% of all atmospheric ozone, and this ozone protects the earth's biosphere from the harmful effects of ultraviolet radiation. Our discussion of stratospheric chemistry has focused on radical-catalyzed pathways for ozone destruction. It is clear that ClO_x and BrO_x radicals, which are present in the stratosphere largely as a result of human activity, contribute significantly to ozone loss at mid-latitudes and dominate the massive ozone loss observed in the springtime Antarctic lower stratosphere.

Tropospheric radical chemistry is extremely complex, owing largely to the presence in the troposphere of a multitude of organic compounds that are too short-lived to be transported to the stratosphere. Our discussion of tropospheric radical chemistry has focused on the complex chain reactions involving ozone, hydroxyl radicals, nitrogen oxide radicals, and organics that maintain the oxidizing power of the troposphere, that is, the ability of the troposphere to cleanse itself of pollutants. The chemistry of important radical initiators of the degradation of tropospheric pollutants was reviewed, and the atmospheric oxidation of two representative organics, ethane and isoprene was discussed in detail. Understanding the production of HO_x radicals from isoprene oxidation is an issue of significant current interest to the atmospheric chemistry community.

Looking to the future, there is currently intense interest in the atmospheric chemistry community in gaining a fundamental understanding of the chemistry of SOA formation. Gas-phase radical chemistry of large semivolatile organics is likely to be important in SOA formation as are aqueous-phase radical pathways.

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Basic Concepts on Radical Chain Reactions

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1 FUNDAMENTAL CONCEPTS

1.1 Structure and Stability of Carbon-Centered Radicals

The three structures available to carbon-based radicals are depicted in Figure 1. These structures are classified by the number of ligands attached to the radical center.

If three ligands are present, most alkyl radicals have a planar geometry at carbon and the radical resides in a p orbital, orthogonal to this plane. In some instances, $R_3C^\bullet$ radicals prefer a pyramidal (sp^3 hybridized) shape, for example in geometrically and/or conformationally constrained systems such as the adamant-1-yl radical, or in electronically perturbed systems such as the trifluoromethyl radical (see **Analysis of Radicals by EPR and Structures and Reactivity of Radicals Followed by Magnetic Resonance**). Nevertheless, sp^2 hybridization and a trigonal planar shape is more common and, in this aspect, an $R_3C^\bullet$ radical is more akin to its one-electron-less carbocation counterpart (R_3C^+) than its one-electron-more carbanion congener (R_3C^-). An important consequence of the planar shape of $R_3C^\bullet$ radicals is that the configuration of a stereocenter will not be retained during a process that involves bond breaking/bond formation through a radical intermediate (i.e., $R_3C-X \rightarrow [R_3C^\bullet] \rightarrow R_3C-Y$).

When only two ligands are attached to a carbon radical, one of them must be joined through a double bond. Alkenyl, aryl, and acyl radicals are among the most important members of this family. These are also sp^2 hybridized $C^\bullet$ species but, in this case, the radical resides in an sp^2 orbital that is roughly in plane with the C and its two covalently bonded atoms. The shape of the molecule in the immediate vicinity of $C^\bullet$ is bent and, unless constrained in a small ring (as is the case in a phenyl radical, for example), inversion between the two “bent” forms is possible. The transition state for this inversion process has a local linear geometry at $C^\bullet$ with the radical in a p orbital, hence sp hybridized at $C^\bullet$.

Carbon radicals carrying a single substituent that is attached through a triple bond are much less common. In this case, the radical resides in an sp hybridized orbital and the radical has a linear shape.

Carbon radicals can be stabilized by both electronic and steric effects. Generally speaking, substituents that stabilize *either* carbocations *or* carbanions will stabilize a radical. The order of stability of simple alkyl radicals is $H_3C^\bullet < RH_2C^\bullet < R_2HC^\bullet < R_3C^\bullet$, hence alkyl radical stability follows carbocation stability (see **Radical Stability—Thermochemical Aspects**). In addition to this inductive electronic effect, orbital overlap with an adjacent π bond or lone pair also leads to increased stabilization; the simple resonance picture will suffice for both, if you are satisfied with a zwitterionic

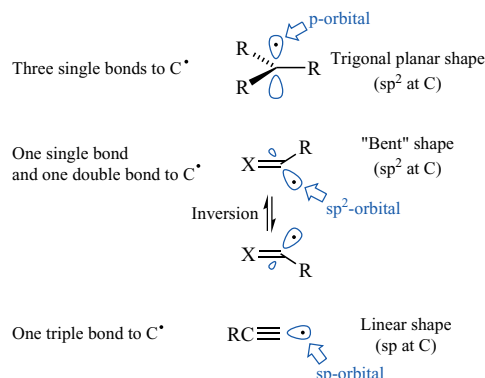
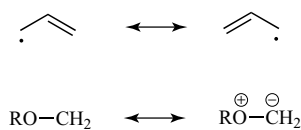


Figure 1 The structures and shapes of carbon-based radicals.



Scheme 1 Resonance forms for allyl and alkoxymethylene radicals.

radical cation/anion pair as a resonance contributor (Scheme 1).

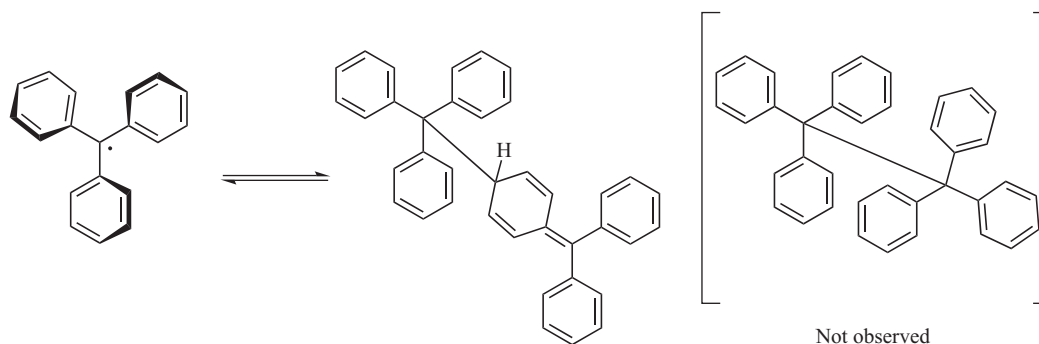
The stabilization of radicals by electronic effects reaches a somewhat unexpected peak in so-called *captodative* radicals,¹ where both electron releasing and electron withdrawing groups are attached to the same carbon radical center. The combined radical stabilizing effect of the two groups is significantly higher than additive.

Steric effects are also an important factor in radical stability but, when it comes to explaining the

origin of radical longevity/unreactivity, it is often difficult to tease apart a steric effect from an electronic one. The case in point is triphenylmethyl, Gomberg's first carbon radical (see **The History of Free Radical Chemistry**). The species exists in equilibrium at ambient temperature with its unsymmetrical dimer (Scheme 2). *A priori*, one might draw the planar structure of triphenylmethyl and think of electron delocalization as the origin of radical stability. Triphenylmethyl has a propeller shape, however, and the origin of its stability is primarily a steric effect: it is too sterically hindered to undergo coupling to form hexaphenylethane. In fact, coupling necessitates a dearomatization of one of the aromatic rings of the triphenylmethyl radical. Presumably, this contributes to the reluctance of triphenylmethyl to undergo self-reaction. Incidentally, Gomberg proposed the unsymmetrical dimer structure correctly in 1904. Nevertheless, the incorrect hexaphenylethane structure was widely accepted as the product of radical dimerization of triphenylmethyl until 1968.²

As we will see, it is most often the case that a radical will react very rapidly indeed with another radical. Those that do not undergo fast self-reaction are termed *persistent radicals*.³ Persistent radicals (Figure 2) may still undergo reaction with other radicals or triplet oxygen. Their persistence is often due to a combination of electronic stabilization and steric hindrance toward recombination and the lack of a β -H, which is needed for disproportionation.

The stability of a radical $R^\bullet$ (see **Radical Stability—Thermochemical Aspects**) can be estimated from consideration of the bond dissociation energy (BDE) of the corresponding $R-H$ compound (Figure 3). The lower the BDE, the weaker the



Scheme 2 Dimerization of the triphenylmethyl radical.

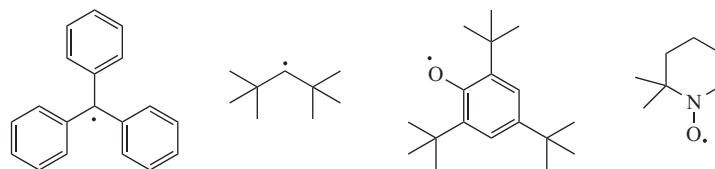


Figure 2 Examples of persistent radicals.

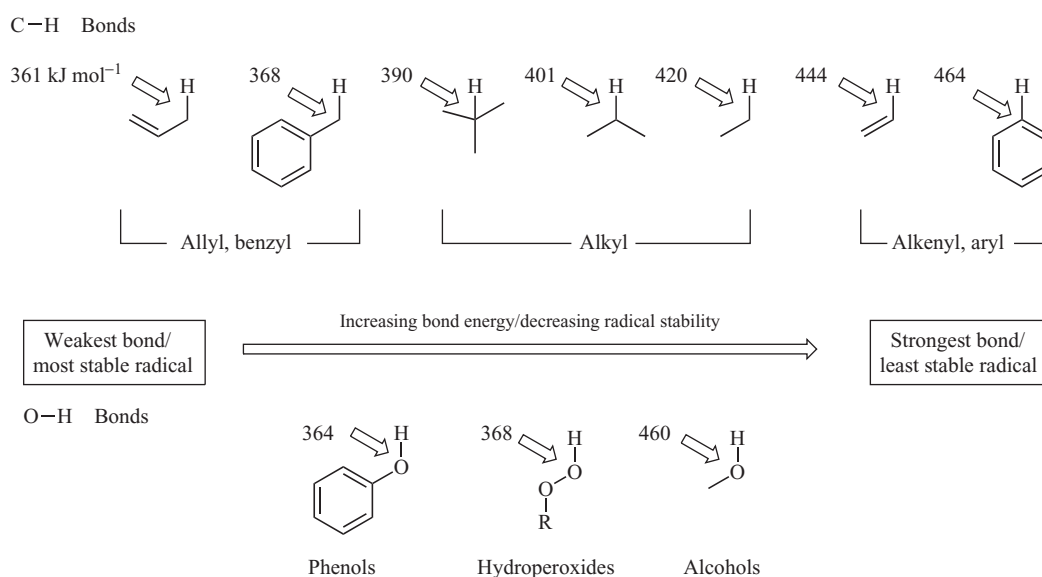


Figure 3 Radical stability and the relationship with bond dissociation energy (BDE).

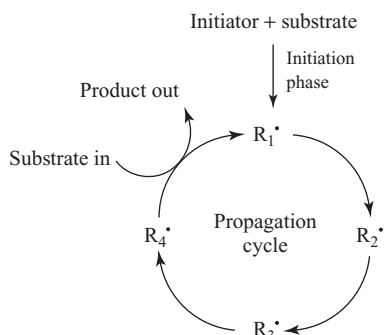
bond and hence the more stable the radical. At first sight, the significant difference in strengths of C–H bonds (and O–H bonds) comes as a surprise: an aryl C–H bond strength is almost 100 kJ mol^{-1} stronger than a benzyl C–H bond, for example. Evidently, these bond strengths/stabilities have a significant influence upon chemical reactivity and the ability to set up an effective chain reaction. We will now look at radical chain reactions in more detail, and the discrete processes of which they are comprised.

1.2 Introduction to Chain Reactions and Discrete Radical Processes

Apart from a relatively small number of examples that are strongly stabilized through steric and electronic effects, radicals are typically promiscuous

species. In fact, most radicals react with one another at rates approaching the diffusion controlled limit. If essentially all collisions lead to productive bond formation, then it is inevitable that reactions involving radical–radical unions are going to be unselective. The development of modern chain reactions—made possible through fundamental physical organic chemistry studies (see **Radical Kinetics and Clocks**)—was the breakthrough that enabled selectivity in transformations involving radicals. As we will see, transformations of incredible intricacy and selectivity can be achieved through radical chain processes.

The mechanisms of radical chain reactions (Scheme 3) can be conveniently broken down into two stages: *initiation* (see **Overview of Radical Initiation**), which involves the formation of a few radicals to get things going and a *propagation cycle*, which is the business end of the reaction and involves the conversion of the precursor into



Scheme 3 A generalized radical chain mechanism.

the product. Both initiation and propagation stages of a radical chain reaction can involve several discrete mechanistic steps. *Chain termination* involves the consumption of radicals and is undesirable. Synthetically useful radical chain reactions require only small amounts of initiator, have efficient propagation steps, and minimize termination events.

The majority of radical reactions involve the stringing together of a surprisingly small number of different classes of discrete, concerted events (Scheme 4). This subsection serves as a general introduction to these different events. We will examine them in more detail in subsequent subsections.

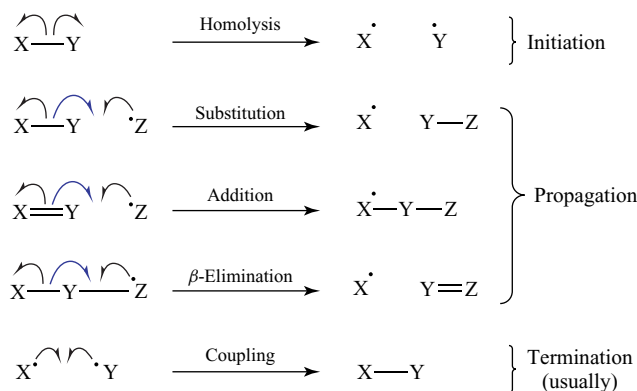
Radicals are generated through *homolysis* processes. In its simplest form, homolysis involves the scission of a weak σ bond and is brought about by delivering a sufficient amount of energy to the substrate to break the bond. All covalent bonds will break homolytically if heated to high enough temperatures but for most synthetic purposes, an initiator with a covalent bond of BDE

$<200 \text{ kJ mol}^{-1}$ is employed. Halogens, dialkyl-, and diacyl-peroxides are examples of such compounds, which undergo homolysis to form halogen atoms, alkoxy, and acyloxy radicals, respectively (Scheme 5). Dialkyl-azo compounds are especially important in radical chemistry: these compounds undergo a double homolysis, generating two alkyl radicals and a molecule of nitrogen.

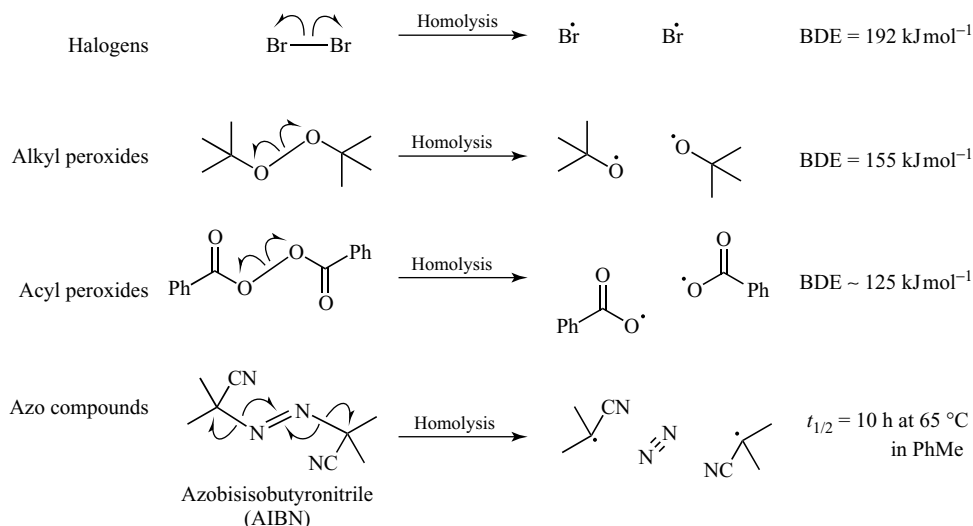
The initiation phase of radical chain reactions (see **Overview of Radical Initiation**) often involves a homolysis step, although there are many exceptions. For example, the reaction between Et_3B and oxygen can be used to generate ethyl radicals at low temperature (i.e., -78°C).⁴ Reactive organohalides can be converted into carbon-centered radicals by halogen abstraction by metals and their complexes (see **Transition Metals and Radicals**). One electron oxidation or reduction (see **Redox Properties of Radicals**), radiation (see **Radiation-Induced Radical Reactions**), and photolytic methods (see **Photo Induced Radical Reactions**) can also initiate radical chain reactions through mechanisms that do not involve the direct homolytic cleavage of a weak covalent bond.

Radical substitution, addition, and β -elimination processes are the three most common processes in the propagation phase of radical reactions (Scheme 6). They are well suited to chain reactions for the simple reason that they lead to a change in bonding while transmitting radical character from one species to another.

Unlike *nucleophilic* substitution processes, which readily occur through either dissociative ($\text{S}_{\text{N}}1$) or concerted ligand replacement ($\text{S}_{\text{N}}2$) mechanisms at

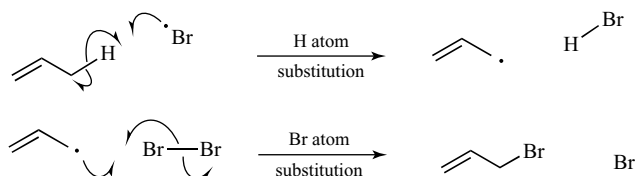


Scheme 4 The most common single step (i.e., concerted) radical events. The arrows colored blue are sometimes omitted.

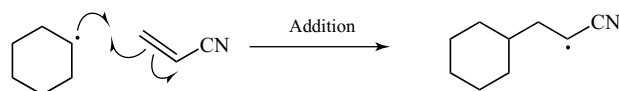


Scheme 5 A selection of common radical initiators that undergo homolysis on exposure to heat or light.

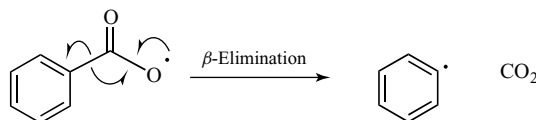
Radical substitution is most common at hydrogen and halogen centres...



Radical addition to virtually all multiple bonds is possible...



β -Elimination is the reverse of addition...

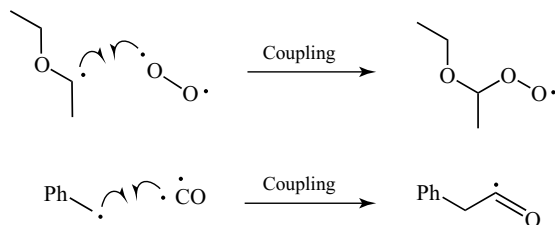


Scheme 6 Simple examples of radical substitution, addition, and β -elimination.

carbon, direct radical substitution at carbon is a rare event. In contrast, radical substitution at the halogen atom of a C–X bond and the hydrogen of a C–H bond, both of which lead to carbon-centered radicals, are rather common. The concerted homolytic substitution mechanism, which operates in these and many other cases, bears the descriptor S_H2 (substitution, homolytic, bimolecular) (see **Intramolecular**

Homolytic Substitutions in Synthesis). Examples of common types of bonds broken in S_H2 processes (Scheme 6) are the relatively weak X–X, C–X, C–H, and Sn–H bonds. Those that are commonly formed are relatively strong O–H, C–H, and Sn–X bonds.

Radical additions (Scheme 6) are perhaps the single most important radical process, at least if



Scheme 7 Radical coupling steps witnessed in chain reactions.

judged in terms of synthetic application. Radicals add readily to many types of π bonds (see **Unusual Radical Acceptors**) and, in thermodynamic terms, the driving force for the process is the formation of a stronger σ bond at the expense of a weaker π bond. Steric, electronic, strain, and geometrical/conformational factors all impact upon the ease with which a radical and alkene react. β -Elimination is the reverse of addition and, in the absence of other factors listed in the preceding sentences, the position of the equilibrium is determined by the stabilities of the species (radicals and π bonds) involved. Nevertheless, β -elimination can be promoted by higher temperatures (entropy driven) or can be brought about by the removal of a volatile by-product from the reaction, according to Le Chatelier's principle.

As mentioned earlier, coupling is the process by which most radical chain reactions terminate and, in such a situation, is undesirable. Effective chain reactions use only small amounts of initiator, which allows the concentration of radical species in solution to be kept low, thereby minimizing unwanted termination through radical coupling events. Nevertheless, a relatively small number of radical chain reactions involve coupling processes as an integral part of the propagation cycle. Autoxidation, for example, involves the union of carbon-centered radicals with triplet O_2 as a key step (Scheme 7); a process that is perhaps best thought of as a radical–radical coupling event.

Carbon monoxide reacts well with carbon-centered radicals to form acyl radicals.⁵ Again, this can be thought of as a radical coupling process (as an aside, the reverse reaction, α -elimination, which involves the loss of CO from an acyl radical and is a lot like homolysis, is also known). Finally, it must be noted that there are

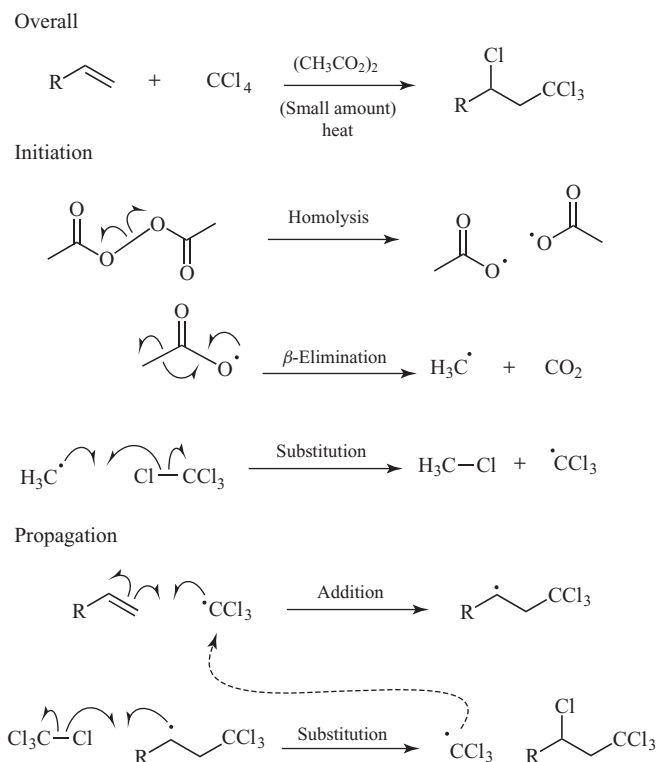
several preparatively useful *non-chain* radical reactions that involve coupling processes. These include the *pinacol reaction* (see **Organic Synthesis Using Samarium Diiodide**), the *McMurry reaction*, and the *acyloin condensation*.

While the five fundamental processes depicted in Scheme 4 form the basis of the majority of radical chain reactions, this collection is not exhaustive. Electron transfer processes are also important (see **Organic Electron Donors** and **The $S_{RN}1$ Reaction**), as are disproportion events. Certain rearrangements involving radicals involve concerted mechanisms, too (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**).

We will complete this subsection with a look at a specific example of a simple radical chain reaction, which will bring together many of the concepts from the first two subsections of this article. The selected example is a *Kharasch reaction*, first reported in the mid-1940s.⁶ This chain reaction involves the overall addition of a C–Cl bond of CCl_4 across an alkene (Scheme 8).

Diacetyl peroxide serves as an initiator in these reactions, which undergoes homolysis to form acyloxy radicals that, in turn, undergo β -elimination to form methyl radicals. These reactive species abstract a chlorine atom from CCl_4 to generate $Cl_3C\cdot$ and chloromethane. This completes the initiation phase of the mechanism. The propagation cycle involves, firstly, an intermolecular radical addition of $Cl_3C\cdot$ to the less substituted end of the alkene bond of 1-octene. This is a thermodynamically favored process due to the formation of a C–C σ bond at the expense of a C=C π bond. The resulting secondary alkyl radical participates in an intermolecular substitution event, abstracting a Cl atom from CCl_4 to form the product and a $Cl_3C\cdot$ radical. It is important to recognize that the purpose of the initiation phase of the mechanism is to generate a radical that is part of the propagation cycle.

A combination of any two radicals would represent a termination event and is thus undesired. Radical–radical coupling is kept to a minimum in this—and many other—radical chain reactions by using only a small amount of initiator, which leads to a very small concentration of radicals in solution. For the propagation cycle to be effective, the two different radicals involved must be selective in their reactivity. In the case of the trichloromethyl radical, this should not be an issue, since reaction



Scheme 8 The mechanism of a Kharasch reaction ($\text{R} = n\text{-hexyl}$).

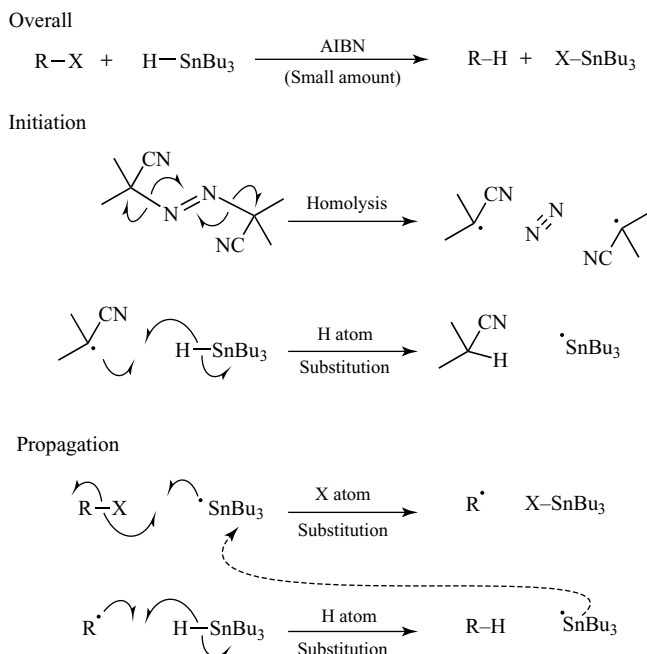
with another CCl_4 molecule would be neither a productive nor a destructive process. In the case of the secondary alkyl radical, reaction with another 1-octene molecule would represent the first step in a telomerization process. Evidently, success in the Kharasch reaction hinges upon the secondary alkyl radical abstracting a chlorine atom, rather than adding to another alkene π bond. We will return to this important issue at a later stage. In the next subsection, we will delve deeper into the design of radical chain reactions through an examination of the different types of reagents (initiators, mediators, and catalysts) that are employed to bring them about.

1.3 Introduction to Radical Mediators

There are several different ways to subdivide the many different known radical chain reactions. Here, we will adopt an approach that involves a consideration of the reagents used to bring about the

conversion of the precursor(s) into the product(s). The need for a reagent known as an *initiator* to produce a radical that is part of the propagation cycle was discussed in the preceding subsection. Despite its employment in a sub-stoichiometric quantity, the initiator is rarely a *catalyst* in radical chain reactions, since virtually all initiators are irreversibly transformed into radicals, which are further converted into some other by-product. Some reactions (e.g., Kharasch reaction, Scheme 8) do not need additional reagents to transform precursor into product; the initiator reacts directly with a substrate to generate a radical that is a part of the propagation cycle. In many instances, however, an additional reagent called a *mediator* is needed. A radical mediator is a reagent that is intimately involved in the conversion of the precursor(s) but contributes only a hydrogen atom to the product.

The most celebrated—and infamous—radical mediator is tri-*n*-butyltin hydride (see **Tin Hydrides and Functional Group Transformations**).⁷ Despite its toxicity (a problem that is further



Scheme 9 Radical chain reductive dehalogenation of organohalides with Bu_3SnH as mediator.

aggravated by the difficulty associated with removing its residues from organic products), Bu_3SnH still enjoys widespread use in synthesis. It is cheap and easily synthesized. It functions through the intermediacy of $\text{Bu}_3\text{Sn}^\bullet$, readily generated from the stannane by H atom abstraction by an initiator-derived radical. Scheme 9 depicts the simplest possible iteration of its use, namely for the reductive dehalogenation of organohalides. In the propagation phase, the mediating $\text{Bu}_3\text{Sn}^\bullet$ radical abstracts a halogen atom from the organohalide to generate carbon-centered radical $\text{R}^\bullet$, which abstracts a hydrogen atom from Bu_3SnH to form the dehalogenated product and a $\text{Bu}_3\text{Sn}^\bullet$ radical, thereby completing the cycle.

As we will see in Section 2 of this article, the immense power of Bu_3SnH and related mediators in synthesis stems from the fact that they bring about the formation of carbon-centered radicals with high selectivity under extremely mild conditions. In reductive dehalogenations (Scheme 9), the initially formed carbon-centered radical $\text{R}^\bullet$ simply abstracts a H atom from the mediator. Many different reactions have been invented, however, from sequences of discrete processes involving these initially formed

carbon-centered radicals *before* the H atom abstraction step.

Other tri(organo)tin hydrides $\text{R}_3\text{Sn-H}$ have been used as radical chain mediators but all suffer from the same toxicity issue as Bu_3SnH . Several less toxic replacements for stannanes have been introduced, including various silanes (see **Silanes as Reducing Reagents in Radical Chemistry**), germanes, phosphanes (see **Main-Group Elements in Radical Chemistry**), and boranes (see **Boron in Radical Chemistry**) (Figure 4). Without a doubt, the most successful is tris(trimethylsilyl)silane, $(\text{Me}_3\text{Si})_3\text{Si-H}$,⁸ which functions in a very similar manner to Bu_3SnH in many scenarios. The success of $(\text{Me}_3\text{Si})_3\text{Si-H}$ can be traced to the BDE of the Si-H bond in this compound, which is similar to that of the Sn-H bond in Bu_3SnH . The only drawback with this reagent is the cost (it is relatively difficult to prepare). Other silane-based mediators have Si-H bonds that are too strong, which impacts negatively upon their ability to sustain an efficient radical chain reaction. This is also the problem with germanes $\text{R}_3\text{Ge-H}$ (which are also rather expensive) and P-H-based reagents (which are cheap).

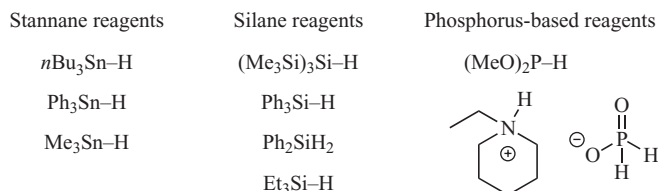
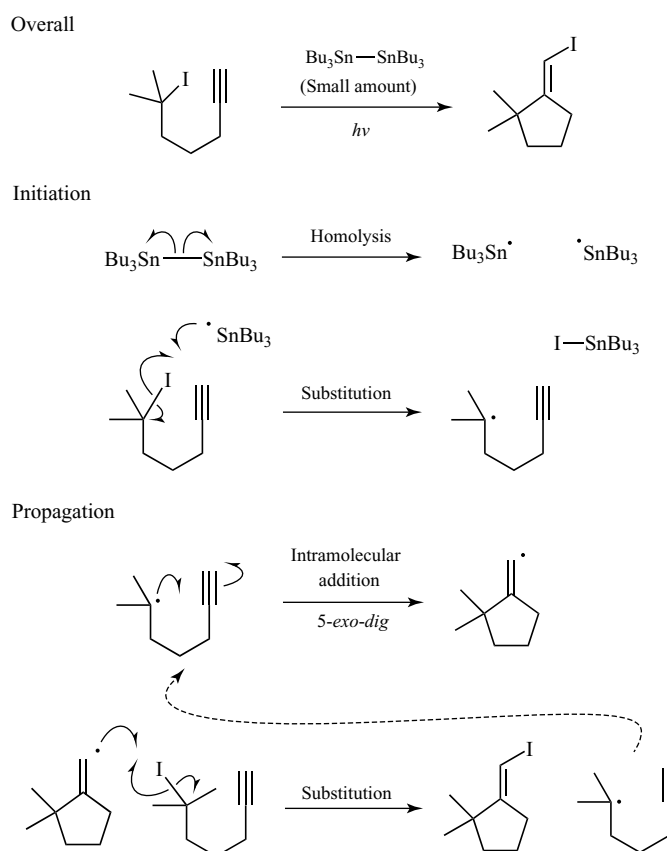


Figure 4 A selection of common radical mediators.

The problem of toxicity of tributyltin compounds and the problems of removal of tributyltin residues has been addressed in a number of ways. Some of the more interesting, from a mechanistic perspective, involve the use of Bu_3SnH as *catalyst* along with a stoichiometric amount of a reducing agent to convert the Bu_3SnX by-product back into Bu_3SnH . Notable contributions in this area by Corey,⁹ Stork,¹⁰ and Fu¹¹ have been made.

1.4 Introduction to Atom Transfer and Group Transfer Processes

The mediators discussed in the preceding subsection are reducing agents and they tend to lead to a decrease in functional group content in the molecule since, overall, a functional group in the substrate is removed and the H from the mediating reagent is incorporated. By employing chain reactions involving *atom transfer* and *group*



Scheme 10 The first example of an atom transfer radical cyclization (ATRC).

transfer processes, transformations that retain functional group content in the product have been devised (see **Halogen and Chalcogen Transfer Chemistry**). These reactions have the additional advantage that they do not require a mediator.

There are many examples of atom transfer radical chain processes. We have already seen the Kharasch reaction (Scheme 8), the very first reported example of what is now known as atom transfer radical addition (ATRA). A non-reducing version of the mediator Bu_3SnH , namely $\text{Bu}_3\text{Sn-SnBu}_3$, was used as an initiator by Curran in the first example of atom transfer radical cyclization (ATRC) in 1986 (Scheme 10).¹² It should be noted that a sub-stoichiometric amount of hexabutylditin is employed in this reaction. The initiation phase of the reaction might involve homolysis of the Sn-Sn bond to generate two $\text{Bu}_3\text{Sn}^\bullet$ radicals, one of which abstracts an iodine atom from the precursor to generate a tertiary alkyl radical and tributyltin iodide. This completes the initiation phase of the reaction and tin-containing species take no further part. In fact, the propagation cycle involves two steps and only the precursor. The tertiary alkyl radical undergoes 5-*exo-dig* radical cyclization (explained later) to form an alkenyl radical, which abstracts iodine from the precursor. This iodine atom transfer process works in thermodynamic terms since, in addition to the overall replacement of a $\text{C}=\text{C}$ π bond by a stronger σ bond, the product has a significantly stronger C-I bond than does the precursor.

Moving on from atom transfer processes, another very important class of radical chain reactions involves a related process known as *group transfer*. Such processes involve the overall substitution (usually through a stepwise addition-elimination sequence) at a group (usually thiocarbonyl-containing) as key steps in a propagation cycle. We will examine representative examples of group transfer processes in the second half of Section 2 of this article.

2 RADICAL CHAIN REACTIONS IN SYNTHESIS

In Section 1, the basic aspects of radical chain reactions were introduced. In the second part of this tutorial review, we will examine some of the more

commonly encountered issues pertaining to reaction design in radical chain reactions. The approach taken is one based upon mechanistic analyses of synthetic case studies and is divided into two sections: the first covers chain reactions that are sustained by reductive mediators and the second describes non-reductive processes. The literature coverage is by no means exhaustive. Furthermore, of the topics that are covered in this subsection, more detailed surveys are often provided in separate articles of this encyclopedia.

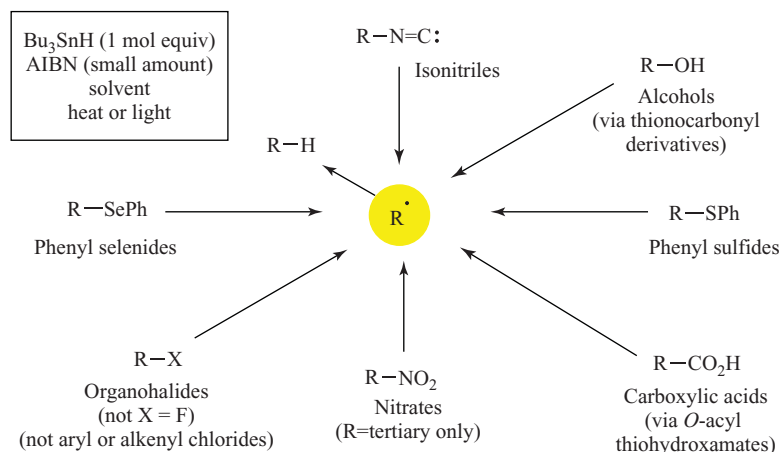
2.1 Radical Chain Reactions Employing Reductive Mediators

This subsection covers the major reaction classes that employ reductive mediators, namely, functional group removals, *intermolecular* radical additions, radical cyclization reactions, and related processes.

2.1.1 Reductive Removal of Functional Groups

Reductive radical mediators such as Bu_3SnH were introduced in Section 1 of this article. We saw that a $\text{Bu}_3\text{Sn}^\bullet$ radical, easily formed through initiation processes, readily generates a carbon-centered radical through halogen atom abstraction from an organohalide. This carbon-centered radical then abstracts a hydrogen atom from a Bu_3SnH molecule to complete the propagation cycle (Scheme 9).

Bu_3SnH has an almost ideal reactivity profile as a mediator, since it has an excellent balance of high chemoselectivity and broad substrate scope. A selection of the many possibilities for carbon-centered radical generation (and the reductive removal of functional groups) using mediators such as Bu_3SnH is shown in Scheme 11 (see **Tin Hydrides and Functional Group Transformations**). Thus, in addition to undergoing an $\text{S}_\text{H}2$ reaction at the halogen of an organohalide (Scheme 9), $\text{Bu}_3\text{Sn}^\bullet$ will also undergo radical substitution at the sulfur of sulfides (PhS groups are popular) and the selenium of selenides (phenyl selenides are most frequently used) to generate carbon-centered radicals. Some nitro-compounds and isonitriles also yield carbon-centered radicals on reaction with $\text{Bu}_3\text{Sn}^\bullet$,



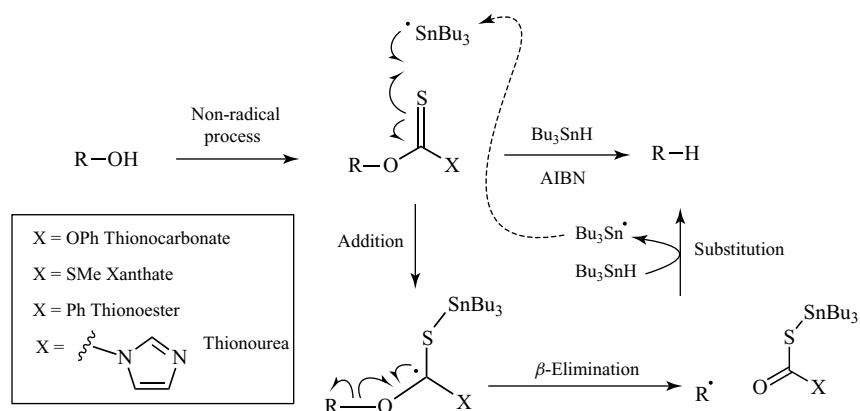
Scheme 11 A selection of the many functional group removals that can be brought about by Bu_3SnH and related mediators.

in reactions that involve addition/elimination mechanisms to obtain overall substitution by Bu_3SnH at the functional group. Even alcohols and carboxylic acids serve as precursors to carbon radicals through *Barton–McCombie deoxygenation*^{13,14} and *Barton decarboxylation*.^{15,16} In the latter case, the process occurs with loss of one carbon.

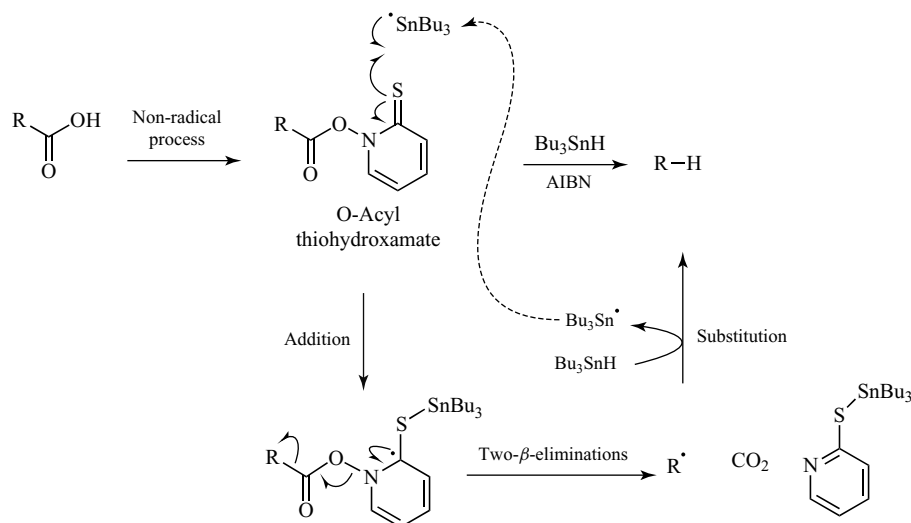
The alcohol or carboxylic acid precursor is converted into a derivative containing a thiocarbonyl group through an esterification-type process; it is the thionocarbonyl derivative that is used in a reaction with Bu_3SnH (or other mediator). In Barton–McCombie deoxygenation (Scheme 12), commonly encountered thiocarbonyl derivatives are xanthates, thionoureas and, particularly, aryl thionocarbonates. The Bu_3SnH radical adds to the

thiocarbonyl group in the first step of the propagation cycle. The resulting adduct radical undergoes β -elimination to form the carbon-centered radical and a carbonyl-containing by-product, and then hydrogen atom delivery to $\text{R}^\bullet$ by the mediator completes the propagation cycle in the usual manner. This reaction tends to work best for deoxygenation of secondary alcohols. With primary alcohol derivatives, higher temperatures are generally needed to increase the rate of the β -elimination step, which is less favored when $\text{R}^\bullet$ is a primary alkyl radical. The deoxygenation of thionocarbonate derivatives of tertiary alcohols can be complicated by a competing pericyclic (Chugaev) elimination process.

The Barton decarboxylation sequence (Scheme 13) is similar, in that it also involves a



Scheme 12 Barton–McCombie deoxygenation of alcohols.

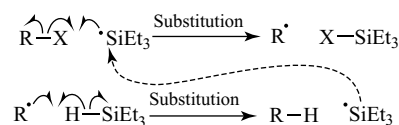


Scheme 13 Barton decarboxylation.

non-radical esterification-type process to form the substrate for the radical reaction. The substrate is an *O*-acyl thiohydroxamate derivative, which undergoes addition at the sulfur of the thiocarbonyl group by the mediating radical (thiols have also been used). A sequence of two β -elimination steps gives the carbon-centered radical, which collects a hydrogen atom from the mediator to complete the propagation cycle. The overall transformation for the two steps is $\text{R-CO}_2\text{H} \rightarrow \text{R-H}$, with the carbon lost as CO_2 . The thermodynamic driving force for this reaction comes from the aromatization of the heterocyclic ring of the *O*-acyl thiohydroxamate precursor and the replacement of the weaker $\text{C}=\text{S}$ bond with the stronger $\text{C}=\text{O}$ bond.

Of course, it is not necessary for a carbon-centered radical formed in one of these reactions to complete the propagation cycle directly; instead, the formation of $\text{R}^\bullet$ can serve as a starting point for other sequences of bond-forming and -breaking events before finally collecting a H atom from the mediator. Furthermore, we shall see in a later subsection that *O*-acyl thiohydroxamates and *S*-xanthates have been employed with great effect in group transfer chain reactions, processes that do not mandate the presence of a mediator.

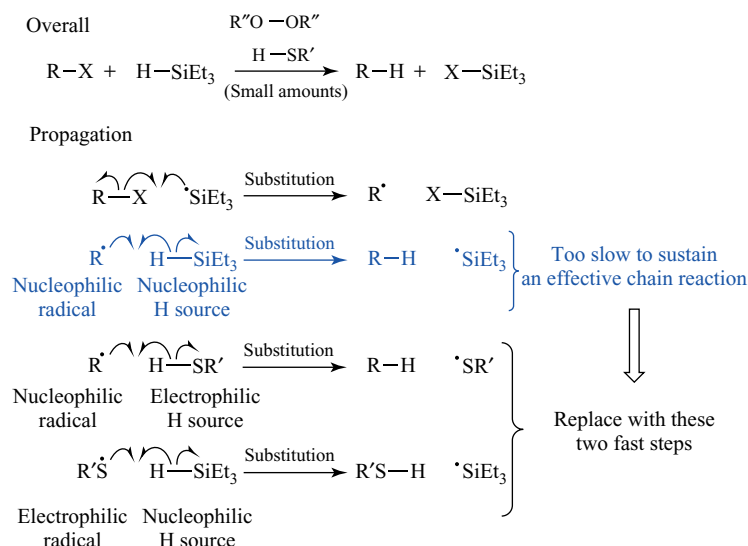
One of the more intriguing aspects of radical reactions is that they are influenced by polar effects. The Si-H BDE in $\text{Et}_3\text{Si-H}$ is 398 kJ mol^{-1} , which is significantly higher than that of the Sn-H bond



Scheme 14 A reasonable-looking propagation cycle for the reductive dehalogenation of organohalides by Et_3SiH .

in Bu_3SnH (308 kJ mol^{-1}) and the Si-H bond in $(\text{Me}_3\text{Si})_3\text{Si-H}$ (351 kJ mol^{-1}). Nevertheless, the $\text{Et}_3\text{Si-H}$ bond strength is still lower than that of most C-H bonds (Figure 3), so the sequence shown in Scheme 14 should be a reasonably effective propagation cycle for the reduction of most organohalides (see **Silanes as Reducing Reagents in Radical Chemistry**).

Experimentally, these chain reactions are rarely synthetically useful since the second step is too slow at usual working temperatures. The problem is that alkyl radicals are nucleophilic species and the silane is an electron-rich source of hydrogen atoms, hence the reaction has unfavorable polar characteristics. Of course, $(\text{Me}_3\text{Si})_3\text{SiH}$ and Bu_3SnH also suffer the same problem but presumably, the significantly weaker Si-H (Sn-H) bond strengths in these mediators compensate somewhat. The solution with Et_3SiH , cleverly developed by Roberts, involves the addition of a catalytic amount of a hydrogen atom donor that reacts rapidly with alkyl radicals. A thiol serves as a *protic polarity reversal catalyst* in this



Scheme 15 Polarity reversal catalysis in the reductive dehalogenation of organohalides by Et_3SiH .

reaction and replaces the one slow step with two fast ones, substitutions that benefit from favorable polar effects (Scheme 15).¹⁷

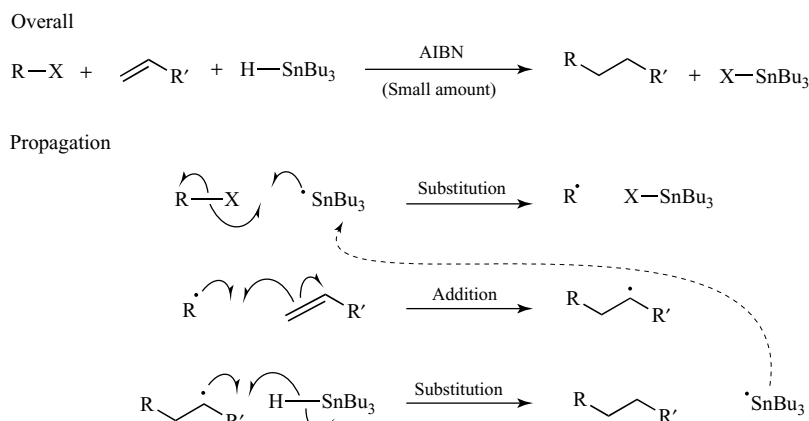
This is only one example of the many effective *polarity reversal catalysis* processes in radical reactions that have been developed by Roberts.¹⁸ As we will see, polar effects are a general feature of radical reactions.

2.1.2 Intermolecular Radical Additions to Multiple Bonds

The Kharasch reaction (Scheme 8) and more modern metal-catalyzed variants (Section 2.2) form a new C–C bond through an intermolecular addition of a carbon-centered radical to an alkene. In the process, a new C–X bond is also forged. A reductive variant of this process was developed by Bernd Giese.¹⁹ *Giese reactions* involve the union of organohalides and alkenes, are mediated by Bu_3SnH (or similar), and are of broader scope than Kharasch reactions. A generalized reaction is depicted in Scheme 16. The mechanism is essentially identical to radical reductive dehalogenation, except that an intermolecular radical addition step occurs after the abstraction of the halogen atom by $\text{Bu}_3\text{Sn}\cdot$ and before the transfer of a hydrogen atom to the carbon-centered radical by Bu_3SnH .

To optimize the yield of the addition product, some planning is usually needed with respect to how these chain reactions are conducted in the laboratory, specifically with respect to the relative concentrations of organohalide, alkene, and tributyltin hydride. A fine balance is needed here, since too high a concentration of Bu_3SnH will lead to premature trapping of the initially formed carbon-centered radical ($\text{R}\cdot$ in Scheme 16) and formation of the direct reduction product of the organohalide. Conversely, the concentration of the alkene must be kept high to favor the addition step. This is achieved through the slow addition of Bu_3SnH (and a small amount of initiator such as AIBN) to a concentrated solution of alkene (usually in excess) and organohalide in a non-H atom donor solvent (cyclohexane and benzene are commonly used).

It turns out that the rate of the addition step—and the success of these intermolecular radical addition reactions—is strongly dependent upon the nature of both the alkene and the organohalide. The fastest reactions occur between *either* electron-rich (nucleophilic) radicals and electron-deficient (electrophilic) alkenes *or* electrophilic radicals and nucleophilic alkenes. These polar effects are best explained by consideration of the frontier molecular orbitals (FMOs) of the radical and the alkene components (Figure 5).



Scheme 16 Intermolecular reductive radical addition to C=C bonds: the Giese reaction.

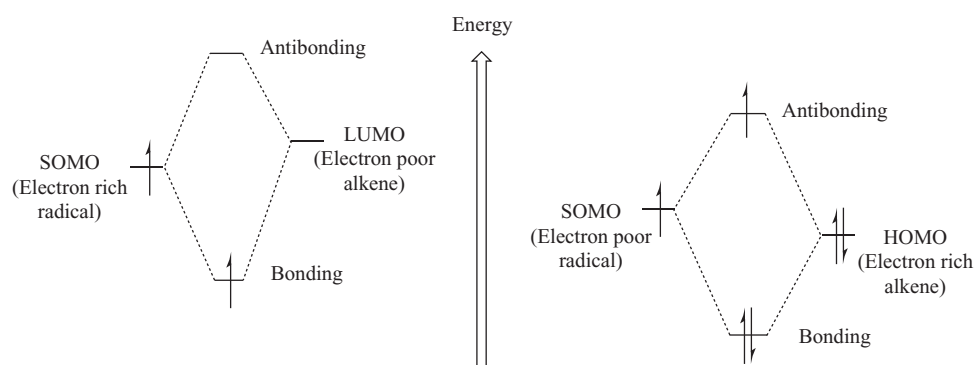


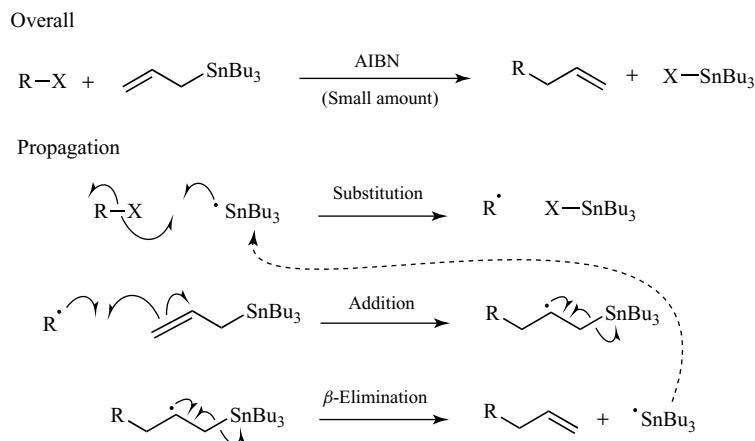
Figure 5 FMO interactions in radical additions to alkenes.

The radical SOMO (singularly occupied molecular orbital) is expected to reside between the energies of a π bond HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). With the electron-rich radical (high lying SOMO)/electron poor alkene (low lying HOMO and LUMO) pairing, the dominant FMO interaction is between the radical SOMO and alkene LUMO. With an electrophilic radical and electron-rich alkene, the SOMO(radical)–HOMO(alkene) FMO interaction dominates. Despite an electron being placed in an anti-bonding orbital, this latter mixing of MOs still leads to a net energy gain.

Polar effects explain many aspects of radical reactions. In the Kharasch reaction (Scheme 8), for example, the trichloromethyl radical (an electrophilic radical) adds to 1-octene (an electron rich olefin). The resulting alkyl radical is nucleophilic,

hence its propensity for addition to 1-octene is lower, and the reaction can be stopped at the mono-addition stage. Evidently, such factors are of paramount importance in both synthetic organic chemistry and polymer chemistry.

An ingenious variation on the theme of intermolecular radical addition reactions involves the radical chain allylation of organohalides. *Keck allylation* (Scheme 17) employs allyltributyltin as the alkene component.²⁰ Following addition of the organohalide-derived carbon radical to the less substituted end of the alkene, β -elimination ensues, resulting in the formation of the allylated product and a $\text{Bu}_3\text{Sn}^\bullet$ radical, which completes the propagation cycle. Thus, *overall* radical substitution occurs through a stepwise addition/ β -elimination sequence, since the alkene carries a “radical leaving group” substituent (Bu_3Sn) at the allylic site.



Scheme 17 Intermolecular radical allylation: the Keck reaction.

The importance of intermolecular additions in the development of modern synthetic radical chemistry cannot be overstated. It is fair to say, however, that the biggest impact of this work was in its extension to *intramolecular* additions. In total synthesis, radical cyclization technology is a widely used synthetic tool of broad application.

2.1.3 Intramolecular Radical Additions to Multiple Bonds

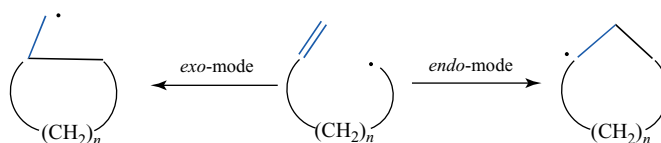
When a radical center and a π bond are connected by a tethering chain, intramolecular addition is possible and two distinct cyclization modes can ensue (Scheme 18). These two modes involve either formation of a bond to the more proximate atom in the chain, in which case, the radical will end up outside of the ring (*exo* mode). Alternatively, formation of a new σ bond to the more distant atom of the π bond results in the radical ending up inside of the ring (*endo* mode).

More generally, radical cyclizations are classified by *Baldwin's rules of ring closure*, which take into consideration the ring size formed, whether the

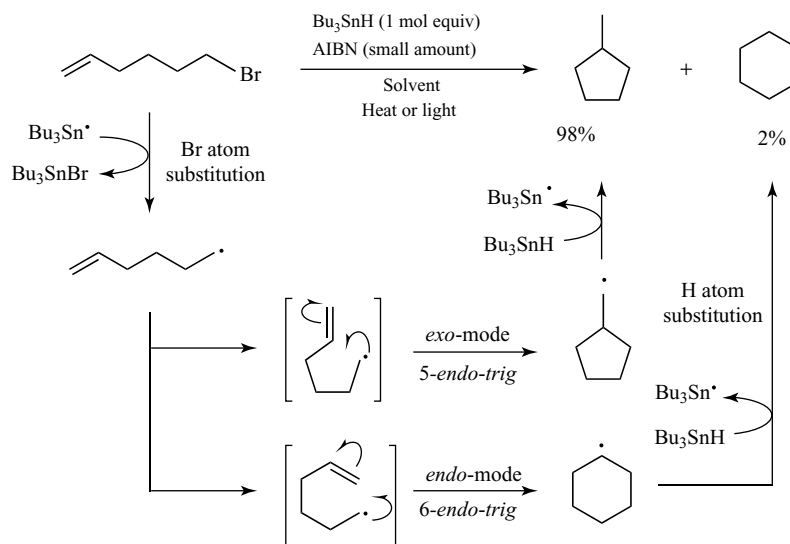
mode is *exo* or *endo*, and the type of center to which the bond is formed (tetrahedral, trigonal planar, or digonal).²¹ These empirical rules, which are not solely applicable to radical cyclizations, were based upon analysis of conformational features impacting upon orbital overlap during cyclization reactions, and led to a classification of cyclization types as *favored* or *disfavored*. Baldwin's rules will not be discussed in detail here but for our purposes, it is important to note that 5-*endo-trig* radical cyclizations in all-carbon systems are *disfavored* (see **Unusual Cyclizations**).

One of the classic examples of radical cyclization reactions involves the 5-hexenyl radical, a species that can be conveniently generated through halogen atom abstraction from the halide by $\text{Bu}_3\text{Sn}^\bullet$ (Scheme 19).²² Under kinetically controlled conditions, the major product of the Bu_3SnH -mediated process is methyl cyclopentane, resulting from a 5-*exo-trig* radical cyclization. Cyclohexane, generated through the alternative 6-*endo-trig* mode of cyclization, is formed as a very minor product.

On face value, the preference for the *exo*-cyclization mode is unexpected for three reasons: both the five-membered ring and the



Scheme 18 Radical cyclization modes.



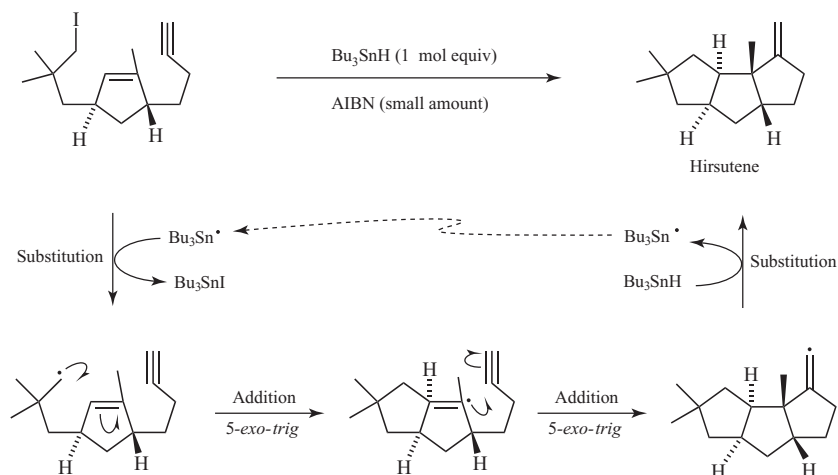
Scheme 19 Radical cyclization of 1-bromo-5-hexene through a Bu_3SnH -mediated chain reaction.

primary alkyl radical are less thermodynamically stable than the six-membered ring and the secondary alkyl radical, which result from the alternative *endo*-cyclization mode. Furthermore, addition to the less substituted end of the alkene (i.e., *endo*-mode addition) would be expected to have less steric impact. The preference for *exo*-mode of cyclization is explained by the need for good overlap between the SOMO and the orbitals associated with the alkene π -system. The angle of approach of a radical to a $\text{C}=\text{C}$ bond—calculated to be around 109° —is significantly better accommodated by the transition state leading to *exo*-mode cyclization.

The kinetic preference for the *5-exo-trig* mode of cyclization is quite general, with substrates containing heteroatoms in the chain also usually giving the smaller ring size. Substituted 5-hexenyl radicals also show a marked preference for the *exo*-mode of cyclization, with the exception of 1,1-disubstituted alkenes. In this case, steric strain destabilizes the transition state leading to the *5-exo-trig* product, thus the *6-endo-trig* product is mildly favored. The higher homolog, the 6-heptenyl radical, also preferentially undergoes an *exo*-mode cyclization, albeit with a slightly diminished selectivity relative to the lower homolog. Diastereoselectivity in reactions of substituted precursors is predictable on the basis of *Beckwith–Houk transition state models*,^{23,24} which consider chair- and boat-like transition states and a

preference for substituents to adopt equatorial orientations (see **Stereoselective Radical Reactions**). Polar effects still operate in intramolecular radical additions but their effects are less important than in intermolecular additions. Operationally, it is often advantageous to keep both the substrate concentration and Bu_3SnH concentration low during radical cyclization reactions, to minimize premature trapping of the uncyclized radical by H atom transfer from the mediator.

One rather obvious feature of a radical cyclization step is the formation of another radical. In a carefully designed precursor, this cyclized radical can participate in a second radical cyclization. Domino radical chain sequences are among the most powerful ways to rapidly generate complex structures (see **Radical Cascade Reactions**). An early example of a double radical cyclization is Curran's landmark synthesis of hirsutene, generally accepted as a classic in synthesis design and execution (Scheme 20).²⁵ In the propagation cycle, a $\text{Bu}_3\text{Sn}^\bullet$ radical abstracts the iodine atom from the monocyclic precursor, generating a primary alkyl radical. A *5-exo-trig* radical cyclization onto the cyclic alkene generates a bicyclic tertiary alkyl radical, which cyclizes in a *5-exo-dig* manner to generate a tricyclic alkenyl radical. Abstraction of a H atom from Bu_3SnH forms the natural product and completes the propagation cycle.



Scheme 20 Curran's domino radical cyclization approach to hirsutene.

Whereas the formation of five- and six-membered rings are the most common, radical cyclizations have been employed to form all ring sizes, from three-membered systems to macrocycles (see **Unusual Cyclizations**). Cyclizations to form three- and four-membered rings are generally fast and reversible, with the equilibrium usually favoring the ring opened form.

Radicals add intramolecularly to all manner of different π bonds. The reversible addition to the carbonyl bond of ketones, for example, forms the basis of the *Dowd–Beckwith ring expansion* protocol.^{26,27} Radicals will add intramolecularly to benzene rings, with new bonds being formed to either the ipso- or the ortho-positions (see **Radical Arylations**).

Finally in this subsection on chain reactions controlled by reductive mediators, we will consider a very useful process that is related to radical cyclizations (and is often followed by one). The process is an intramolecular radical substitution at hydrogen, which often proceeds through a six-membered transition state. This process was popularized through the *Barton reaction*,²⁸ a non-chain remote functionalization method famously applied to steroids. That intramolecular hydrogen atom transfers (HATs), as they are known, can be useful in reductive chain reactions and is demonstrated by the example shown in Scheme 21.²⁹

In this example, an alkenyl radical selectively abstracts the hydrogen atom from a tertiary

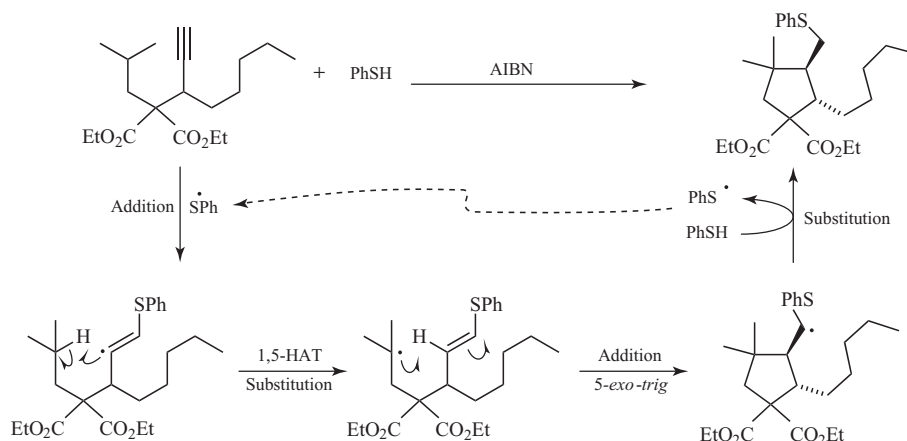
alkyl C–H bond, then cyclizes back onto the alkene. The alkenyl radical is generated through the addition of a thiyl radical to an alkyne precursor, which is usually an efficient process (see **Radical Thiol–X Click Chemistry**). The last step in the propagation cycle involves abstraction of the H atom of the thiol by the cyclized alkyl radical. Intramolecular HAT processes are extremely useful in synthesis. Alkenyl, aryl, and alkoxy radicals are the most frequently encountered abstracting species and alkyl C–H bonds are the ones usually suffering substitution.

2.2 Non-Reductive Radical Chain Reactions

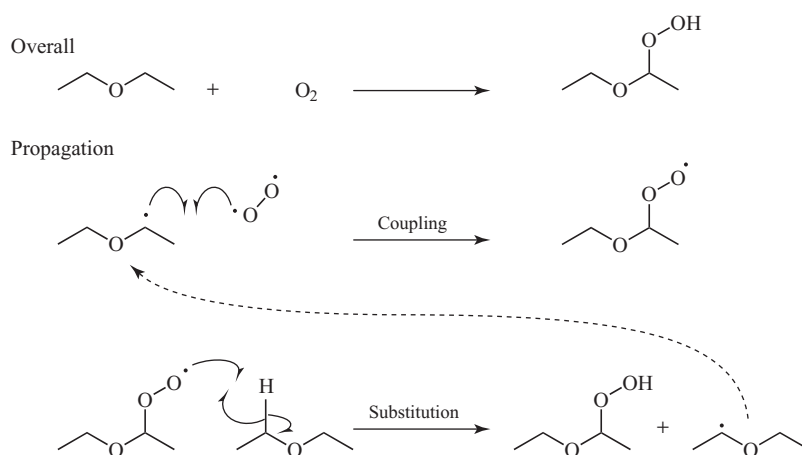
In this final subsection of our article on fundamental aspects of chain reactions, we will look at some of the most notable radical chain processes that proceed *without* the assistance of a reductive mediator. These include autoxidation, radical halogenation, and atom and group transfer sequences.

2.2.1 Introduction of Functional Groups: Autoxidation and Radical Halogenation

One of the most important radical chain reactions is autoxidation. This rather poorly named process involves a radical chain reaction between an organic substrate and oxygen, and occurs for



Scheme 21 An example of a reductive chain reaction involving an intramolecular 1,5-hydrogen atom transfer (1,5-HAT).



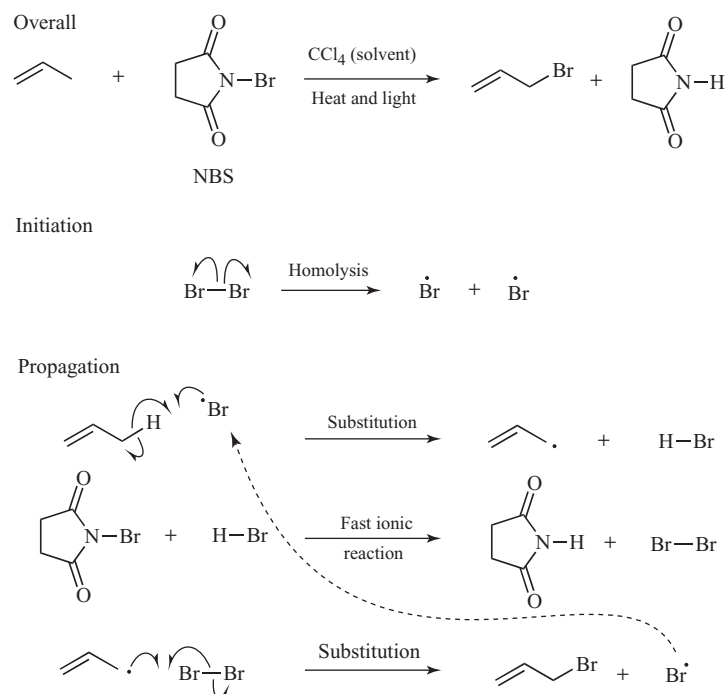
Scheme 22 Autoxidation of diethyl ether.

all organic compounds (including biological ones) carrying relatively weak C–H bonds. The autoxidation of diethyl ether is provided as an example (Scheme 22).

The initiation phase of autoxidation is unclear, but ultimately involves the generation of a carbon-centered radical. In the case of diethyl ether, it is the more stable of two possible carbon-centered radicals. This radical then couples with triplet oxygen to form a hydroperoxyl radical, which, in the second and last step of the propagation cycle, abstracts a hydrogen atom from one of the weaker C–H bonds of the substrate. Once initiated, the autoxidation mechanism is usually very efficient,

with a relatively small number of radicals needed to transform large amounts of substrate. The autoxidation chain reaction can be disrupted by the addition of a better H atom donor than the substrate. Such compounds include substituted phenols such as BHT (2,6-di-*tert*-butyl-4-methylphenol) and toco-pherol. These antioxidants function by delivering a H atom to the hydroperoxyl radical involved in the propagation cycle (see **Antioxidants in Chemistry and Biology**).

Radical chain halogenations of alkanes are well-established reactions. One of the most useful is the *Wohl–Ziegler reaction*,³⁰ in which an allylic or benzylic C–H bond is replaced by a C–Br



Scheme 23 Allylic (benzylic) bromination with *N*-bromosuccinimide (NBS).

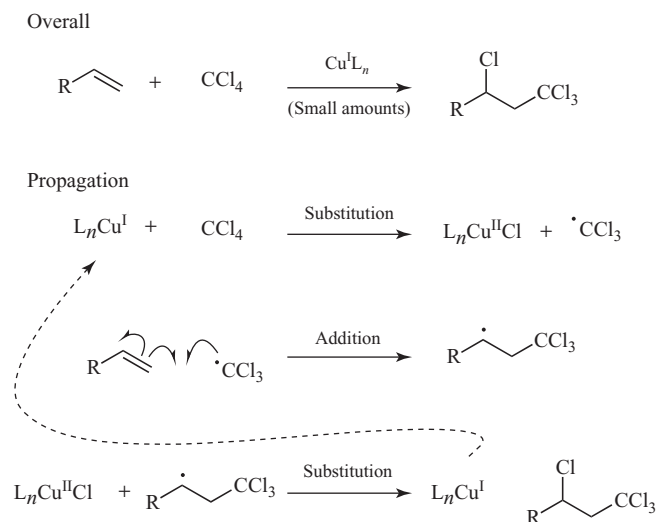
bond. The mechanism of this chain reaction is intriguing, since it involves an ionic process in the radical chain reaction. The reagent of choice is *N*-bromosuccinimide (NBS) (Scheme 23).

Following the initiation phase of the reaction, which involves the homolysis of the weak Br–Br bond (Br_2 is present as a minor contaminant in samples of NBS), the bromine radical abstracts a hydrogen from the weakest C–H bond in the molecule, which is the allylic one, thereby forming the allyl radical and HBr. The HBr reacts with NBS to form succinimide and Br_2 in an ionic reaction. The allyl radical then abstracts a bromine atom from Br_2 in the last step of the propagation cycle. In principle, Br_2 could be used as the reagent for this reaction (imagine the propagation cycle of Scheme 23 without the ionic step). In practice, the reaction with Br_2 would be thwarted by competing electrophilic additions of the reagent and the by-product, HBr. NBS is so effective in this reaction since it keeps the concentration of HBr and Br_2 very low, thereby minimizing unwanted electrophilic additions.

2.2.2 Atom and Group Transfer Radical Chain Reactions

Kharasch-type ATRA reactions (Scheme 8) were of enormous importance in the development of radical chemistry (see **Halogen and Chalcogen Transfer Chemistry** and **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). Nevertheless, Kharasch reactions are of rather limited scope, since they are plagued by the problem of selectivity; specifically, the atom transfer step cannot adequately compete with intermolecular addition to another molecule of alkene, so telomerization sometimes occurs.

The problems of selectivity in classical Kharasch chain reactions has been addressed through the use of Cu, Ni, Fe, and Ru metal complexes as *catalysts* (in some cases, the metal in elemental form has been used) (see **Halogen and Chalcogen Transfer Chemistry**). The mechanisms of these reactions (Scheme 24) involve, firstly, the generation of a carbon-centered radical (e.g., $\cdot\text{CCl}_3$) from a reactive organohalide compound (e.g., CCl_4) by overall



Scheme 24 Possible mechanism of a metal-catalyzed ATRA reaction.

abstraction by the metal catalyst in its lower oxidation state (e.g., $\text{Cu}^{\text{I}}\text{L}_n$). The $\cdot\text{CCl}_3$ radical then undergoes addition to the alkene and the resulting adduct radical abstracts a halogen atom from the higher oxidation state metal complex, $\text{L}_n\text{Cu}^{\text{II}}\text{Cl}$. The catalytically active, lower oxidation state metal complex is thus regenerated and feeds back into the propagation cycle.

The metal complex-catalyzed chain reaction is more effective than the traditional Kharasch reaction since the higher oxidation state metal halide is a better halogen atom donor than the organohalide. Nevertheless, the scope of these reactions is once again limited by the nature of the halide precursor and product: generally speaking, the product must carry a significantly stronger C–X bond than that of the precursor.

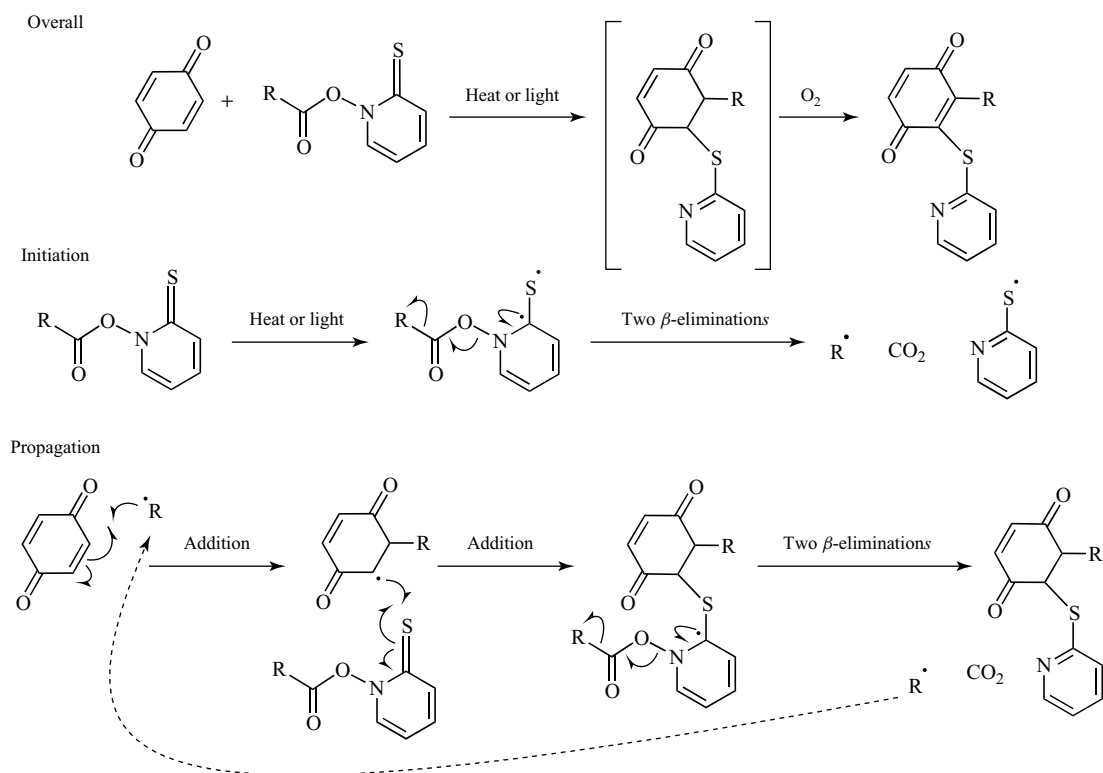
Evidently, the adduct radical might go on to react with another alkene molecule, which in turn can add to another, and so on. This process, termed *atom transfer radical polymerization* (ATRP) (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**) has been used to great effect for the controlled preparation of polymeric materials. ATRP and ATRA are notable since they do not require a radical initiator. Nevertheless, it has been demonstrated recently that the addition of small amounts of AIBN improves the efficiency of these reactions with respect to the loading of the metal complex. It is believed that

the AIBN assists by forming a steady stream of carbon radicals, which abstract chlorine from the higher oxidation state metal catalyst, thus reducing it to the catalytically active form.³¹

As the name suggests, *group* transfer radical reactions are related to their atom transfer counterparts in that a group, rather than an atom, is relocated during the chain reaction. Chalcogen “pseudohalides” (e.g., SPh, SePh) have been employed in this manner, in which case, the transfer step is analogous to that with the halide (see **Halogen and Chalcogen Transfer Chemistry**). Different types of group transfer radical reactions are possible, however, with relocatable groups carrying a thiocarbonyl bond. *O*-Acyl thiohydroxamates and *S*-xanthates are useful functionalities in this regard.

The chemistry of *O*-acyl thiohydroxamates, or *Barton esters*, is rich and varied. Earlier in this article, the decarboxylation of carboxylic acids through the treatment of Barton esters with a reductive mediator was discussed. Replacement of the H atom donor with CCl_4 gives rise to a mild and general alternative to the classical Hunsdiecker reaction.³² Intermolecular additions to alkenes are also feasible, as demonstrated by the reaction with *para*-benzoquinone,³³ depicted in Scheme 25.

In the initiation phase, Barton esters undergo heat or light-mediated fragmentation to the alkyl



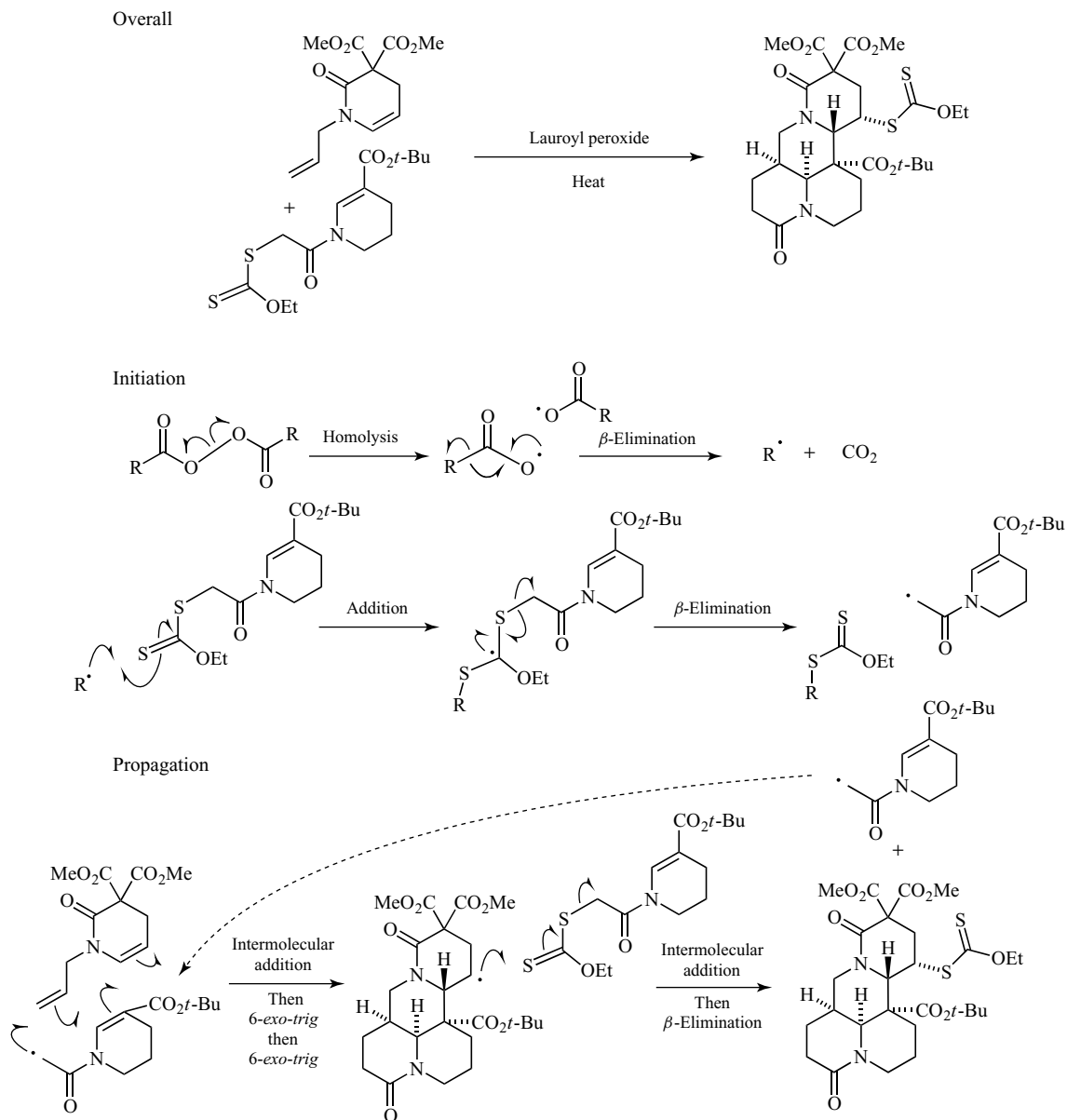
Scheme 25 Group transfer radical chain reaction involving an *O*-acyl thiohydroxamate.

radical $R^\bullet$. In the propagation phase, intermolecular addition of $R^\bullet$ to the benzoquinone gives the adduct radical, which then adds to another molecule of the Barton ester. Aromatization–fragmentation to the acyloxy radical followed by decarboxylation gives the product, a dihydroquinone, which is oxidized to the quinone, presumably through tautomerization to the hydroquinone and then oxidation. The by-product in this last β -elimination step is the alkyl radical $R^\bullet$, which completes the propagation cycle.

Zard has employed *S*-xanthates (not to be confused with *O*-xanthates, the derivatives used in the Barton–McCombie reaction) in imaginative ways (see **Xanthates and Related Derivatives as Radical Precursors**). Scheme 26 depicts a representative example from the Zard group, involving a domino radical addition approach to the alkaloid natural product matrine.³⁴ This final example involves the union of two monocyclic building blocks to form the tetracyclic framework of the natural product in

one step. The diacyl peroxide initiator breaks down through successive homolysis and β -elimination of CO_2 to form alkyl radicals $R^\bullet$. These add to the thio-carbonyl sulfur atom to generate the adduct radical, which breaks down through β -elimination to give the first radical of the propagation cycle, an α -acyl carbon radical species. In the propagation cycle, intermolecular addition of the α -acyl carbon radical to the monosubstituted alkene generates a secondary alkyl radical. Two successive 6-*exo-trig* radical cyclizations give the tetracyclic radical. Intermolecular addition to the *S*-xanthate precursor followed by β -elimination gives the final product and another α -acyl carbon radical by-product, thereby completing the propagation cycle.

Three new C–C bonds and five contiguous stereocenters are formed in this remarkable transformation, which showcases the synthetic power not only of group transfer radical reactions but of free radical chain reactions in general.



Scheme 26 *S*-Xanthate group transfer domino radical chain reaction by Zard ($R = C_{11}H_{23}$).

3 CONCLUSIONS

A chain reaction involves a sequence of events that generates a product or by-product that serves as a substrate for a further reaction. While relatively uncommon in cationic and anionic chemistry, chain

reactions are the principal method in radical chemistry. A chain reaction channels the high chemical reactivity of radicals and permits highly selective chemical transformations, not only in chemical synthesis but also in material applications and biological scenarios.

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Intramolecular Homolytic Substitutions in Synthesis

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1 INTRODUCTION

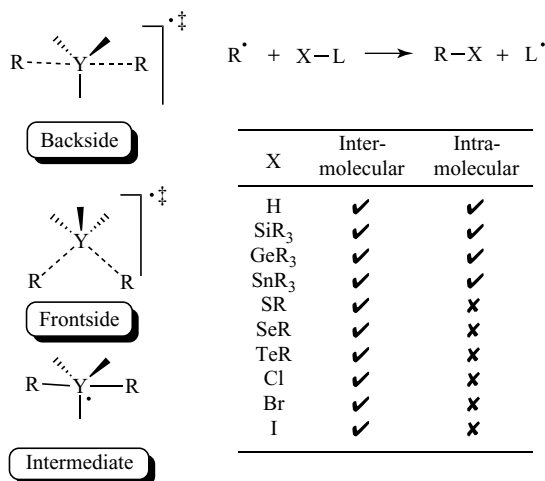
Free radical chemistry contributes to the modern chemists' toolbox in ways that were unimaginable only a few decades ago. There can be no doubt that the construction of carbocyclic and heterocyclic ring systems through the intramolecular addition of alkyl, aryl, and other radicals to unsaturated functionalities is a major contribution to synthetic methodology; this chemistry is the topic of other contributions to this collective work. It is important to recognize that the fundamental principles that guide the use of intramolecular homolytic addition chemistry in synthesis, eloquently summarized by Giese in his 1986 monograph,¹ also apply to intramolecular homolytic substitution chemistry. It was recognized some time ago that most organic free radical addition reactions are under kinetic control and this means that an understanding of fundamental rate and mechanistic data are crucial in designing useful chemical reactions based on these free radical processes¹; the same holds true for reactions involving homolytic substitution chemistry.

Intramolecular homolytic substitution chemistry for the construction of heterocycles was in its infancy as recently as 20 years ago, having largely been used for constructing sulfur-containing ring systems. One of us contributed to a comprehensive review on homolytic substitution chemistry some 15

years ago,² and more recently, presented a feature article,³ while other reviews have been written on the topic since then.^{4,5} The purpose of this article is to provide a practical guide to intramolecular homolytic substitution chemistry, focusing primarily on chemistry developed over the past decade. It is intended to deliver a cross-section of information of relevance to the synthetic practitioner as well as to provide relevant experimental procedures. It is deliberately not meant to be comprehensive, but rather, through examples, intended to provide useful information about the state-of-play of radical substitution chemistry, and what is possible using this relatively new addition to the chemists' toolbox.

2 FUNDAMENTAL PRINCIPLES

To fully appreciate the scope and limitations of homolytic substitution processes at higher heteroatoms, one needs to appreciate the mechanisms by which these reactions proceed, and their associated rate constants. It has been generally agreed that three mechanisms exist for these reactions (Scheme 1).² These include a backside mechanism similar to S_N2 , leading to Walden inversion, as well as a frontside mechanism that would result in retention of configuration at asymmetric heteroatoms such as silicon, germanium, or tin. The third possibility involves a hypervalent



Scheme 1 Inter- versus intramolecular homolytic substitution at main group higher heteroatoms.

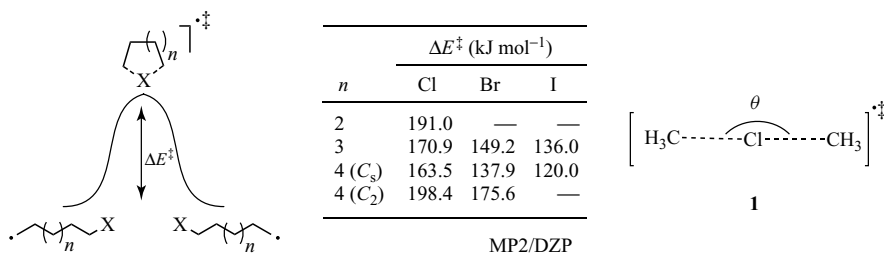
intermediate that may or may not undergo pseudorotation before dissociation, possibly resulting in racemization when the heteroatom undergoing attack is stereogenic.

Homolytic group (and atom) transfer reactions can involve either inter- or intramolecular homolytic substitution processes. Scheme 1 summarizes the trends observed for these reactions, and these trends provide useful information in relation to cyclization reactions at main group higher heteroatoms. The data provided in Scheme 1 indicate that intermolecular group transfer reactions have been reported for hydrogen, as well as for most of the main group elements. However, the analogous intramolecular process is only observed for hydrogen, silicon, germanium, and tin. To the best of our knowledge, there are no reported examples of intramolecular homolytic substitution at the pnictogens (N, P, As); however, several intermolecular examples exist.⁶

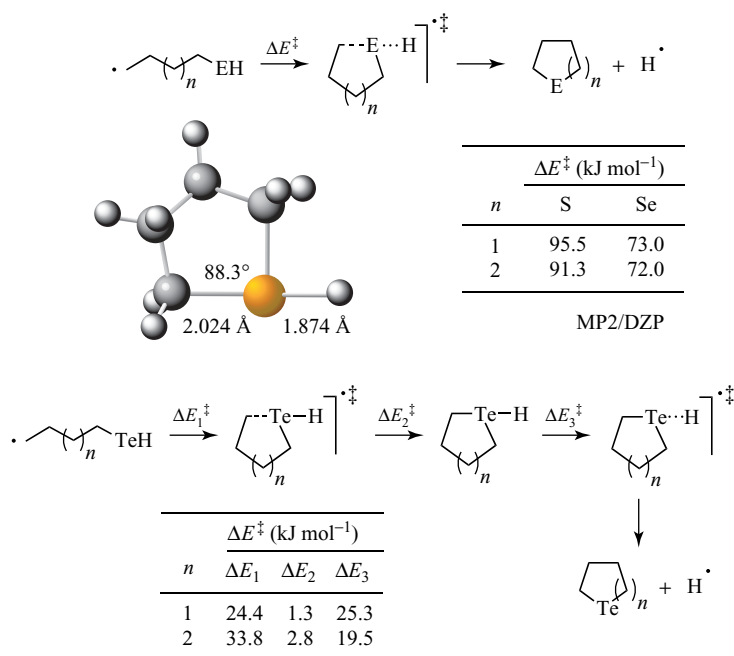
These observations raise obvious questions such as why do group 14 elements undergo this intramolecular chemistry while there are no reported examples for the chalcogens and halogens? Computational chemistry as well as carefully constructed experiments have shed light on the underlying reasons for the trends observed for these group transfer reactions.^{7–12}

Other than the substitution at hydrogen, which would appear to “go around corners” because of the orbitals involved during homolytic substitution, for the remaining main group elements, the backside mechanism requires a collinear (or nearly so) arrangement of attacking and leaving radicals with deviations from this geometry resulting in unfavorable processes with high-energy transition states. For example, Wild showed that 1,4-, 1,5-, and 1,6-homolytic translocations of chlorine, bromine, and iodine have prohibitively high-energy barriers as determined by MP2/DZP calculations (Scheme 2) consistent with substantially “bent” transition state geometries at the halogen (120–145° for 1,5-translocations).⁷ Wild also determined the angular dependence of the MP2/DZP calculated energy for the transition state (**1**) involved in the degenerate reaction of methyl radical with chloromethane. As the angle (θ) is reduced from 180° (ideal) there is a continual rise in transition state energy to a maximum at 90° at which point the transition state has suffered an increase in energy of about 112 kJ mol⁻¹.⁷ While there was a 3.4 kJ mol⁻¹ decrease in progressing to 80°, no saddle point for a frontside mechanism was located. It is clear from this study that homolytic substitution at halogen has a strong preference for backside attack in which the attacking and leaving radicals adopt a collinear arrangement.⁷

Similar observations are made for translocation reactions involving chalcogen. Computational studies suggest that group transfer processes



Scheme 2 Dependence of geometry on homolytic halogen translocation reactions.



Scheme 3 Some calculated homolytic ring closures at sulfur, selenium, and tellurium.

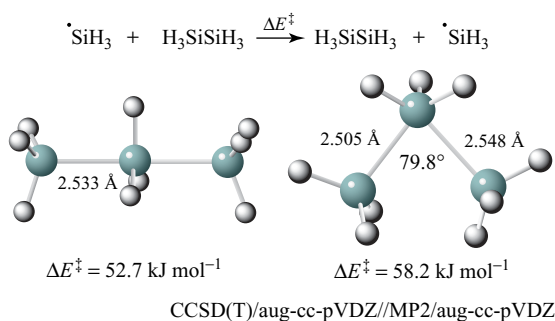
involving homolytic substitution at sulfur and selenium proceed through a backside mechanism and, as was predicted for halogen, have prohibitively high energy barriers, once again the result of significant deviations from the ideal geometry for backside attack at these heteroatoms.⁸ MP2/DZP calculations provide energy barriers in the 90–140 kJ mol⁻¹ range for 1,5-, 1,6-, and 1,7-chalcogen transfer, depending on the heteroatom. However, unlike halogen, Wild was able to locate a second transition state for intramolecular homolytic substitution at sulfur and selenium, and that transition state led to the formation of the corresponding heterocycle.⁸ Indeed, so unfavorable is intramolecular translocation at sulfur and selenium that even a hydrogen atom is calculated to prefer to leave, resulting in the formation of the heterocycle in preference to group transfer (Scheme 3)! So, here we have a fundamental difference between chalcogen and halogen: the second substituent on the chalcogen can act as a leaving group; indeed, it would appear to be easier to adopt the required “backside attack” orientation of attacking and leaving radicals during ring formation, than during translocation.

The story is slightly more complicated for reactions involving tellurium in that radical attack at

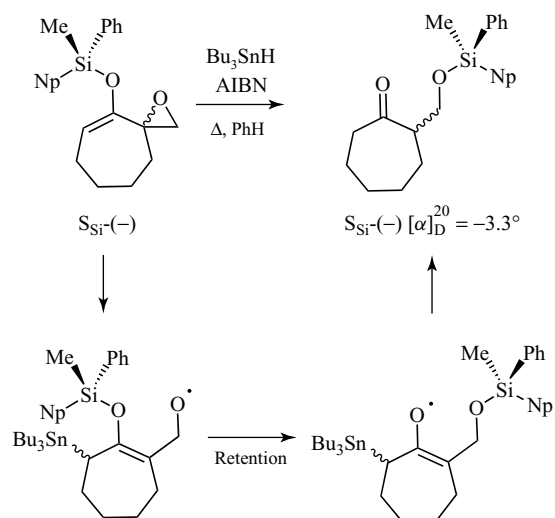
tellurium mostly results in the formation of hypervalent intermediates; however, they are calculated to lie in very shallow wells on their respective potential energy surface and, as a consequence, behave in a similar manner to their sulfur and selenium counterparts in relation to the overall chemistry observed (Scheme 3).⁸

Given these computational data, one might begin to imagine ways of engineering systems that would result in efficient ring formation and it is no surprise that many synthetically useful examples of this chemistry are carried out using stable radical leaving groups such as *tert*-butyl and benzyl.

So, what about silicon, germanium, and tin? Computational and mechanistic studies have revealed that homolytic substitution at these heteroatoms can proceed by using either frontside or backside substitution mechanisms, with both pathways often in competition with each other.⁹ For example, the degenerate reaction of silyl radical with disilane is calculated to have CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ energy barriers of 52.7 and 58.2 kJ mol⁻¹ for the frontside and backside pathways, respectively (Scheme 4).⁹ Similar results have been obtained for other systems.^{10,13} Clearly, unlike the chalcogens



Scheme 4 Backside versus frontside mechanisms in the homolytic substitution of silyl radical at disilane.



Scheme 5 Example of a 1,5-translocation involving an asymmetric silicon substituent.

and halogens, this chemistry at the group 14 higher heteroatoms does not require collinear arrangements of attacking and leaving radical, and the (approximately) 80° requirement for the frontside transition state is convenient for group transfer chemistry.

These computational studies were nicely complemented by the work of Horvat who showed that homolytic translocation involving a stereogenic silicon atom proceeds with retention of configuration, consistent with the involvement of a frontside transition state (Scheme 5).¹¹

To summarize this section, homolytic substitution at the chalcogens and halogens proceeds via backside mechanisms that involve transition states

in which the attacking and leaving radicals prefer to adopt a collinear (or nearly so) arrangement. This requirement introduces prohibitive amounts of strain in the transition states for 1,*n*-translocation reactions. However, it can be harnessed to generate chalcogen-containing ring systems that include molecules such as tetrahydroselenophene. In the case of elements such as silicon, germanium, and tin, this chemistry can proceed via frontside or backside mechanisms leading to translocation and cyclization possibilities. Examples of these chemistries are provided below.

3 INTRAMOLECULAR HOMOLYTIC SUBSTITUTION AT THE CHALCOGENS

3.1 Kinetic Data for Ring-Closure Reactions

Unlike intramolecular homolytic addition chemistry that abounds with useful rate data for the synthetic practitioner to use in crafting the optimum conditions for their reactions of interest (see **Radical Kinetics and Clocks**), fewer rate data are available for ring-closure reactions involving radical attack at higher heteroatoms. As mentioned earlier, because radical reactions are usually under kinetic control, the availability of rate constants for key (model) reactions is crucial for their success in the laboratory. For that reason, we have decided to include the available kinetic data for ring closure at sulfur, selenium, and tellurium in this article (Table 1). While most of the data for sulfur were reported in the 1996 review,² or in the more recent compilation by Crich,⁵ rate constants for these reactions at selenium and tellurium have never been reported together before; their inclusion here provides valuable insight into intramolecular homolytic substitution involving these elements.

The data presented in Table 1 clearly show that rate constants for homolytic substitution at the chalcogens depend on three key factors: (i) the nature of the heteroatom, (ii) the size of the ring being formed, and (iii) the stability of the leaving group. Keeping ring size and leaving radical the same, in progressing down the group from sulfur to selenium and tellurium, there are significant increases in rate constant; from sulfur to selenium this increase is often 2 to 3 orders of magnitude, with a similar change observed in progressing from

Table 1 Representative rate constant data at 80 °C for homolytic ring closures of sulfides, selenides, and tellurides.

Entry	Radical	Solvent	k_c (s ⁻¹)	Arrhenius ^a	References
1		PhH ^b	$\sim 7 \times 10^1$	n.d.	14
2		PhH ^b	$\sim 4 \times 10^2$	n.d.	14
3		<i>t</i> -BuPh ^c	4.4×10^2	$(10.2 \pm 0.6) - (51 \pm 4)/\theta$	15
4		PhH ^b	$\sim 1 \times 10^3$	n.d.	14
5		<i>t</i> -BuPh ^c	6.9×10^3	$(10.8 \pm 0.2) - (47 \pm 2)/\theta$	15
6		<i>t</i> -BuPh ^c	3.7×10^4	$(9.9 \pm 0.2) - (36 \pm 2)/\theta$	15
7		PhH ^b	$\sim 2 \times 10^4$	n.d.	14
8		PhH	6.7×10^4	n.d.	16
9		PhH ^b	1.4×10^6	n.d.	14
10		PhH ^b	2.9×10^7	n.d.	14
11		PhH	$\sim 5 \times 10^7$	n.d.	12
12		PhH	$> 3 \times 10^8$	n.d.	12
13		PhH ^b	4.3×10^8	n.d.	14
14		PhH ^c	2.2×10^5	$(9.5 \pm 0.6) - (28 \pm 4)/\theta$	17, 18

(continued overleaf)

Table 1 (continued)

Entry	Radical	Solvent	k_c (s ⁻¹)	Arrhenius ^a	References
15		PhH ^c	1.1×10^6	$(9.3 \pm 0.5) - (22 \pm 3)/\theta$	17, 18
16		<i>t</i> -BuPh ^c	4.3×10^6	$(8.9 \pm 0.1) - (15.3 \pm 0.6)/\theta$	19
17		PhH ^c	7.3×10^6	n.d.	17, 18
18		<i>t</i> -BuPh ^c	2.1×10^7	$(8.9 \pm 0.2) - (10.6 \pm 0.8)/\theta$	19
19		PhH	$\sim 3 \times 10^7$	n.d.	20
20		MeCN	6.3×10^7	n.d.	(A. N. Hancock, J. Tanko, and C. H. Schiesser, unpublished)
21		THF	$> 10^9$	n.d.	21

THF, tetrahydrofuran; n.d., not determined.

^a Arrhenius function in kJ mol⁻¹; $\theta = 2.3RT$ kJ mol⁻¹.

^b Rate constant adjusted from original temperature assuming log A = 10.

^c Rate constant determined from Arrhenius expression.

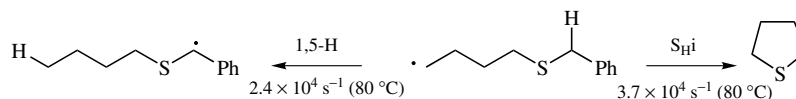
selenium to tellurium, although there is only one example of the latter in the list. This trend is attributable to the size of the orbitals involved in the substitution process, with the larger orbitals provided by selenium and tellurium clearly preferred by the attacking radical to those offered by sulfur.

The choice of leaving group is also critical, although this can be somewhat negated by the heteroatom undergoing substitution, as discussed above. The usual reactivity order is observed with $1^\circ < 2^\circ < 3^\circ < \text{Bz} < \text{Bn} < \text{Ph}_2\text{C} < \text{RS}$. It is interesting to note that judicious choice of leaving group can turn a poor reaction (e.g., Entry 3) into an excellent reaction (e.g., Entry 10) and this should be kept in mind when designing synthesis based on this chemistry.

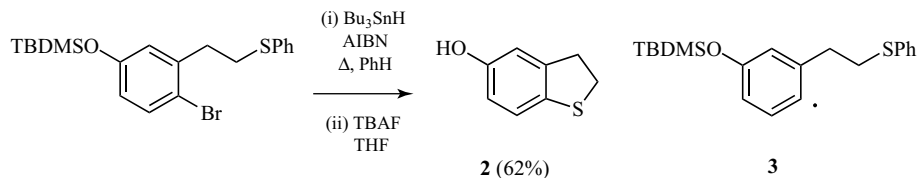
In a similar manner to that observed for intramolecular homolytic addition chemistry, and

for similar reasons, the size of the ring being formed has an influence on the rate constant because it affects the energy of the transition state involved in ring closure. Five-membered transition states are most favorable because the required collinear arrangement of attacking and leaving radicals is more easily accommodated with four bridging atoms than with the five involved in the formation of the analogous six-membered ring.⁸ As can be seen from the data in Table 1, six-membered rings are often formed 1 to 2 orders of magnitude more slowly than their five-membered counterparts.

Despite providing guidance, the data in Table 1 do not provide any information about competing side-reactions. The most common side-reaction is 1,*n*-hydrogen transfer from the “leaving group” to the incoming radical, an example of which is provided in Scheme 6.¹⁵ Benzylic leaving groups



Scheme 6 Hydrogen transfer often competes with homolytic substitution at sulfur.



Scheme 7 An example of homolytic ring closure at sulfur with an aryl leaving group.

on sulfur are not suitable for this chemistry; the relatively slow homolytic substitution process at sulfur provides excellent conditions for hydrogen transfer to be competitive. For this reason, *tert*-butyl or thiyl leaving groups are recommended for sulfur. With faster reactions at selenium, benzylselenenides are excellent substrates for constructing selenium-containing heterocycles; competing hydrogen transfer in these systems is typically not observed.²⁰

Having established some fundamental principles and with an understanding of the kinetics of homolytic substitution processes, examples of synthetically useful chemistry involving sulfur, selenium, and tellurium are now presented.

3.2 Ring Closures at Sulfur

Intramolecular homolytic substitution at sulfur has received considerable attention, and there are several reports in the literature that provide reliable methods for the synthesis of sulfur-containing heterocycles. Examples can be found of alkyl, aryl, and acyl radicals undergoing this chemistry efficiently at the sulfur atom in sulfides,⁵ sulfoxides,^{12,22,23} sulfinates,^{24–26} and sulfonamides,^{24–26} but not at sulfones.^{22,27}

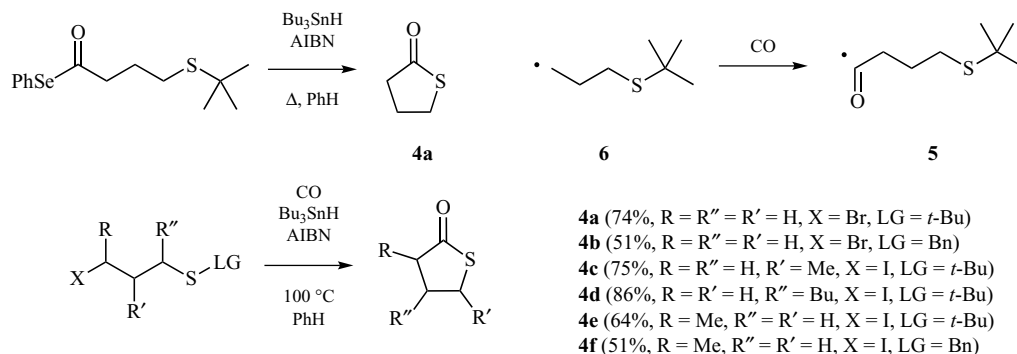
Scheme 7 illustrates the application of this chemistry to the preparation of the dihydrobenzothiophene-containing tocopherol-like antioxidant (**2**); α -tocopherol is the main component of vitamin E. In the key step, aryl radical (**3**), generated under standard conditions, was able to undergo homolytic substitution at sulfur; subsequent deprotection gave 5-hydroxy-

2,3-dihydrobenzo[*b*]thiophene (**2**) in 62% yield over two steps.²⁸ It is interesting to note that in this example, because the attacking radical is aryl, even the normally unfavorable phenyl radical can be encouraged to act as a leaving group.

Ryu and coworkers reported examples of the preparation of γ -thiolactones (e.g., **4a**) through the application of homolytic substitution by acyl radicals (**5**) at sulfur.¹⁶ The acyl radicals were generated from the corresponding acyl phenylselenide, or through the application of radical carbonylation chemistry developed in their laboratories. In the latter examples, abstraction of the bromine or iodine gives the alkyl radical (**6**) which, under a high-pressure atmosphere of carbon monoxide, forms the corresponding acyl radical (**5**) that then undergoes substitution at sulfur to give the γ -thiolactones (**4**) with expulsion of the *tert*-butyl radical (Scheme 8).

Systems examined include primary and secondary alkyl radicals generated from either bromides or iodides with good leaving groups at sulfur. The best results were obtained for the starting materials shown below. γ -Thiolactones were prepared in 86 and 75% yields from **7** and **8** respectively, while secondary iodides **9** and **10** gave the corresponding γ -thiolactones in moderate yields (Figure 1).¹⁶

A typical example of the application of this chemistry is in the preparation of **4d** from 1-(*tert*-butylthio)-2-(iodomethyl)hexane (**7**). In this case, **7** (316 mg, 1.00 mmol), *n*-tributyltin hydride (351 mg, 1.20 mmol), and AIBN (33 mg, 0.2 mmol) were dissolved in benzene (100 ml) in a 200-ml stainless steel autoclave equipped with an inserted glass liner. The vessel was pressurized to 80 atm and heated to 100 °C for 2 h. The autoclave



Scheme 8 Examples of ring closures by acyl radicals at sulfur.

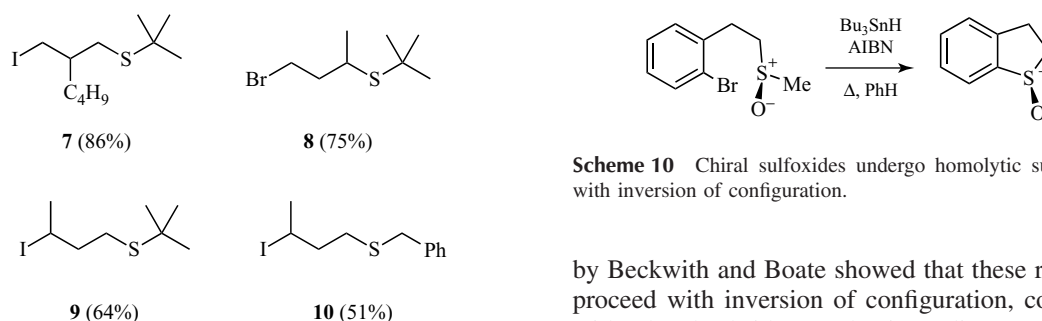


Figure 1 Substrates for the preparation of γ -thiolactones by radical carbonylation/homolytic substitution methodology.

was cooled to room temperature and the pressure released before the solvent was removed *in vacuo*. β -Butyl- γ -thiobutylactone (**4d**) was obtained (135 mg, 86%) after column chromatography.

This methodology was further extended to include α,β -unsaturated acyl radicals, as well as acyl radicals generated from aryl radicals, to yield the corresponding thiolactones (e.g., **11**, **12**) in good yields (Scheme 9).¹⁶

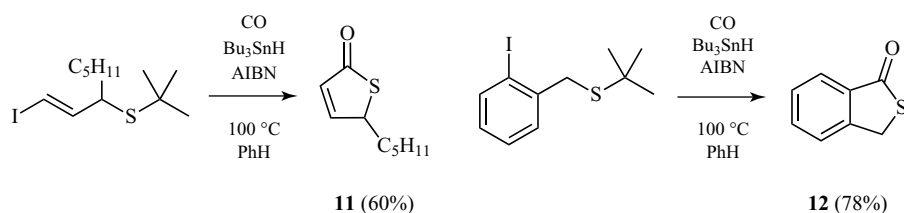
There are few examples of radical substitution reactions involving oxidized sulfur. An early report

Scheme 10 Chiral sulfoxides undergo homolytic substitution with inversion of configuration.

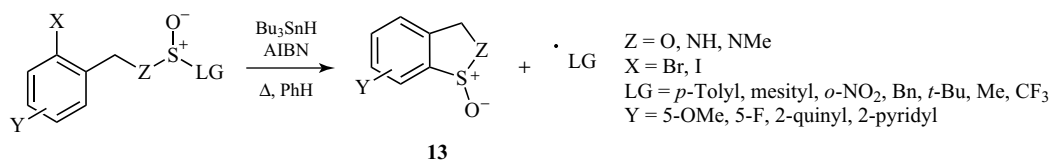
by Beckwith and Boate showed that these reactions proceed with inversion of configuration, consistent with the backside mechanism discussed above (Scheme 10).¹²

More recently, Malacria and coworkers reported the use of this chemistry at sulfinates and sulfonamides to afford interesting sultines and cyclic sulfonamides (**13**).^{24,25} As shown in Scheme 11, a number of variables were explored during their investigation; these included the nature of the (precursor) halide (X), the nature of the aryl ring (Y), the substitution (Z) on the tether, as well as the nature of the leaving radical (LG).

The best results were observed for the starting materials shown below. The nature of the halide did not appear to influence the efficiency of the reaction; however, the leaving radical (LG) proved to be important with *tert*-butyl giving the highest yields



Scheme 9 Vinyl and aryl radicals are efficient in radical carbonylation/homolytic substitution chemistry.



Scheme 11 Sulfonates and sulfonamides undergo efficient homolytic substitution by aryl radicals.

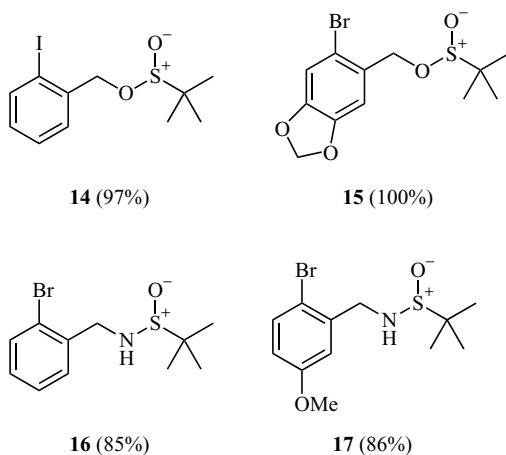
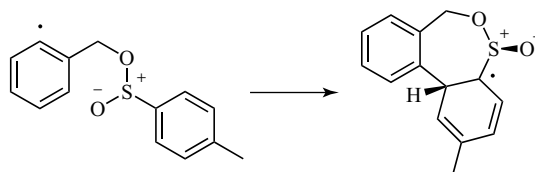


Figure 2 Key substrates for radical ring closures in sulfonates and sulfonamides.

of product. Primary, benzyl, and trifluoromethyl leaving radicals proved to be less efficient. The nature of the aryl group was also investigated and this study concluded that electron-donating groups (Y) on the aryl ring were beneficial; however, electron-withdrawing groups were also tolerated, as were thiophenes. For example, sulfonates **14** and **15** led to the synthesis of the corresponding sultines (**13**, $Z = \text{O}$) in 97% and quantitative yields respectively, while cyclic sulfonamides (**13**, $Z = \text{NH}$) were prepared in 85 and 86% yields from **16** and **17**, respectively (Figure 2).

It should be noted that with aryl leaving groups (LG), intermolecular addition to LG is reported as being a competitive process, an example of which is depicted in Scheme 12.^{24,25}

Malacria also reported the use of alkyl radicals in substitution chemistry at sulfonates.^{24,25} Primary, secondary, and tertiary radicals, generated from the corresponding bromide, were all successfully employed. It should be noted that when a secondary alkyl radical is used, a new stereogenic center is created, with the size of the new substituent

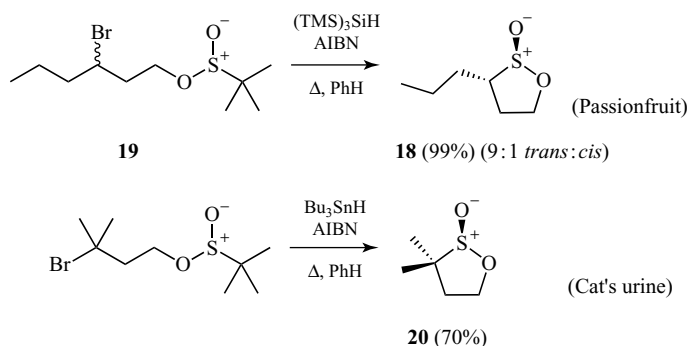


Scheme 12 Homolytic addition often competes with homolytic substitution when aryl leaving groups are used in sulfonates.

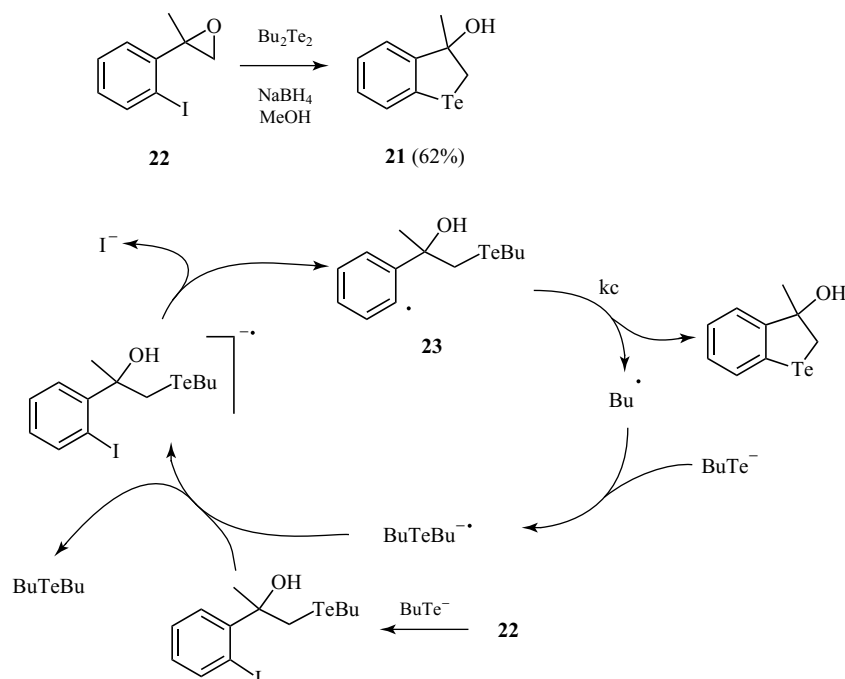
influencing selectivity; the trans diastereoisomer is favored in all such examples. These alkyl sultine scaffolds are small molecule natural products that exhibit interesting olfactory and flavor properties. For example, sultine (**18**) is found in passion fruit extracts and was prepared in a 9 : 1 trans : cis mixture of diastereomers by reaction of the secondary bromide (**19**) with tris(trimethylsilyl)silane (Scheme 13),²⁵ while sultine (**20**) was formed from a tertiary radical under standard radical conditions; this compound is a component of cat's urine.²⁹

3.3 Ring Closures at Selenium and Tellurium

Radical cyclization chemistry involving selenium is generally easier to conduct than its sulfur counterpart because of the more-favorable rate constants for homolytic attack at selenium over sulfur (Table 1); consequently, since its "discovery" in the early 1990s,^{20,30,31} there have been numerous examples of this chemistry, mainly from our laboratories.^{3,17,32–35} In the case of selenium, the benzyl radical has generally been the leaving group of choice, and its use in selenium chemistry is not complicated by competing 1,*n*-hydrogen transfer chemistry because the substitution process is some 2 to 3 orders of magnitude faster than that for the similar reaction involving sulfur.²⁰ However, because of the increased reactivity of the selenium atom toward radicals, that include chain-carrying radicals such as *n*-tributylstannyl,² most of the



Scheme 13 Alkyl radicals give rise to interesting sultines, sometimes with excellent stereocontrol.



Scheme 14 Formation of dihydrobenzo[*b*]tellurophenes by intramolecular homolytic substitution chemistry.

synthetically useful homolytic chemistry carried out at selenium has utilized the (more reactive) iodide (over the bromide) as radical precursor, or has made use of precursors that do not require chain-carriers.^{30,31,33–39}

In contrast, there are relatively few examples of intramolecular homolytic substitution reactions at tellurium, and this can be attributed to a number of factors that include (i) the intrinsic photolability of organic tellurides, (ii) the propensity for organic tellurides to react with oxygen, and (iii) their

intrinsic reactivity toward chain-carrying radicals; indeed organic tellurides are often more reactive toward radicals such as *n*-tributylstannyl, than are the corresponding iodides.^{2,21} Nevertheless, there are some examples of this chemistry (see below), and success required the invention of new ways of generating radicals in the presence of tellurium, in particular, the use of aryl iodides together with sodium *n*-butyltelluroate.^{21,40}

In the example provided in Scheme 14, 2, 3-dihydro-3-hydroxy-3-methylbenzo[*b*]tellurophene

21 was isolated in 62% yield upon treatment of the aryl iodide (**22**) with sodium *n*-butyltellurolate generated *in situ*.^{21,40} Under these reaction conditions (in the dark) **22** undergoes single-electron transfer to generate the aryl radical **23**, which undergoes homolytic substitution at tellurium to give the required product.⁴⁰ It should be noted from the data in Table 1 that the nature of the leaving group at tellurium is essentially irrelevant in this chemistry because even the *n*-butyltelluride (last entry) ring closes with a rate constant in excess of 10^9 s^{-1} at 80°C .²¹

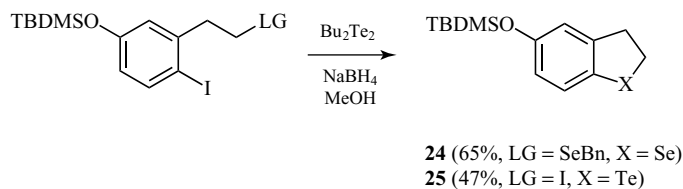
The experimental procedure for the preparation of **21** is as follows: sodium borohydride (47 mg, 1.24 mmol) was added to a solution of di-*n*-butyl ditelluride (216 mg, 0.59 mmol) in tetrahydrofuran (2 ml). The reaction vessel was purged with nitrogen, and methanol (circa 1 ml) was added dropwise, with caution, until a persistent pale yellow solution was obtained. 1-(2-iodophenyl)-1-methyloxirane (**22**) (118 mg, 0.45 mmol) in tetrahydrofuran (1 ml) was added rapidly and the resultant mixture was stirred overnight, shielded from background light. Following aqueous work up, the residue was purified

by column chromatography to give 2,3-dihydro-3-hydroxy-3-methyl-benzo[*b*]tellurophene(**21**) as a yellow solid (74 mg, 62%) with a melting point of $71\text{--}73^\circ\text{C}$.

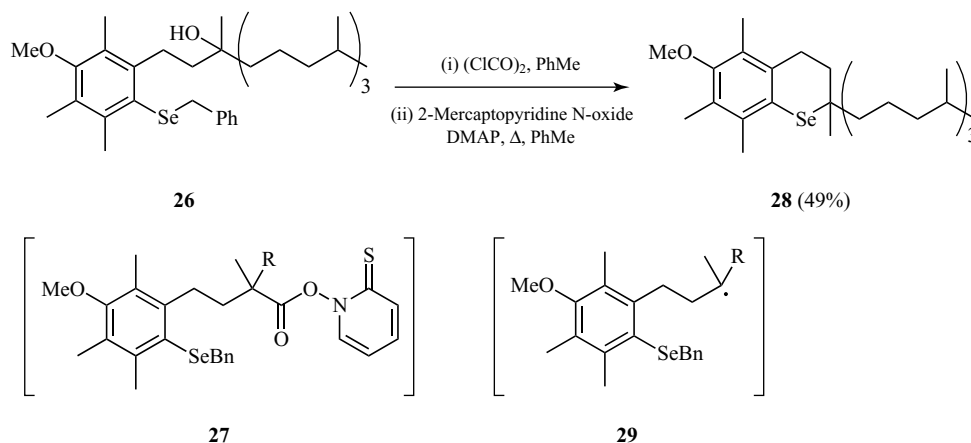
This methodology was also successfully applied to the preparation of tocopherol-like antioxidants containing selenium (**24**) and tellurium (**25**) in yields of 65 and 47%, respectively (Scheme 15).⁴⁰

Intramolecular homolytic substitution at selenium was the key step in the synthesis of selenotocopherol reported by Engman *et al.*⁴¹ As shown in Scheme 16, the alcohol (**26**) was reacted with oxalyl chloride followed by 2-mercaptopyridine N-oxide. The pyridine-2-thioneoxycarbonyl (PTOC) imidate ester precursor (**27**) was formed *in situ* and upon heating gave the selenochroman (**28**) presumably by through a process involving the tertiary radical **29**. Subsequent deprotection of **28** with borontrifluoride gave the racemic selenotocopherol.

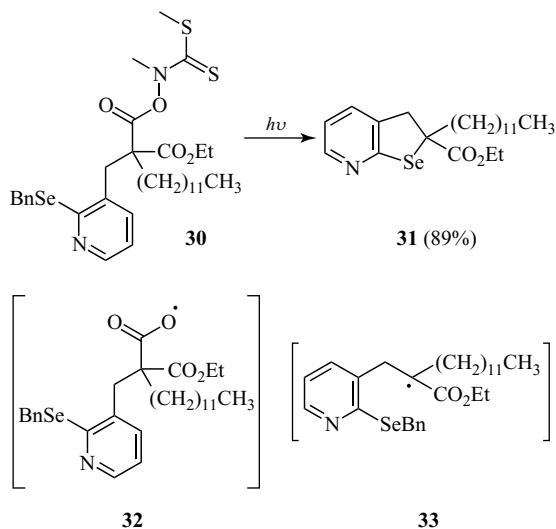
The use of thiohydroximate esters (PTOC, Barton, Kim esters) as carbon-centered radical precursors has the advantage that chain-carrying radicals such as *n*-tributylstannyl ("standard radical conditions", **Basic Concepts on Radical Chain Reactions**) can be avoided.^{31,38,39} In a further



Scheme 15 Formation of selenium and tellurium heterocycles mediated by sodium *n*-butyltellurolate.



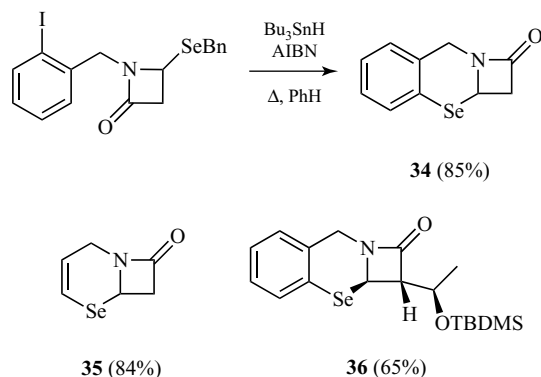
Scheme 16 Formation of selenotocopherol through the use of intramolecular homolytic substitution chemistry involving selenium.



Scheme 17 Formation of 2,3-dihydroselenolo[2,3-b]pyridines by intramolecular homolytic substitution chemistry.

example, Fenner demonstrated that photolysis of the thiohydroximate (Kim) ester (**30**) afforded the pyridine-fused selenophene (**31**) in 89% yield.^{39,42} Presumably, this transformation involves cleavage of the nitrogen–oxygen bond to give the acyloxyl radical **32**; rapid decarboxylation generates the tertiary radical **33**, which undergoes further homolytic substitution at selenium (Scheme 17).

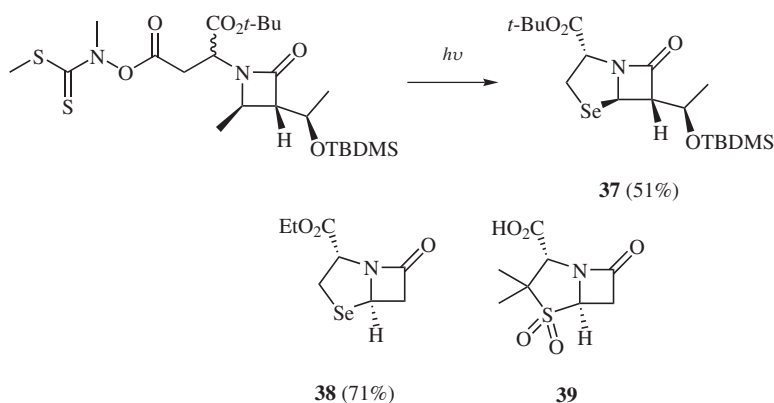
The synthesis of selenapenam and selenacephalosporin “core” structures as compounds of biological interest was achieved by Carland and Martin through the use of intramolecular homolytic substitution of aryl, vinyl, and



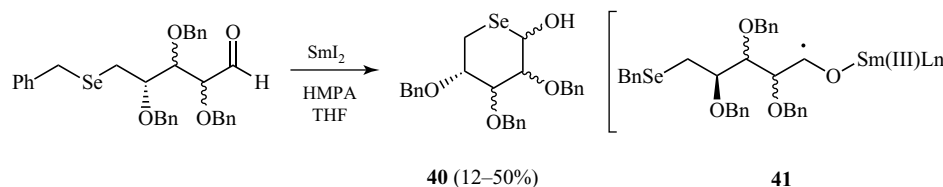
Scheme 18 Selenacephems can be prepared by radical ring-closure chemistry involving selenium.

alkyl radicals at selenium in suitably substituted 4-benzylseleno- β -lactams.^{38,43} For example, under standard radical conditions, the benzo-fused selenium-containing heterocycle **34** was prepared in 85% yield (Scheme 18). Under similar conditions both selenium-containing heterocycle **35** and selenapenam **36** were synthesized in 84 and 65% yields, respectively.

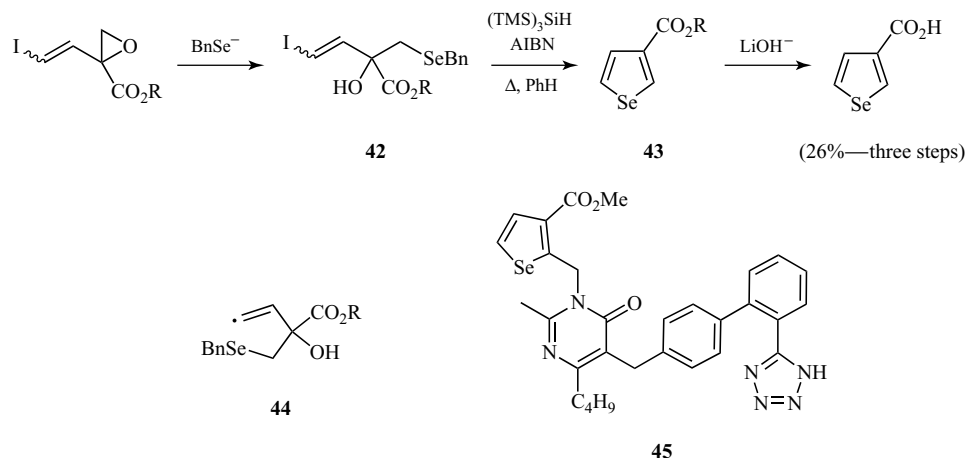
Thiohydroximate esters were also successfully employed as precursors in the synthesis of optically active selenium analogs of β -lactam antibiotics. As shown in Scheme 19, the selenapenam **37** was formed in 51% yield upon irradiation. The selenium-containing heterocyclic core (**38**) of the β -lactamase inhibitor, sulbactam (**39**) was prepared under similar conditions as a mixture of diastereoisomers which epimerized to a single compound upon standing.³⁸



Scheme 19 Selenium analogs of the β -lactamase inhibitor, sulbactam, can be prepared by homolytic substitution chemistry.



Scheme 20 Samarium iodide-mediated homolytic substitution chemistry can lead to selenium analogs of pyranose carbohydrates.



Scheme 21 Intramolecular homolytic substitution chemistry is the key step in the synthesis of *selenomilfasartan*, a potent angiotensin AT₁ receptor antagonist.

In an attempt to make water-soluble antioxidants, Zheng showed that a series 5-selenapentopyranose derivatives (**40**) could be prepared in low to moderate yields by samarium(II) iodide-mediated radical chemistry as depicted in Scheme 20.^{44,45} The key step in this chemistry involves cyclization at selenium of the samarium-containing radical (**41**).

More recently, radical cyclization reactions involving selenium have been employed in the synthesis of analogs of selective AT₁ receptor antagonists (*sartans*). In particular, Grange showed that treatment of iodide (**42**) with tris(trimethylsilyl)silane gave the selenophene-3-carboxylate (**43**) (Scheme 21),³² presumably through the action of the vinyl radical (**44**). Subsequent chemistry led to the synthesis of *selenomilfasartan* (**45**) which proved to be a more potent antagonist than the parent thiophene analog, *milfasartan*.³²

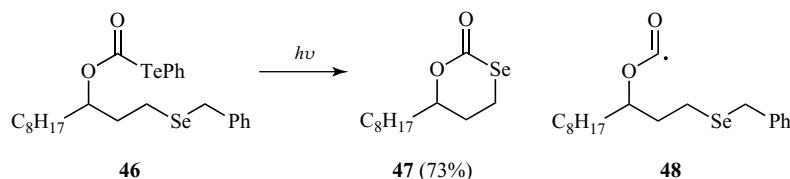
To the best of our knowledge, there is only one reported example of an oxyacyl radical involved in substitution chemistry at selenium. Lucas reported that, upon irradiation, telluroformate (**46**) affords

the cyclic selenocarbonate (**47**) in 73% yield, presumably through the involvement of radical **48** (Scheme 22).³⁶

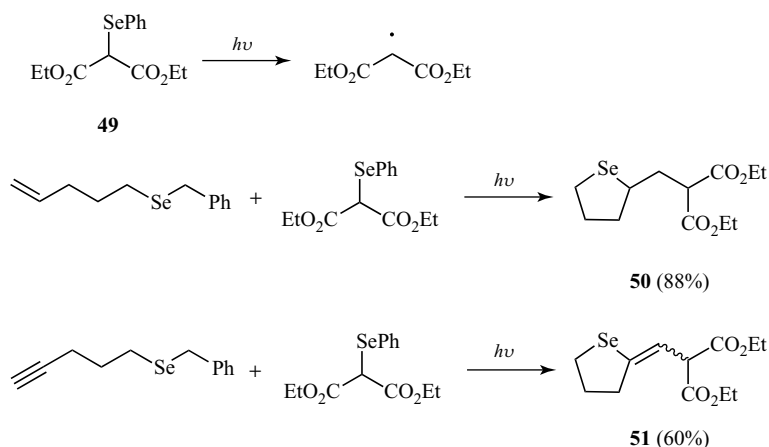
3.4 Tandem Radical Sequences Involving Homolytic Substitution at Selenium

The application of tandem (cascade) radical chemistry to the preparation of interesting molecules is now accepted as a common place by the synthetic practitioner because it allows for the rapid one-pot construction of multiple bonds; other articles of this work are devoted to this chemistry (**Radical Cascade Reactions**). Until recently, however, there were no reported examples of tandem radical chemistry that included intramolecular homolytic substitution of a selenium atom as a key component of the overall sequence.

As shown in Scheme 23, it is possible to construct tandem sequences involving intermolecular homolytic addition followed by substitution. The chemistry depicted in Scheme 23 makes



Scheme 22 Ring closure by oxyacyl radicals at selenium can lead to interesting cyclic selenocarbonates.



Scheme 23 Examples of tandem homolytic addition/substitution sequences involving selenium.

use of the photochemical lability of diethyl 2-(phenylseleno)malonate (**49**),⁴⁶ which, upon irradiation, affords the diethyl malonyl radical. Subsequent addition at terminal alkenes or alkynes, followed by substitution at selenium gave the tetrahydroselenophenes (**50**, **51**) in 88 and 60% yields, respectively.⁴⁷ Other leaving groups were examined, with substrates **52–54** providing **50** in good to moderate yields, as depicted in Figure 3.

In a further recent example of this chemistry, Staples showed that selenochromanes can be

conveniently prepared through a tandem radical sequence involving intermolecular addition by benzylic radicals to suitably substituted alkenes, followed by intramolecular homolytic substitution at selenium. For example, irradiation of the dithiocarbonate (**55**) in the presence of methyl acrylate afforded **56** in 40% yield (Scheme 24).³³ This reaction presumably proceeds through the involvement of the radical (**57**) which adds to methyl acrylate; the adduct radical then undergoes homolytic substitution at selenium to give the observed product.

As shown in Scheme 25, this chemistry can be initiated using triethylborane/oxygen at lower temperatures; however, these reactions now require significantly electron-withdrawn alkenes to be effective; for example, *N*-benzyl maleimide gave selenochromane **58** in 71% yield. This methodology was also employed in the synthesis of the nitro-substituted and pyridyl selenochromanes **59** and **60** in good to moderate yields.

A typical protocol for one of these tandem reactions is illustrated in the synthesis of selenochromane **56**. In this case, *O*-ethyl-*S*-(2-(benzylseleno)benzyl) dithiocarbonate (**55**) (209 mg, 0.55 mmol) and methyl acrylate

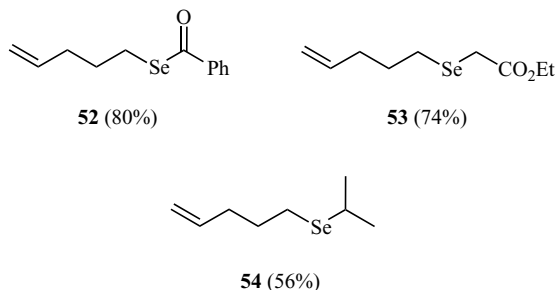
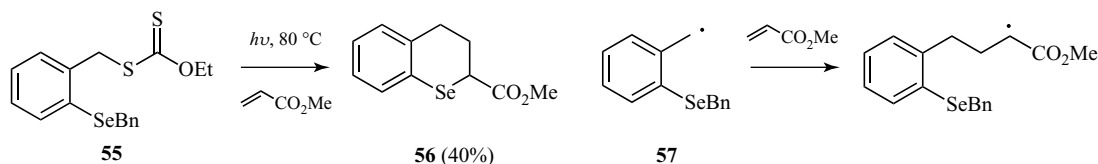
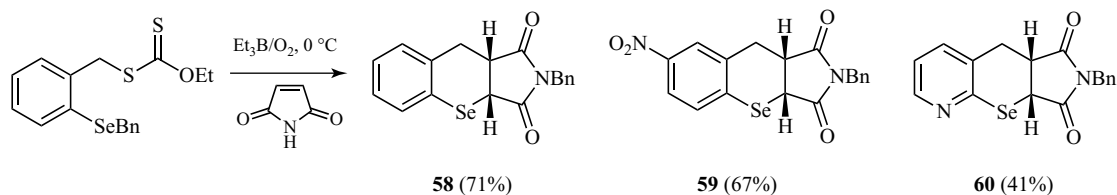


Figure 3 Some substrates for tandem homolytic addition/substitution chemistry.



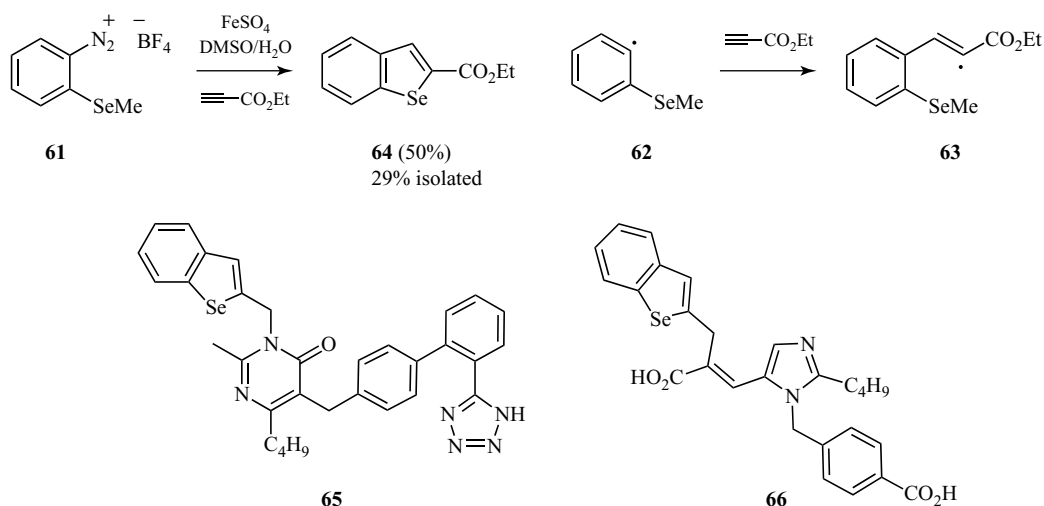
Scheme 24 Preparation of the selenochromane ring system using tandem radical chemistry.



Scheme 25 Examples of selenochromanes prepared by radical cyclization chemistry.

(76 ml, 0.82 mmol) were dissolved in toluene (1.5 ml) in a Pyrex tube after “degassing” by bubbling a steady stream of nitrogen through the solvent. The reaction vessel was sealed and irradiated for 12 h with a 125-W medium pressure mercury lamp at a distance of 15 cm while maintaining the temperature at 80 °C. Methyl 3,4-dihydro-2*H*-1-benzoselenin-2-carboxylate (**56**) was purified by column chromatography (5% ethyl acetate/petroleum spirits) to afford a colorless oil (0.22 mmol, 40%).³³

Staples was able to extend this novel tandem addition/substitution methodology to the preparation of benzo[*b*]selenophenes, an example of which is depicted in Scheme 26.³⁴ It should be noted that this chemistry requires the involvement of an alkane bearing an electron-withdrawing group and was inspired by the contributions of Zanardi and coworkers toward the construction of benzo[*b*]thiophenes.⁴⁸ Presumably, the diazonium salt (**61**) reacts in the presence of iron to generate the aryl radical (**62**), which then



Scheme 26 Selenium-containing angiotensin AT₁ receptor antagonists can be prepared by tandem homolytic addition/substitution chemistry.

undergoes intermolecular addition onto the alkyne. The adduct(vinyl) radical (**63**) reacts at selenium to give ethyl benzo[*b*]selenophene-2-carboxylate (**64**) in 50% yield (29% isolated yield). Despite the moderate yield, this one-pot procedure represents a significant improvement over traditional multi-step methods for the preparation of benzoselenophenes.^{49,50} Key intermediate **64** was incorporated into benzo[*b*]selenophene analogs (**65**, **66**) of the antihypertensive drugs, *milfasartan* and *eprosartan*.³⁴

4 INTRAMOLECULAR HOMOLYTIC SUBSTITUTION AT OXYGEN

Homolytic substitution at unactivated oxygen is relatively rare because of a mismatch of orbital overlap between the attacking radical and the oxygen atom. However, several examples exist of this chemistry taking place at oxygen atoms that are activated by strain or by a metal, or in peroxides that contain intrinsically weak oxygen–oxygen bonds.^{2,51,52}

Nugent and RajanBabu showed that epoxides can be used as radical precursors that can undergo electron transfer when treated with stoichiometric titanocene dichloride (see **Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**). Ring opening of the epoxide results in the formation of an oxygen–metal bond.^{53–56}

Gansäuer and Grimme *et al.* were able to further develop this methodology to tandem radical chemistry that included a step in which the radical underwent homolytic substitution at oxygen, as depicted in Scheme 27.^{57,58} In this example, half an equivalent of 2,4,6-trimethylpyridine hydrochloride is required to liberate Cp_2TiCl_2 which is then

reduced by manganese dust (0.2 equiv) to give the reactive species, Cp_2TiCl . Ultimately, the tetrahydrofuran (**67**) was isolated in 67% yield as a single diastereomer through a process presumably involving reductive epoxide ring opening (mediated by the titanocene(III) complex), 5-exo cyclization and homolytic substitution at oxygen.

The effect of substitution of the alkene was investigated and a variety of different products were successfully synthesized under conditions similar to those in Scheme 27. The tricyclic compound (**68**) was obtained as a single isomer in 73% yield. Both the 1,3-dithiane (**69**) and diethyl malonate (**70**) systems gave similar results with the products isolated in 65 and 62% yields, respectively. Styrene substrates were also explored as radical acceptors

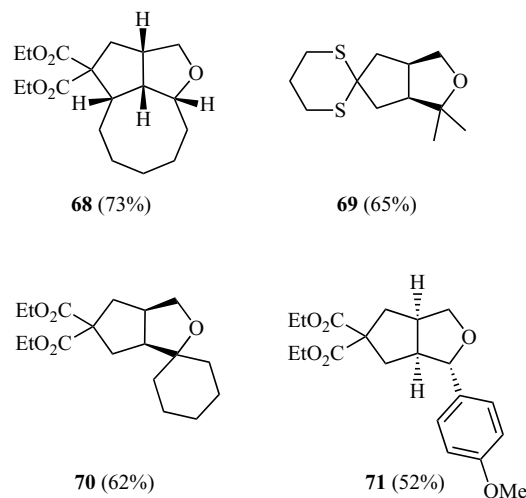
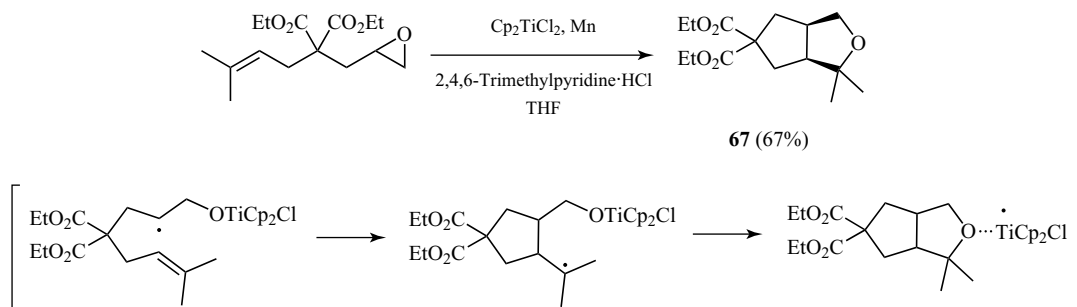
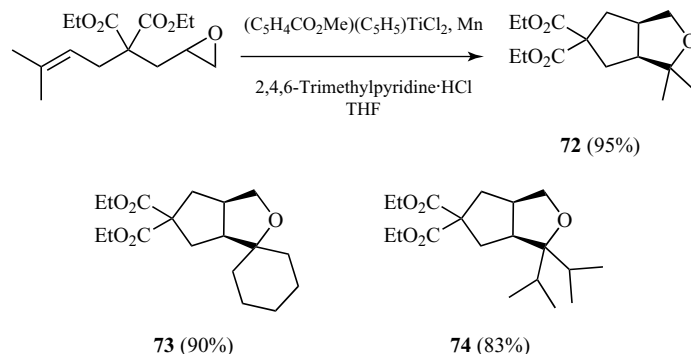


Figure 4 Examples of tetrahydrofurans prepared by titanium-mediated radical chemistry.



Scheme 27 Titanium-mediated homolytic substitution chemistry involving oxygen can lead to the formation of tetrahydrofurans.



Scheme 28 Improved procedure for the preparation of tetrahydrofurans by radical cyclization at oxygen.

leading to the synthesis of **71** in 52% yield (Figure 4).

Further improvements to the reaction's synthetic utility were made in a more recent study (Scheme 28).⁵⁹ Increasing reaction temperature was found to be beneficial, while a computational investigation resulted in an improvement to the catalyst being made; indeed a catalyst with increased Lewis acidity was identified to favor epoxide binding and resulted in an improvement in the product yield. Using this new procedure, tetrahydrofuran **72** was isolated in 95% yield, while key compounds **73** and **74** were isolated in 90 and 83% yields, respectively. The yield of **74** is particularly noteworthy because it is sterically hindered; indeed **74** was not formed when the original conditions were employed.

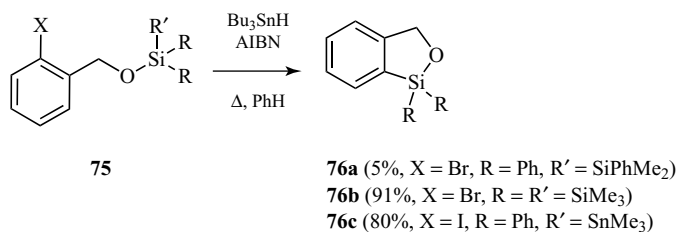
The protocol for this chemistry is illustrated by the synthesis of **72** as follows: the titanocene catalyst (61.2 mg, 0.200 mmol), collidine hydrochloride (158 mg, 1.00 mmol), and manganese dust (22 mg, 0.400 mmol) were heated under vacuum until the collidine hydrochloride began to sublime slightly before use. Then dry tetrahydrofuran (20 ml) and the epoxide (568 mg, 2.00 mmol) were added and the mixture stirred at 95 °C for 4 h. After addition

of *tert*-butyl methyl ether (10 ml), the mixture was washed with 2 M hydrochloric acid (10 ml), the aqueous layer was extracted with CH₂Cl₂ (2 × 10 ml) and *tert*-butyl methyl ether (10 ml). The combined organic layers were washed with brine (10 ml) and dried (MgSO₄). The solvents were removed under reduced pressure and the crude product was purified by column chromatography to afford **72** (597 mg, 95%) as a 5:1 mixture of diastereoisomers.

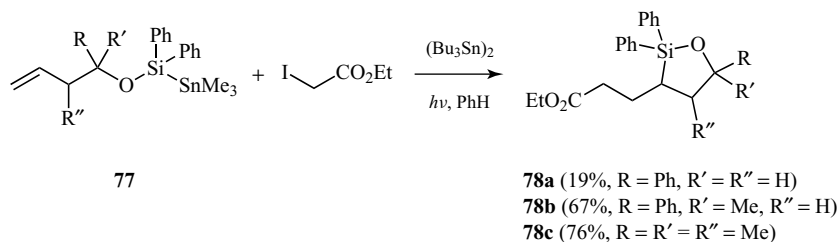
5 INTRAMOLECULAR HOMOLYTIC SUBSTITUTION AT SILICON, GERMANIUM, AND TIN

5.1 Homolytic Substitution at Silicon

The first examples of cyclization reactions involving substitution at silicon were reported by Giese and coworkers⁶⁰ and Utimoto *et al.*⁶¹ almost 20 years ago; these were included in the 1996 review.² Since then, Studer *et al.* studied the effect of aryl radicals at a variety of substituted alkoxy-silanes (**75**) as shown in Scheme 29.⁶² When



Scheme 29 Intramolecular homolytic substitution at silicon can lead to cyclic alkoxy-silanes.



Scheme 30 Tandem homolytic addition/substitution for the formation of cyclic alkoxyasilanes.

R' = dimethylphenylsilane the substitution reaction proved difficult. Only 5% of the desired alkoxyasilane (**76a**) was isolated, along with 43% of unidentified material. The authors attributed this to the strong Si–Si bond in the starting material. Better results were obtained for the tris(trimethylsilyl)silane (**75b**), leading to **76b**. Addition of sub-stoichiometric *n*-tributyltin hydride (0.5 equiv) through a syringe pump gave 91% of **76b**. The trimethylstannyl-substituted silane could be reacted with 0.2 equiv of *n*-tributyltin hydride (added in two portions) to give alkoxyasilane **76c** in 80% yield. Owing to the ease with which the Si–Sn bond could be cleaved it was concluded that stannyl-substituted silanes were most suitable for radical ring-closure chemistry at silicon.⁶²

Alkyl radicals have also been cyclized at silicon using similar methods, and tandem radical addition/substitution reactions proved to be particularly effective, enabling the efficient synthesis of alkoxyasilanes (**78**) from trimethylstannyl-substituted silanes (**77**) (Scheme 30).⁶³ These reactions could be conducted in the absence of a hydride source, and this observation led to a photochemical protocol involving sub-stoichiometric hexabutylditin (0.1 equiv). This proved to be a necessary improvement, as alkyl radicals seem to react relatively slowly in their cyclization chemistry at silicon. Stereoselectivity was also investigated and good diastereoselectivity was reported. For example, reaction of ethyl iodoacetate with a racemic silyl ether resulted in the isolation of the *trans*-alkoxyasilane (**79**) in 87% yield; **80** and **81** were also isolated in good to moderate yields (Figure 5).⁶³

Studer and coworkers also conducted important kinetic experiments and these studies provided the approximate rate constants for radical ring closure at silicon that are listed in Table 2.⁶³ It should be noted that the data for the slower systems contain substantial errors attributed to low amounts

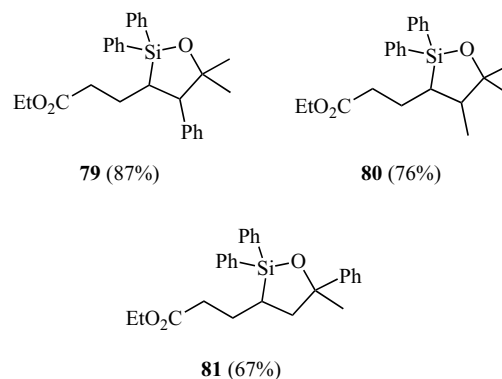


Figure 5 Key silacycles prepared by tandem homolytic addition/substitution.

of cyclized product detected under the reaction conditions; these numbers should be treated with caution, but are nevertheless helpful to practitioners wishing to design syntheses based on this chemistry.

As was observed for the chalcogens, rate constants for cyclization at silicon are strongly dependent on the leaving group. Not unexpectedly, increases in rate constant are observed as the leaving radical stability improves: $\text{SnMe}_3 > \text{GeMe}_3 > \text{SiMe}_3$. With values of k_c in excess of 10^5 s^{-1} at 80°C , it is not surprising that stannyl-substituted silanes are the best substrates for this chemistry. The other important variable available to silicon that is not available to the chalcogens, is substitution on the heteroatom itself. The data in Table 2 suggest that phenyl and trimethylsilyl substituents are preferred over methyl, presumably because of their stabilizing influence on the transition state during cyclization.

The knowledge gained during these earlier investigations were later exploited by Studer where they successfully coupled intramolecular addition together with homolytic substitution at silicon to achieve a stereocontrolled synthesis of cyclic vinyl

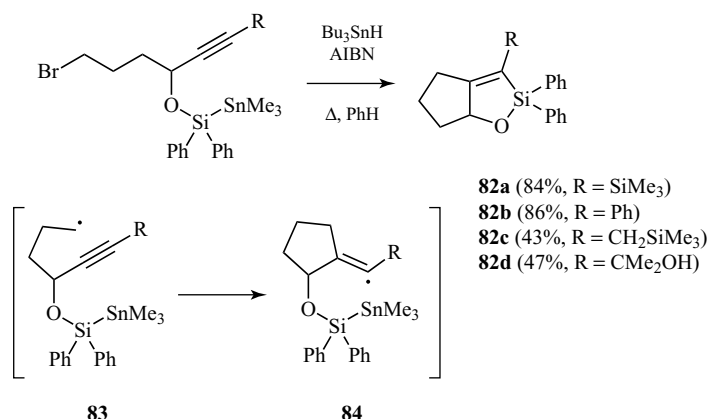
Table 2 Representative rate constant data at 80 °C for homolytic ring closures at silicon (in benzene).⁶³

Radical	Leaving group	Product	k_c (s ⁻¹)
	$\cdot\text{SiMe}_3$		$\sim 10^3 - 10^4$
	$\cdot\text{GeMe}_3$		$\sim 1.5 \times 10^4$
	$\cdot\text{SnMe}_3$		1.2×10^6
	$\cdot\text{SnMe}_3$		1×10^5
	$\cdot\text{SnMe}_3$		1.5×10^5
	$\cdot\text{SnMe}_3$		2×10^6

silanes (**82**) (Scheme 31).⁶⁴ In this chemistry, abstraction of bromine provides alkyl radicals **83** which undergo 5-exo-dig cyclizations onto the alkyne to give the vinyl radical **84**. These reactive radicals are then able to undergo intramolecular substitution at silicon to afford a variety of bicyclic alkoxy silanes (**82**). The trimethylstannyl radical (leaving group) can be exploited as a radical chain carrier, meaning that these reactions can be conducted with sub-stoichiometric amounts of *n*-tributyltin hydride, often added via syringe pump.

The best results were obtained with phenyl and trimethylsilyl substitution on the vinyl radical providing the corresponding alkoxy silanes (**85** and **86**) in 86 and 84% yields, respectively. In contrast to this, only moderate yields were obtained for the alcohol **87** and the trimethylsilylmethyl-substituted product **88** (Figure 6).

Analogous methodology was applied to vinyl iodides (Scheme 32). The vinyl radicals that are generated following abstraction of the iodine atom in **89** were able to undergo homolytic substitution



Scheme 31 Vinyl radicals in intramolecular homolytic ring closures at silicon.

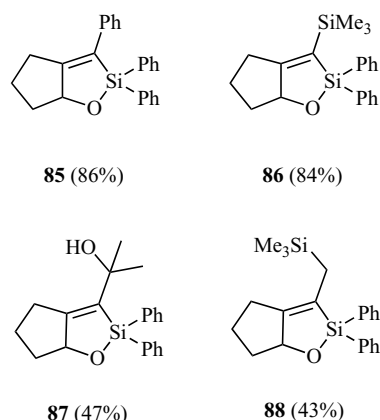


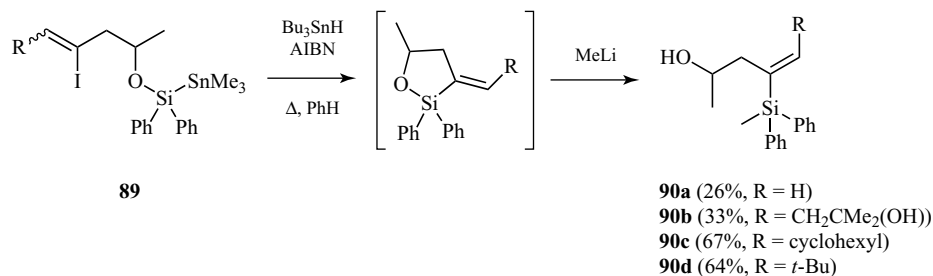
Figure 6 Some key cyclic alkoxyvinylsilanes produced through vinyl radical cyclizations at silicon.

at silicon to give the cyclized products which proved too difficult to isolate directly; subsequent treatment of the crude reaction mixtures with excess

methylolithium gave the corresponding ring opened vinylsilanes (**90**) in good to moderate yields.

Good stereoselectivity could be obtained when a secondary (**91**, trans:cis 93:7) or tertiary (**92**, trans:cis > 98:2) group was bound directly to the alkene, these substrates also gave the best yields. In contrast to this, the primary substituent afforded quite poor selectivity with a trans:cis ratio of only 2:1 in **93** (Figure 7). It was concluded that trans cyclization was favored as this enabled the R group and trimethylstannyl substituent to avoid coming into close proximity with one another.

Together with Studer, Ryu and coworkers were able to demonstrate the first example of an acyl radical undergoing homolytic substitution at silicon to form a silicon-containing ring (Scheme 33).⁶⁵ Abstraction of the bromine atom in **94** gives rise to the alkyl radical (**95**), which under Ryu's carbonylation conditions formed the acyl radical (**96**) which is subsequently able to undergo homolytic substitution at silicon to give diphenylsilacyclopentanone (**97**) and the trimethylstannyl radical. Using *n*-tributyltin



Scheme 32 Some ring closures at silicon from vinyl iodide substrates.

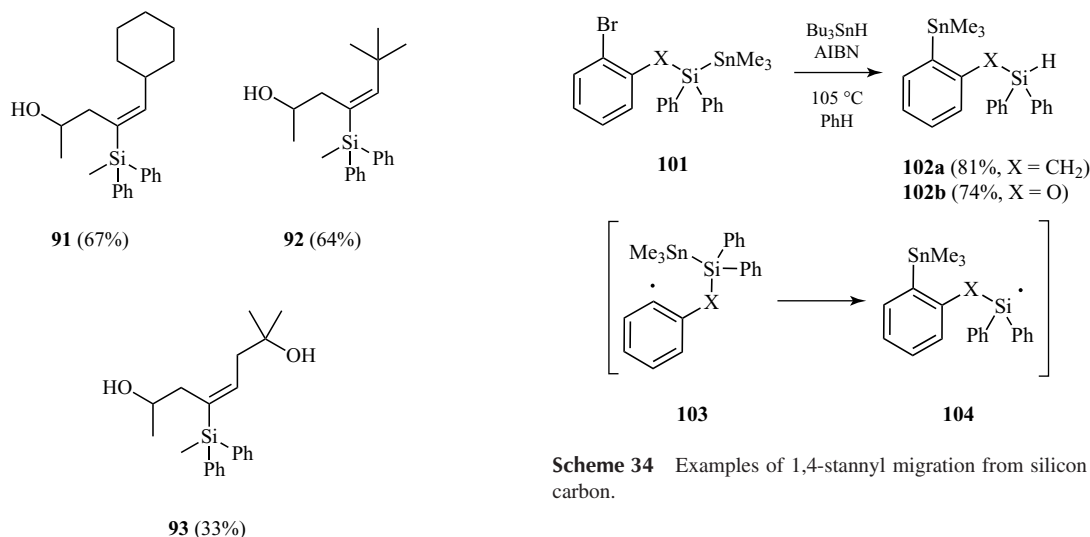
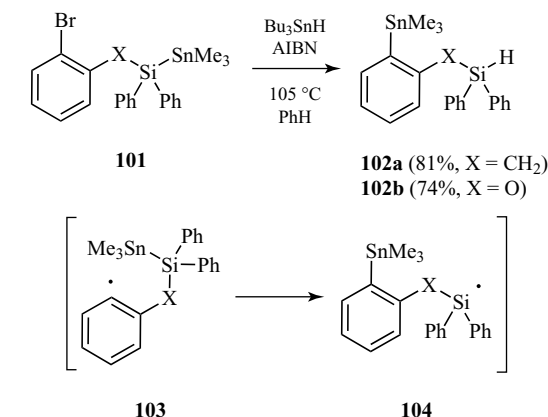


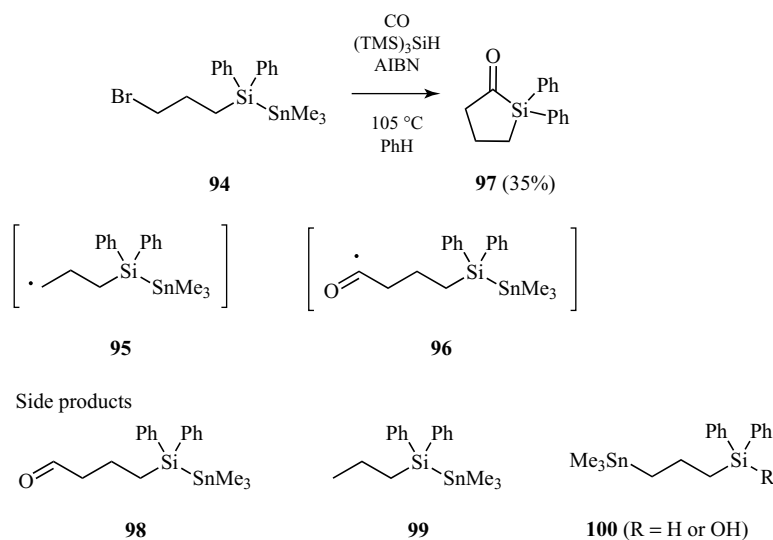
Figure 7 Key products formed from radical precursors 89.

hydride as the chain carrier, the product (**97**) was isolated in 20% yield; however, these reactions were associated with a variety of side-products. Competition between cyclization at silicon and reduction of the acyl radical was observed. Use of tris(trimethylsilyl)silane (see **Silanes as Reducing Reagents in Radical Chemistry**) suppressed the competitive formation of aldehyde (**98**) and also reduced product (**99**) while increasing the yield of silacyclopentanone to 35%.

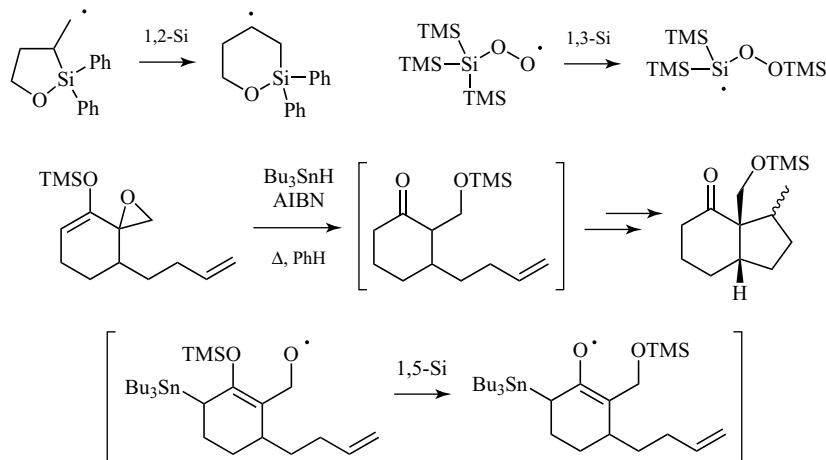


Scheme 34 Examples of 1,4-stannyl migration from silicon to carbon.

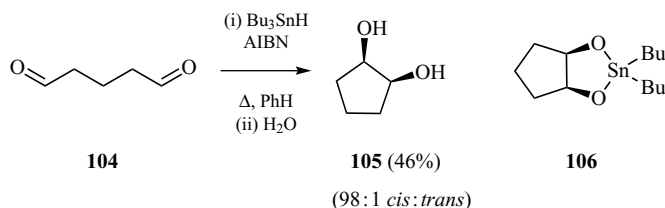
Surprisingly, the 1-silyl-3-stannylpropane (**100**) was also isolated from these reaction mixtures in yields of 16–17%. This product can be attributed to the alkyl radical **95** undergoing the alternate frontside homolytic substitution process, resulting in 1,4-stannyl migration; competitive kinetic experiments provided a rate constant ($k_{1,4}$) of $9.3 \times 10^4 \text{ s}^{-1}$ (80°C) for the 1,4-migration of the trimethyltin group from the silicon atom to the carbon in **95**⁶⁵; $k_{1,4}$ is similar to the values of k_c provided in Table 2. Under carbonylation conditions the yields of the 1,4-stannane migration product were only moderate, while in the absence of carbon



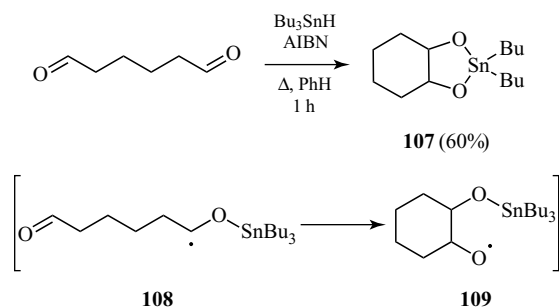
Scheme 33 Radical carbonylation followed by ring closure at silicon is accompanied by several side-products.



Scheme 35 Some examples of 1,*n*-silyl translocations.



Scheme 36 Example of a stannane-mediated pinacol-coupling reaction.



Scheme 37 The stannacycle intermediate can sometimes be isolated.

monoxide the yield of this product was observed to increase to 65%.

The authors also explored the generality of 1,4-stannyl radical migrations (Scheme 34). Aromatic bromides (**101**) were reacted with *n*-tributyltin hydride under standard radical conditions resulting in the formation of the arylstannanes (**102**) as the only isolated products in good yields; these reactions presumably proceed through the intermediacy of radicals **103** and **104**.

There are now numerous examples of 1,*n*-translocation chemistry involving silicon, with a chiral example used to explore the stereochemical requirements of this homolytic substitution process (Scheme 5).¹¹ The majority of these reactions involve 1,2-migrations and include the radical Brook rearrangement, but there are reports of 1,3-, 1,4-, and 1,5-silyl migrations as well. Some illustrative examples of this chemistry are depicted in Scheme 35.^{66–68}

5.2 Homolytic Substitution at Germanium and Tin

Intramolecular homolytic substitution reactions that afford germanium- or tin-containing heterocycles are very rare; indeed, to the best of our knowledge, there are no examples of this chemistry involving germanium; however, Fu and Hays reported stannane-mediated intramolecular pinacol-coupling reactions than involve the formation of stannacycles.⁶⁹ As shown in Scheme 36,

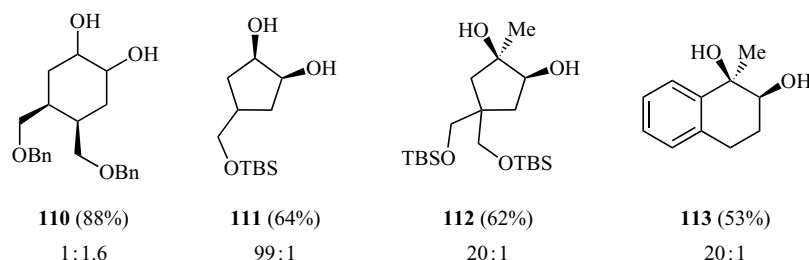
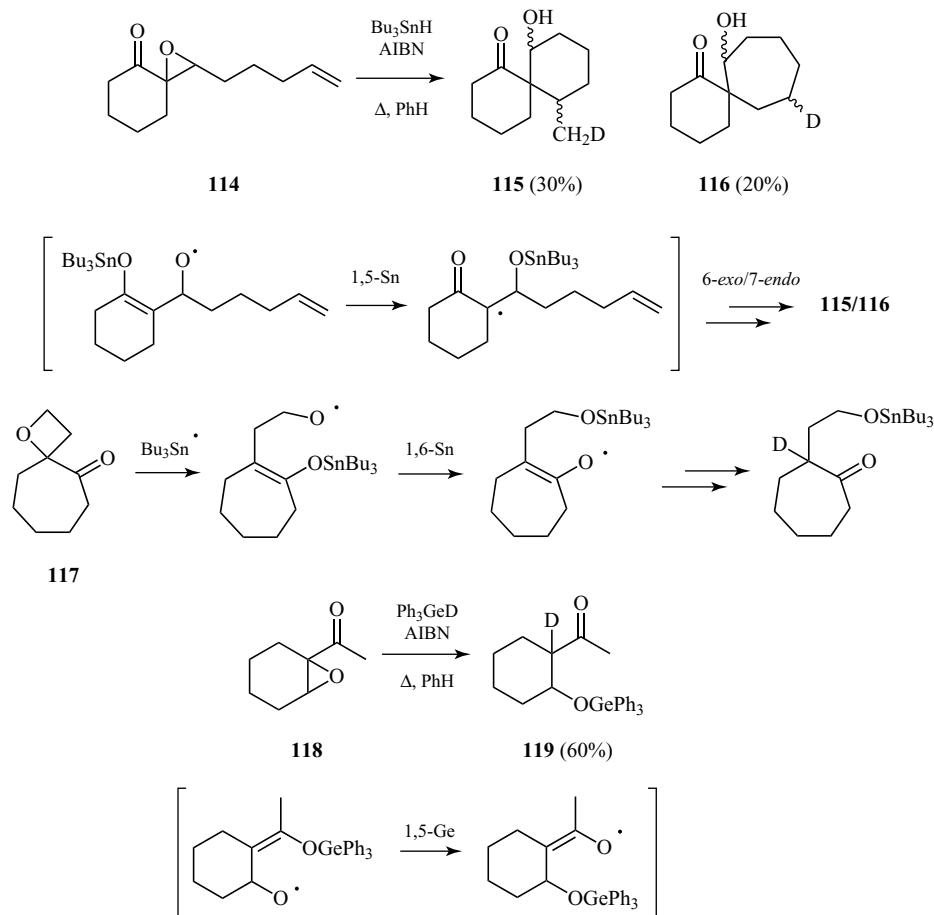


Figure 8 Examples of products from stannane-mediated pinacol-coupling reactions.

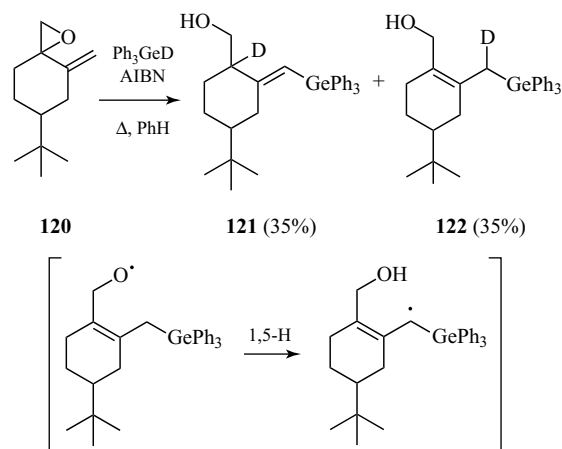


Scheme 38 Examples of homolytic 1,*n*-stannyl and germeryl group translocations.

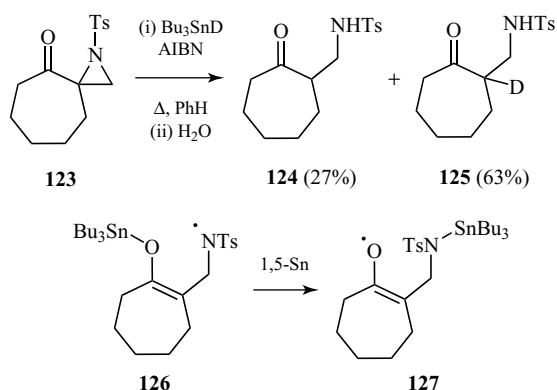
when glutaraldehyde (**104**) was reacted with *n*-tributyltin hydride under standard radical conditions, the cyclopentane-1,2-diol (**105**) could be isolated in 46% yield as a 98:1 ratio of *cis*:*trans* isomers, after aqueous work up. The authors postulate the involvement of stannacycle (**106**), formed by intramolecular homolytic substitution at

tin, which was hydrolyzed to the diol upon aqueous work up.

In support of this hypothesis, the analogous 1,3-dioxo-2-stannolane **107** could be isolated in 60% yield from the corresponding reaction of adipaldehyde with *n*-tributyltin hydride, but required omission of the final hydrolysis step in



Scheme 39 1,5-Hydrogen transfer sometimes competes with germeryl group translocation.



Scheme 40 Example of a 1,5-stannyl group translocation from oxygen to nitrogen.

the overall sequence.⁶⁹ Presumably, addition of the *n*-tributylstannyl radical to one of the aldehydes generates the radical **108** that cyclizes in a 6-exo manner onto the remaining aldehyde to afford the alkoxy radical **109**. The mechanistic sequence is completed when cyclization of **109** at tin provides the 1,3-dioxa-2-stannolane **107** and a chain-carrying *n*-tributyltin radical (Scheme 37).

A variety of pinacol-coupling products were successfully prepared using this methodology, with 1,5-dicarbonyl substrates exhibiting high diastereoselectivity for the corresponding *cis* diol. For example, the diol **110** was obtained in good yield (88%) but with poor stereoselectivity (1 : 1.6 ratio *cis* : *trans*) while **111** was obtained as a 99 : 1 mixture

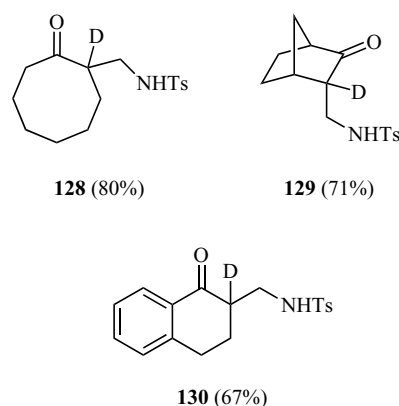


Figure 9 Some products from intramolecular homolytic transfers from oxygen to nitrogen.

of *cis* : *trans* isomers, but in lower yield. Cyclization of ketones was also possible, but in moderate yields; for example, **112** and **113** were isolated in 62 and 53% yields, respectively and in identical (20 : 1) *cis* : *trans* ratio (Figure 8).

There are several reported examples of 1,*n*-germyl and stannyl radical translocation reactions, and the majority of these are discussed in the 1996 review.² However, some examples are included in this article for completeness (Scheme 38). Treatment of epoxide (**114**) with *n*-tributyltin deuteride under standard radical conditions afforded the spiro-fused bicycles (**115**, **116**) in moderate yield in a process that involves a 1,5-translocation of the *n*-tributylstannyl radical between oxygen centers, followed by either 6-exo-trig or 7-endo-trig ring closures.⁷⁰ Similar chemistry involving the oxetane (**117**) resulted in the analogous 1,6-translocation of the tin substituent,⁷⁰ while treatment of epoxide (**118**) with triphenylgermanium hydride resulted in a 60% yield of the germyl ether (**119**).⁷¹

It is important to note that, as observed in homolytic substitution chemistry involving sulfur, if there are abstractable hydrogen atoms available, 1,*n*-hydrogen atom transfer will compete with homolytic substitution at the less reactive elements (Si, Ge) as illustrated (Scheme 39) in the conversion of epoxide (**120**) to the germanes (**121**, **122**).⁷¹

During the past decade, Kim and coworkers reported a 1,5-translocation of a stannyl radical from oxygen to nitrogen.⁷² As shown in Scheme 40, the aziridine (**123**), when reacted with *n*-tributyltin deuteride under standard radical conditions afforded

ketones **124** and **125** in 90% overall yield, after aqueous work up. Deuterium labeling allowed the product (**126**) obtained from homolytic translocation of the tin-containing group at stannane to be distinguished from the product of direct reduction (**127**).

Presumably, the *n*-tributylstannyl radical adds to the ketone with subsequent or concerted rapid ring opening of the aziridine to give the nitrogen-centered radical **126**; direct reduction of **126** gives **124**. Alternatively **126** can undergo a 1,5-translocation to give **127**, which ultimately leads to ketone **125** (Scheme 40).

A number of other aziridines displayed similar reactivity providing the products (**128–130**) of translocation in good overall yield after hydrolysis (Figure 9).⁷²

6 CONCLUSION

Intramolecular homolytic substitution chemistry offers the synthetic practitioner efficient and convenient methods for the preparation of higher heterocycles that complement existing ionic processes, especially for the preparation of ring systems containing sulfur and selenium, as well as silicon. As was observed during the free radical “renaissance period,”⁷³ important discoveries made in the field of intramolecular homolytic addition chemistry led to an appreciation of the factors that control carbon–carbon bond forming chemistry and this information revolutionized the acceptance of radical chemistry in synthesis. Similar key studies have led to an understanding of the factors that control homolytic substitution chemistry. There are now numerous examples of radical ring-closure reactions at sulfur, selenium, silicon and fewer examples involving tellurium and tin. It is particularly rewarding to see this chemistry being applied to molecules of biological significance that include potential next-generation antihypertensive drugs. We look forward to this chemistry developing further through exciting discoveries that are just around the corner.

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Stereoselective Radical Reactions

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1 INTRODUCTION

Radical reactions generally proceed under mild and/or neutral conditions and avoid harsh basic or acidic conditions that can promote decomposition or epimerization of sensitive organic functional groups. It is well known that stereochemical control with radical intermediates is a challenge as radicals are generally planar or nearly planar.¹ The increased understanding of radical chemistry and developments in Lewis acid-mediated catalysis has led to great advancements in stereoselective radical reactions. Several reviews that provide details on various aspects of stereoselective radical chemistry have appeared in the past decade.^{1–9} This article provides an overview on the development of stereoselective radical chemistry and includes both diastereo- and enantioselective reactions. The emerging field on the use of organocatalysts to control stereochemistry in radical reactions is discussed in some detail.

2 DIASTEREOSELECTIVE RADICAL REACTIONS

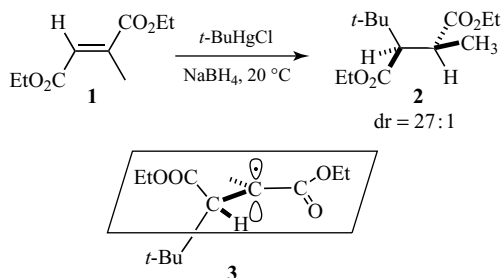
Diastereoselectivity in radical reactions can be established through either a substrate-controlled approach or a chiral-auxiliary-assisted process. Stereoelectronic effects play an important role in determining the level of diastereoselectivity in radical reactions. In general, stereocontrol in cyclic systems are easier to establish in contrast to reactions with acyclic systems. Diastereoselectivity in radical

cyclizations and reactions of cyclic radicals are well understood and many examples of highly selective reactions have been reported in the literature. Since the 1990s, scientists have made significant inroad into understanding acyclic stereoselection in radical chemistry and now the literature has a plethora of examples in which high diastereoselectivity is observed.

2.1 Substrate-Controlled Diastereoselective Radical Reactions

2.1.1 Acyclic 1,2-Induction in Radical Reactions

Hart, Guindon, and Giese have demonstrated that stereocontrol could occur from a center adjacent to a radical carbon atom (1,2-induction) that is substituted by ester or amide groups. Giese has systematically studied reductive tertiary butyl radical addition to α,β -unsaturated ester **1**. As shown in Scheme 1, the diastereoselectivity of the reaction could reach up to 27 : 1 for product **2** and allylic strain effect was used to explain this outcome. A radical adjacent to an ester group is a planar heteroallyl radical system (see side view of radical intermediate **3**). Because of allylic strain, this radical adopts a preferred conformation in which the C–H bond at the carbon center points in the direction of the carbonyl oxygen atom. In this preferred conformation, the ester and tertiary butyl groups shield different faces of the planar radical carbon center. The result showed



Scheme 1 Acyclic 1,2-stereoreduction in radical reactions.

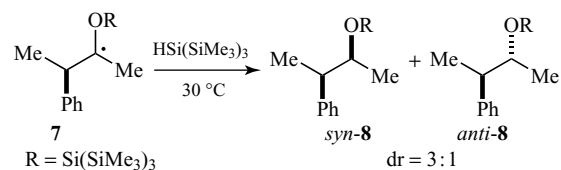
Table 1 Effect of radical traps on 1,2-asymmetric induction.

R ¹	R ²	5 : 6	
		Bu ₃ Sn-D	Bu ₃ SnAllyl
<i>t</i> -Bu	Me	7 : 1	16 : 1
PhMe ₂ Si	Me	9 : 1	4.5 : 1
Ph	Me	1 : 1.4	1 : 2.8
Ph	OMe	4 : 1	17 : 1

that hydrogen abstraction occurred anti to the bulky tertiary butyl group.^{10,11}

Similar trend in selectivity was also observed using different radical trapping agents in 1,2-stereoreduction experiments using intermediates **4**. The degree of stereoselectivity (**5**:**6**) depended significantly on the reagent involved in the reaction (Table 1).¹²

Reduction of α -alkoxy radicals proceeds with modest selectivity. As an example, radical intermediate **7** gave predominantly *syn*-**8** in reduction with tris(trimethylsilyl)silane (TTMSS) (Scheme 2). The selectivity was explained using a Felkin–Anh model and was further confirmed by calculations and ESR experiments.^{13,14}



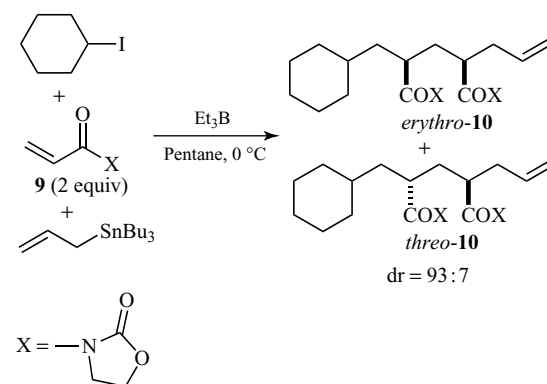
Scheme 2 Diastereoselective reduction of α -alkoxy radicals.

2.1.2 1,3- and 1,*n*-Stereoreduction

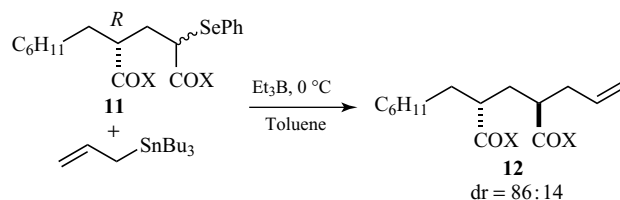
In multicomponent radical reactions, acyclic stereocontrol may be achieved, in principle, by 1,3-steric interactions of the ultimate chiral center in the telomer chain with the radical terminus of the growing chain. This interaction is usually small due to the conformational mobility of the chain. Porter and coworkers observed anti selectivity in the telomer formation by simple chain 1,3-stereocontrol of tandem free radical addition-transfer reaction when using achiral 2-oxazolidinone **9** as the template.¹⁵ Dipole–dipole stabilization for the anti transition state accounts for the observed selectivity in this double radical addition reaction (erythro **10** : threo **10**, Scheme 3).

The same strategy was also successfully applied to the synthesis of enantiomerically pure *anti*-2,4-dialkylglutaric acid via an allyl transfer reaction. As shown in Scheme 4, the enantiomerically pure selenide diastereomers (*R,R*)-**11** and (*R,S*)-**11** on reaction with allyltributylstannane under standard conditions gave the allylated products **12** in a 86 : 14 diastereomer ratio.

Hanessian *et al.*¹⁶ used hydrogen bonding as a stereocontrolling element in free radical C-allylation reactions. As shown in Table 2, high stereoselectivity can be obtained in 1,2-, 1,3-, 1,4-, and 1,5-asymmetric induction in the free radical C-allylation of α -acyl radicals derived from a series of *N*-substituted acyclic amino acid derivatives **13**. It is interesting to note that the level of stereoreduction (**14**:**15**) depends on the distance between the two stereocenters: 1,2-stereoreduction is larger

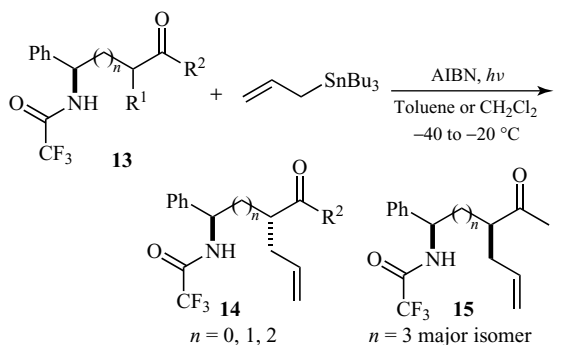


Scheme 3 1,3-Acyclic control in free radical reaction.

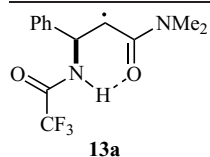


Scheme 4 Stereoselective allylation via 1,3-induction.

Table 2 Hydrogen bonding as a stereocontrolling element in free radical *C*-allylation reaction.



Entry	<i>n</i>	R ¹	R ²	<i>anti/syn</i>	Yield (%)
1	0	SePh	OMe, NMe ₂	>98:2	90
2	1	SePh	NMe ₂	62:38	97
3	2	I	NMe ₂	86:14	79
4	3	I	NMe ₂	26:74	72



than 1,3 and 1,*n*-stereinduction. Intramolecular H-bonding was believed to be the reason for the high diastereoselectivities in this work. Stereochemistry of 1,2-induction was explained using model **13a**, where a hydrogen bond exists between the N–H hydrogen atom and the carbonyl group (Table 2).

2.1.3 Radical Polar Crossover Reactions

Radical polar crossover reaction is a cascade process involving conversion of an intermediate radical formed by its addition to a neutral species, an anion, or a cation (see **Organic Electron Donors**).

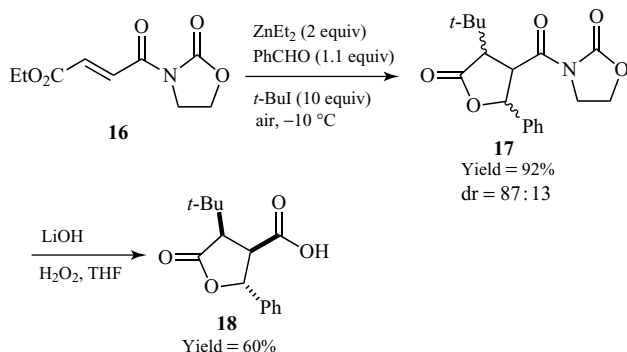
The so formed intermediate is further reacted with an appropriate electrophile or a nucleophile. Alternatively, addition of a nucleophile to an unsaturated system is followed by oxidation to a radical, which is then utilized in a new bond forming reaction. Stereochemistry can be established in the first, second, or both steps.^{17,18}

Example of a radical polar crossover reaction that begins with the regioselective addition of *tert*-butyl radical to the fumarate derivative **16** is shown in Scheme 5.¹⁹ The intermediate radical is converted to a zinc enolate that is subsequently trapped *in situ* by benzaldehyde. The product **17** is isolated as a mixture of diastereomers (87:13). It is important to note that stereochemistry is established in the second ionic step leading to the formation of lactone **18**.

Jahn *et al.*²⁰ reported a different type of radical polar crossover reaction, where the conjugate addition between α,β -unsaturated ester **19** and an amine nucleophile **20** results in the formation of an enolate intermediate **21**. This is followed by conversion of the anion to a radical intermediate **22** by the addition of a single electron transfer (SET) reagent ferrocenium hexafluorophosphate. The intermediate electrophilic radical undergoes a 5-exo cyclization furnishing a nucleophilic radical that is trapped by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) to furnish products **23a** and **b** in good yield with a diastereomeric ratio of 5.8:1 (Scheme 6). Stereochemistry is established in both the ionic step as well as during radical cyclization.

2.1.4 Radical Cyclizations

Intramolecular radical reactions (cyclization) to form five- and six-membered rings are often used to synthesize carbocycles, heterocycles, and polycyclic products because high diastereoselectivities are usually observed for these processes. Diastereoselectivity of 5-exo and 6-exo radical cyclizations



Scheme 5 Dimethylzinc-mediated radical polar crossover reaction.

could be explained using a chair-like transition state model. Chair-like conformation allows for an efficient overlap of the singly occupied molecular orbital (SOMO) of the radical and the HOMO of the alkene. Substituents at C1-4 prefer to adopt pseudo-equatorial positions in the transition state to avoid 1,3-diaxial interactions and this governs the relative orientations of the substituents in the cyclized products.¹

Naito and coworkers have reported a tandem thiyl radical addition to an alkene **24** followed by a 5-exo cyclization onto an oxime ether (Scheme 7). This tandem reaction gave the substituted pyrrolidine **25** in good diastereoselectivity for the cyclization (4:1) and near perfect 1,2-stereoselection with respect to the resident chiral center (anti rule, vide infra).²¹ The relative stereochemistry of the product was explained using a chair-like radical intermediate **26**.¹

A chair-like model was also used to explain the 6-exo cyclization of iodoalkene **27**. As shown in Scheme 8, an atom transfer cyclization proceeds with excellent diastereoselectivity (**28**:**29** $\geq 95:5$) using catalytic amount of $\text{Me}_3\text{SnSnMe}_3$ under photolytic conditions. The product stereochemistry can be explained by placing the ester group in an axial orientation and the alkene in an equatorial orientation in a six-membered transition state (**30**).²²

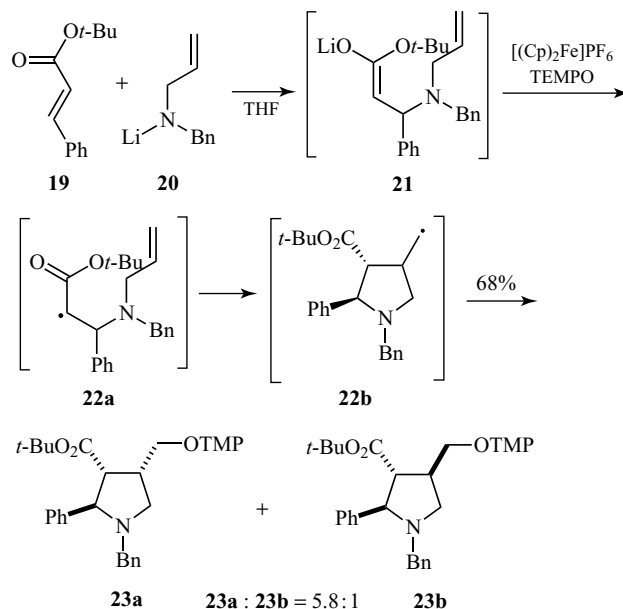
An annulation reaction is defined as a *ring-forming process* in which two molecular fragments are coupled with the formation of two new bonds. The reaction involves the addition of a radical to a neutral species, leading to a product radical, which then cyclizes to form a ring. As an example, the radical derived from 2-iodomalonate **31** using triethylborane as an initiator adds to

oct-1-ene **32** regioselectively. The newly formed radical intermediate then cyclizes selectively in a 5-exo process to produce *cis*-**33** as the major product after an azide group transfer process (Scheme 9).²³

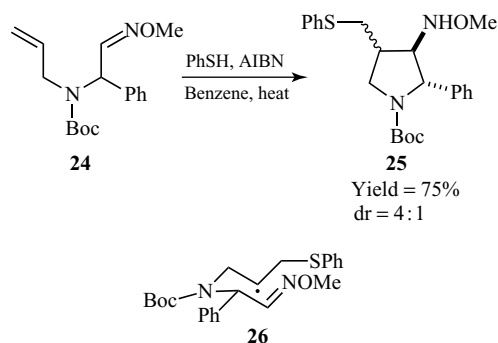
2.1.5 Reaction of Cyclic Radicals

Compared to acyclic systems, cyclic radicals have less number of conformations, which simplifies prediction of stereochemistry in their reactions. Generally, the anti rule applies to reactions with cyclic radicals. Reactions occur preferentially in an anti manner to the substituents present in the cyclic moiety to minimize steric interactions in the transition state.²⁴ For example, excellent diastereoselectivity was observed in the allylation reaction of β -lactam **34** and allyltributylstannane leading to **35**. The allylation occurred selectively from the bottom face of cyclic radical intermediate **36** so as to avoid steric interactions with the sulfone group (Scheme 10).²⁵

Reactions of radicals in five-membered ring systems usually give high diastereoselectivities. For example, only *trans* product **38** was observed in the allylation of the bromolactone **37** (Scheme 11).²⁶ In another example, tertiary butyl radical addition to unsaturated lactone **39** followed by reduction furnished the product in moderate diastereoselectivity. In this example, the diastereoselectivity was established during the hydrogen atom transfer step. The *cis* isomer **40a** was obtained as the major product when using TTMSS as the hydrogen atom source (see **Silanes as Reducing Reagents in Radical**



Scheme 6 Radical polar crossover reaction initiated by ionic conjugate addition.



Scheme 7 Diastereoselectivity of 5-exo-cyclization.

Chemistry), which is in accordance with the anti rule.²⁷

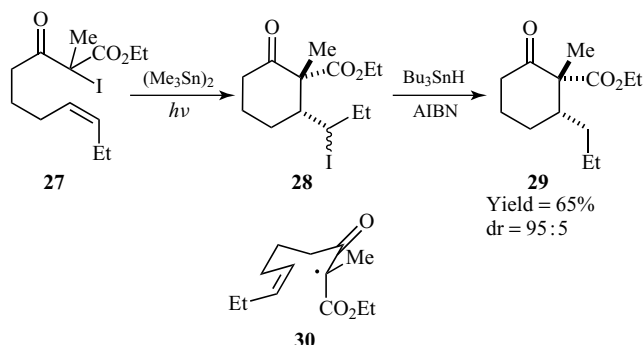
Reactions of radicals on a six-membered ring have been investigated extensively due to their importance in natural product synthesis as well as in carbohydrate chemistry. Generally, the anti rule is still valid in reactions with β -substituted cyclohexyl radicals. The level of the anti attack is usually higher when the β -substituent is axial than when it is equatorial. In the reductive radical alkylation of enamine **41**, for instance, the *cis* isomer **42** was obtained as the major product (Scheme 12).²⁸ The stereochemical outcome could be rationalized by

transition state **43**, where hydrogen atom transfer reagent approaches the intermediate from an anti orientation to the axial sulfonylmethyl group. In another example, the intramolecular atom transfer reaction of **44** furnished the bicyclic product **45** in good yield and high selectivity when using bromotrichloromethane as an atom transfer reagent. In the key atom transfer step, the cyclohexyl radical undergoes halogen atom transfer anti to the neighboring substituent (1,2-stereoselection) yielding **45** with high diastereoselectivity.²⁹

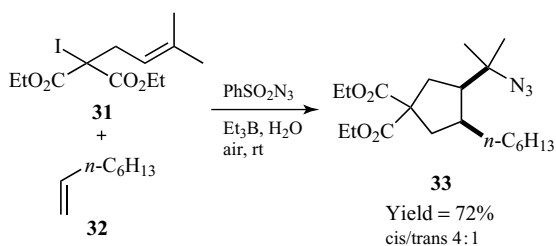
Prediction of stereochemistry for reaction of cyclic radicals becomes complicated when the substrate has more than one substituent. In these cases, one needs to take into account other factors such as conformation of the intermediate, effect of neighboring group, stereoelectronic effect, and position of the transition state in understanding the level and sense of stereoinduction.

2.2 Chiral Auxiliary-Assisted Diastereoselective Radical Reactions

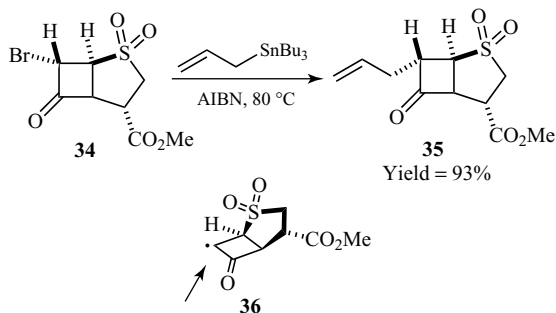
Chiral auxiliary is a chemical entity that is temporarily incorporated into a substrate to enable reactions at its prochiral unit selectively. The stereocenter in the auxiliary allows for the installation



Scheme 8 Diastereoselective 6-exo-cyclization.



Scheme 9 Stereoselectivity in [3 + 2]-radical annulation.



Scheme 10 Diastereoselective allylation of radicals in four-membered ring system.

of a new stereocenter in the substrate using steric hindrance or directing groups to provide diastereomeric adducts. Removal of the chiral auxiliary from the adducts results in the formation of enantioenriched products. A variety of chiral auxiliaries derived from amino acids, carbohydrates, and terpenes have been used for diastereoselective radical reactions.³⁰

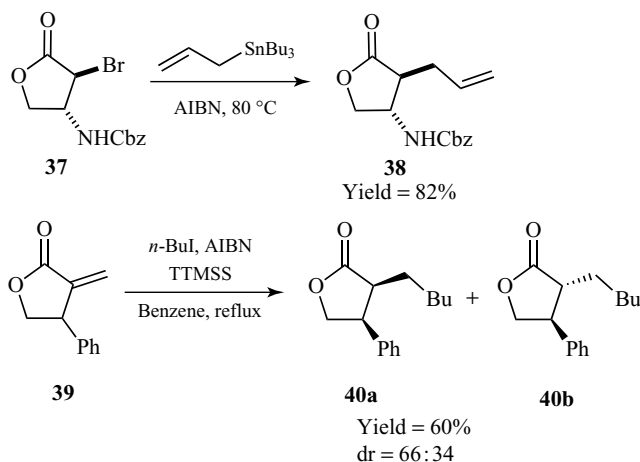
The first example of stereochemical control in free radical addition to an alkene utilized

2,5-dimethylpyrroline carboxamide as the chiral auxiliary. The nucleophilic hexyl radical adds regioselectively β - to the keto carbonyl of substrate **46** to furnish **47**. The stereochemistry in the radical conjugate addition is controlled by the C_2 symmetric pyrrolidine amide (see **48**, Scheme 13). Diastereoselectivity of up to 97 : 3 could be obtained for conjugate addition of *n*-hexyl radical to enone **46** bearing a 2,5-dimethylpyrroline carboxamide auxiliary.³¹

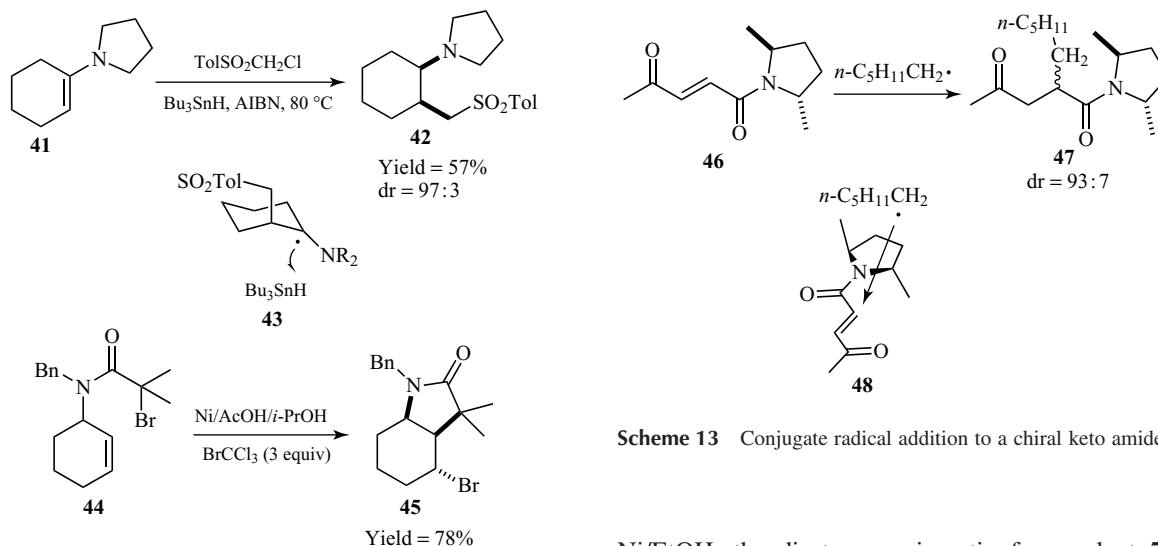
Oppolzer's camphorsultam is an excellent chiral auxiliary and has been used extensively in diastereoselective radical reactions. Nucleophilic radical addition to the chiral camphorsultam-derived glyoxyl oxime **49** at -78°C afforded a 96 : 4 diastereomeric mixture of alkylated products **50** in 73% yield (Scheme 14). In this study, the *anti-s-cis* planar rotamer **A** was expected to be preferred over rotamers **B–D** in order to minimize dipole–dipole interactions between these groups, and radical addition to the *re* (bottom) face is favored to avoid the steric interaction with the axial oxygen of sulfonyl group.^{32,33}

Chiral auxiliaries could also be used to control the configuration of radicals rather than radical acceptors when attached to an appropriate radical precursor. Rosenstein and Tynan³⁴ have evaluated free radical allylation of selenide **51** bearing an oxazolidine as a chiral auxiliary for controlling stereochemistry. As shown in Scheme 15, under photolysis in dichloromethane at -78°C , the allylation could proceed with excellent diastereoselectivity (**52**, dr > 100 : 1) in 80% yield.

Garner *et al.*³⁵ have investigated diastereoselective radical decarboxylation reactions using sugar derivatives as a chiral auxiliary. In this work, an



Scheme 11 Diastereoselective allylation of radicals in five-membered ring system.



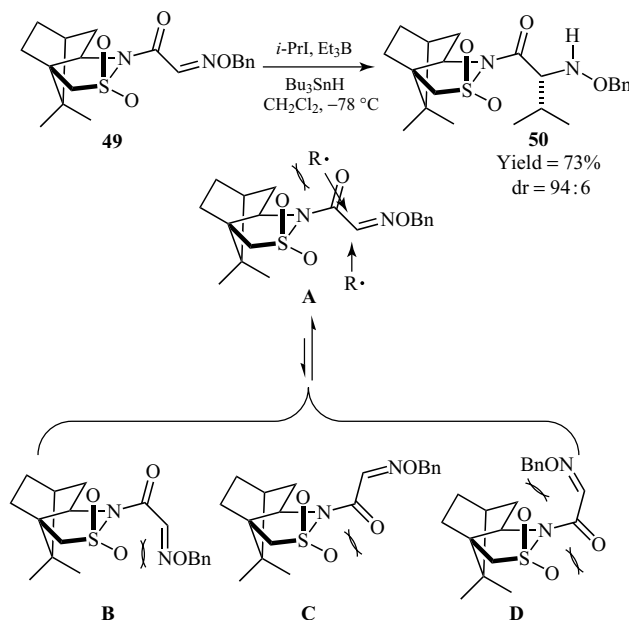
Scheme 12 Diastereoselective reactions of radicals in six-membered ring system.

ether linkage was employed to connect the chiral auxiliary and the α -alkoxy radical precursor derived from the Barton *N*-hydroxypyridine-2-thione (PTOC) esters. Radical decarboxylation of **53** occurs under photolytic conditions to form the desired α -alkoxy radical that adds to methyl acrylate resulting in the formation of an intermediate electrophilic radical. 2-Thiopyridone then traps this intermediate radical. After desulfurization of the newly formed thiopyridyl ethers using Raney

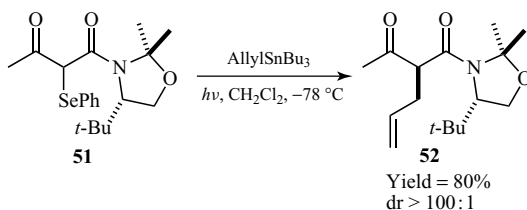
Scheme 13 Conjugate radical addition to a chiral keto amide.

Ni/EtOH, the diastereomeric ratio for product **54** could be determined as 11:1. Thus, the starting material **53** functions as a chiral hydroxyalkyl radical equivalent. A similar sequence using nitroalkenes as the radical acceptor provides a nice protocol for the synthesis of aldols (Scheme 16).³⁶

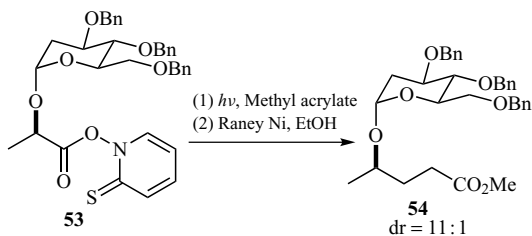
Snieckus and coworkers developed *N*-(*o*-bromo and -iodobenzoyl)-2-*tert*-butyl-perhydropyrimidinones **55** as a new chiral template for enantioselective 1,5-hydrogen atom translocation. As shown in Scheme 17, by the application of the catalytic tin method and trapping by electron-deficient olefins **56**, the addition products **57** could be obtained in moderate yields with excellent selectivities. After cleavage of the template, **57** could be converted



Scheme 14 The use of camphorsultam as a chiral auxiliary for radical addition to oximes.



Scheme 15 Radical allylation of a malonyl radical attached to a chiral auxiliary.



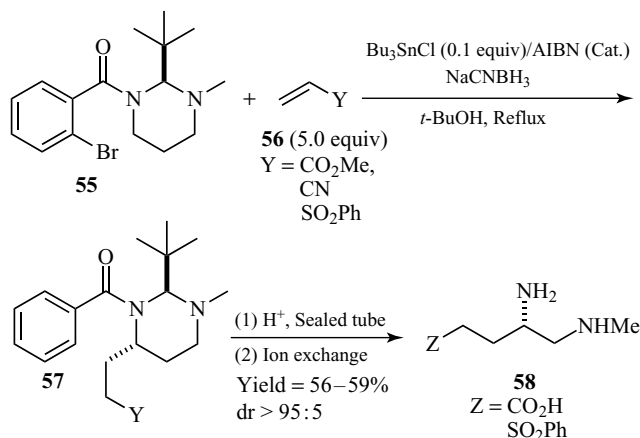
Scheme 16 Carbohydrate-derived chiral auxiliary in radical reactions.

into the corresponding β -substituted β -amino acid derivatives **58** with 97–98% enantiopurity.³⁷

2.3 Lewis Acid-Mediated Diastereoselective Radical Reactions

It is generally difficult to achieve high selectivity in kinetically controlled diastereoselective reactions with acyclic substrates because of their flexibility and also due to reactions proceeding from several potential transition states with similar energy levels. Lewis acid complexation of the acyclic substrate could decrease rotational degrees of freedom of the reactive intermediates and thus enhance the difference in energies between competing transition states. Lewis acid can also influence a reaction by modulating the electronic and/or steric functionalities adjacent to the site of chemical transformation.³⁸ Studies on diastereoselective radical processes under the influence of Lewis acids started in late 1980s.

As one of the earliest example, Guindon and coworkers evaluated influence of Lewis acid on radical reduction of α -iodo- β -alkoxyesters **59** (Table 3).³⁹ They found that this hydrogen transfer process, in the absence of Lewis acid, gave excellent selectivity favoring the anti isomer **60** (>25:1). The stereochemistry was best rationalized by transition state A (Table 3), which takes into account allylic 1,3-strain, dipole–dipole repulsion,



Scheme 17 1,5-Hydrogen atom transfer in optically active *N*-(*o*-bromobenzoyl)-*tert*-butylpyrimidinone.

Table 3 Effect of Lewis acid on radical reduction.

Solvent	Temperature (°C)	Additive	Yield (%)	<i>anti</i> : <i>syn</i>
Toluene	−78	—	90	>25 : 1
CH ₂ Cl ₂	−50	MgBr ₂ · OEt ₂ (25 mol%)	91	>1 : 25

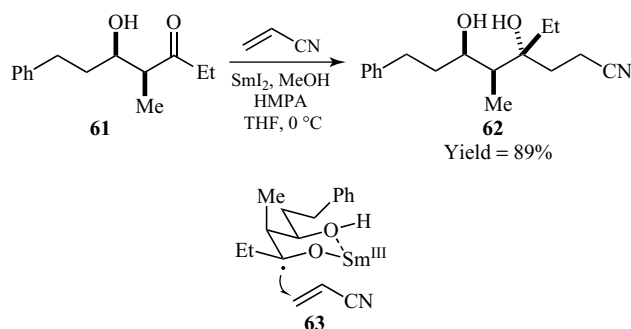
A **B**

and hyperconjugative stabilization. However, when 25 mol% of MgBr₂OEt₂ was employed in this reaction, the *syn* product was formed in good yield with the diastereoselectivity of more than 1 : 25. The reversal of selectivity was explained by the formation of a chelate between the bidentate substrate and the Lewis acid (transition state **B**). Similar Lewis acid effects were also observed in allylation and atom transfer reactions.⁴⁰

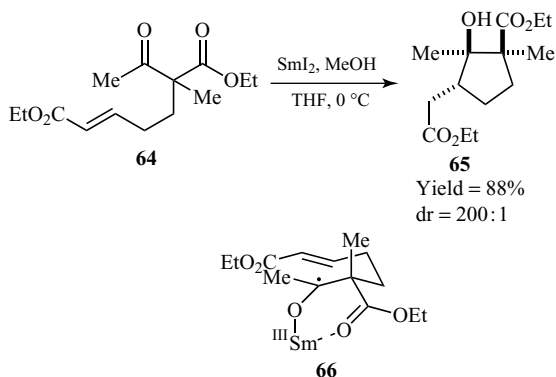
Samarium iodide is a versatile reagent that is used extensively in radical chemistry (see **Organic Synthesis Using Samarium Diiodide**). As an excellent SET reagent, samarium iodide can reduce a variety of aldehydes and ketones to form ketyl radical anions, which then can undergo reaction with different radical acceptors. Importantly, the newly formed samarium(III) species shows

Lewis acidity and could potentially coordinate with the substrate or reaction partners. This coordination can potentially reduce the flexibility of the molecules to a certain extent. Therefore, samarium iodide-mediated radical reactions usually give good selectivities. Matsuda and coworkers showed that the samarium iodide-mediated coupling of erythro- β -hydroxyketone **61** with acrylonitrile led exclusively to the anti diol **62** in high yield.⁴¹ A six-membered chelation model **63** of Sm(III) to the β -hydroxy and the carbonyl groups was proposed to explain the stereochemical outcome for this transformation (Scheme 18).

High diastereoselectivity was also observed in SmI₂-mediated intramolecular cyclization. As shown in Scheme 19, Molander and Kenny⁴²



Scheme 18 Diastereoselectivity in samarium iodide-mediated radical reaction.

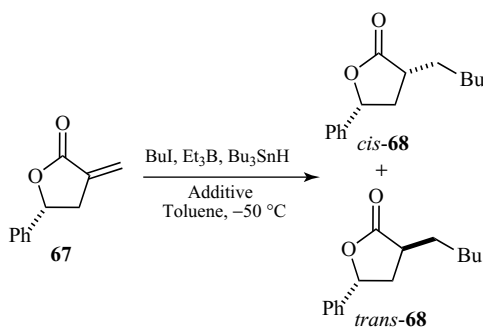


Scheme 19 Diastereoselectivity in radical cyclization mediated by SmI_2 .

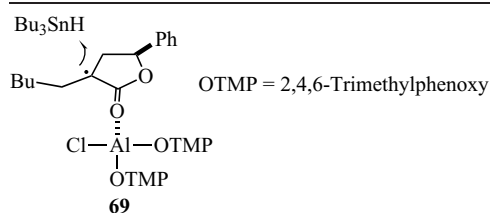
reported the cyclization of olefin branched acetoacetate derivative **64** using samarium iodide. Excellent diastereoselectivity for **65** (200:1) was obtained with the formation of three contiguous stereocenters in high yield. Sm(III) species again played an important role through chelation with the ester group in a chair-like transition state **66**, which accounted for the observed selectivity.

Single-point bonding between Lewis acid and substrate could also significantly change the selectivity of radical reactions. Sato and coworkers have investigated the effect of Lewis acid in the reductive radical alkylation of α -methylenebutyrolactone **67** using *n*-BuI as the radical precursor. They found that in the absence of Lewis acid, the reaction gave high diastereoselectivity (9:1) with *syn* isomer **68** as the major product. The level of 1,3-stereoiduction is quite high because of the rigidity of the ring system. On the other hand, reaction with 1.1 equiv of ClAl(OTMP)_2 as the additive,

Table 4 Single-point binding Lewis acid-mediated radical reaction.

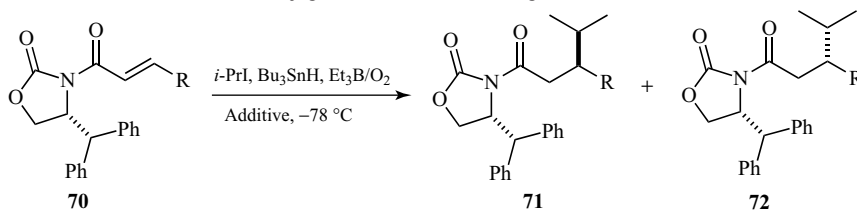


Additive	Yield (%)	cis : trans
—	44	9 : 1
$(\text{TMPO})_2\text{AlCl}$ (1.1 equiv)	90	1 : 1.5

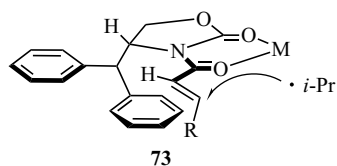
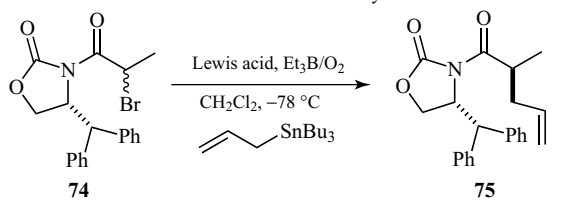


the selectivity was reversed and the *trans* isomer is isolated as the major product (1:1.5). Coordination of the bulky Lewis acid to the carbonyl oxygen occurs opposite to the resident phenyl group. The phenyl group and the Lewis acid impede H-atom transfer from opposite faces and the anti product is formed with a slight preference (model **69**, Table 4).²⁷

Lewis acid-mediated diastereoselective radical reactions using chiral oxazolidinone auxiliaries have proven to be the most successful in a variety of

Table 5 Diastereoselective conjugate radical addition using chiral oxazolidinone.


Additive	Yield (%)	71 : 72
—	60	1.3 : 1
Yb(OTf) ₃ (1 equiv)	89	45 : 1

**Table 6** Lewis acid-mediated radical allylation.


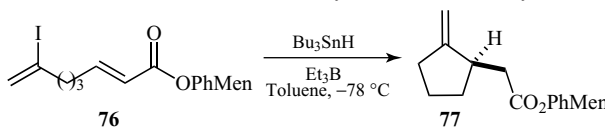
Lewis acid	Yield (%)	Ratio (RS : RR)
—	93	1 : 1.8
BF ₃ ·OEt ₂	85	1 : 1.4
MgBr ₂ (1 equiv)	94	39 : 1

C–C bond formations. Sibi *et al.*⁴³ have investigated diastereoselective conjugate radical addition to a cinnamate substrate bearing a diphenylmethyl oxazolidinone auxiliary (Table 5). In the absence of any additive, the conjugate addition proceeded in good yield. However, the selectivity was very low (1.3 : 1). In contrast, reaction using 1 equiv of Yb(OTf)₃ as the Lewis acid additive gave the product in very high selectivity of 45 : 1. Moreover, the reactivity toward radical conjugate addition also improved significantly and the yield jumped up to 90% using Yb(OTf)₃. The stereochemical outcome was rationalized using **73** as a model in which the substrate conformation was fixed by coordination between the two carbonyl groups and the Lewis acid. The radical attacks the alkene from a face

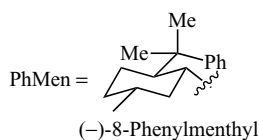
opposite to the diphenylmethyl substituent of the chiral auxiliary. The bulk of the diphenylmethyl group in the auxiliary is critically important for obtaining high selectivity. The use of a chiral auxiliary with a smaller benzyl group at C-4 led to a substantial reduction in selectivity. A similar strategy has also been successfully applied to stereoselective α -allylation and atom transfer reactions.⁴⁴

Sibi and Rheault⁴⁵ have also investigated the effect of Lewis acids in radical allylation. As shown in Table 6, Lewis acid has a significant impact on the allylation of α -bromo propionate bearing a chiral oxazolidinone auxiliary. In the absence of any Lewis acid, the reaction gave very low diastereoselectivity (1 : 1.8). Single-point bonding Lewis acid such as BF₃·OEt₂ had no impact on selectivity. In contrast, the use of MgBr₂, a chelating Lewis acid, provided very high selectivity of up to 39 : 1 for the allylation product. The stereochemistry of the product using MgBr₂ as a Lewis acid was opposite to that obtained in the absence of any Lewis acid.

Significant impact of Lewis acid on selectivity was also observed in the cyclization of vinyl iodide **76** bearing a (–)-8-phenylmenthyl chiral auxiliary. Compared to modest selectivity of 2 : 1 in the absence of Lewis acid, reaction mediated by methyl aluminum bis(2,6-di-*t*-butyl-4-methylphenoxide), a bulky Lewis acid, showed a significant improvement in stereoselectivity of up to 24 : 1 (Table 7).⁴⁶

Table 7 Diastereoselective radical cyclization mediated by Lewis acid.


Additive	Yield (%)	cis : trans
—	92	2 : 1
MAD (1.8 equiv) ^a	79	24 : 1

^aMAD = methyl aluminum bis (2,6-di-*t*-butyl-4-methylphenoxide).

3 ENANTIOSELECTIVE RADICAL REACTIONS

Enantioselective radical reactions have been at the forefront of new synthetic methodology development since the 1980s.^{47–49} Several strategies have been applied to control the enantioselectivity of radical reactions, which includes chirality transfer from enantioenriched reagents, assistance of metal complex, and organocatalysis. The following sections provide illustrative examples for each of the major category of enantioselective radical reactions.

3.1 Chiral Chain-Transfer Reagent

The use of chiral chain-transfer agent is a straightforward strategy for chirality induction in radical chemistry. Organotin hydride has been used as a major chain-transfer reagent and reducing agent for a long time (see **Tin Hydrides and Functional**

Group Transformations). Early investigation on the use of chiral chain-transfer reagent in enantioselective radical chemistry was focused on utilizing a chiral organotin reagent. The results showed that organotin hydride reagent based on chiral tin center provided inefficient chirality transfer and racemization were generally observed.^{50–52} Nanni and Curran⁵³ reported the first example of asymmetric induction using chiral organotin as the chain-transfer reagent based on a chiral carbon backbone. As shown in Scheme 20, chiral C₂-symmetric binaphthyl skeleton-based tin hydride **78** could reduce α -bromoketone **79** in 41% ee with Et₃B/air as the radical initiator.

Metzger and coworkers developed a chiral tin hydride **82-H**, which is similar to Curran's chiral binaphthyl organotin hydride **78** where the methyl group on the tin atom has been replaced with a bulky *t*-butyl group.⁵⁴ Using Et₃B/air as the radical initiator, chiral tin hydride **82-H** could reduce α -bromoester **81** with slightly increased enantioselectivities of up to 52% at -78°C (Table 8).

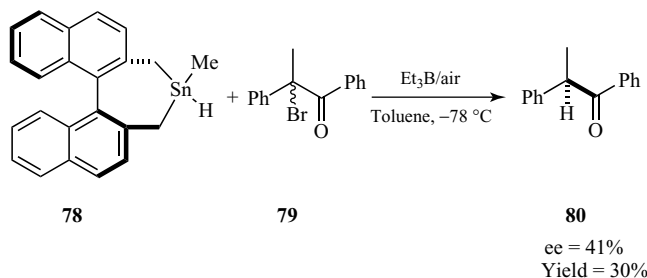
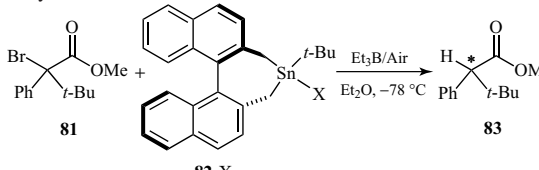
**Scheme 20** Reduction of α -bromoketone using chiral tinhydride.

Table 8 Asymmetric reduction of α -bromoesters using chiral tinhydride.


82-X	Temperature (°C)	ee (%)
82-H (0.5 equiv)	-78	52
82-H (0.5 equiv)	24	28
82-Br (0.1 equiv) + Na(CN)BH ₃ (3 equiv)	24	26

Interestingly, the authors used substoichiometric amounts of chiral tin hydride in entries 1 and 2. The tin hydride reagent could also be generated *in situ* by the addition of sodium cyanoborohydride to chiral tin bromide **82-Br**. The enantioselectivity for the reduction product using catalytic amount of the organotin reagent was comparable to that obtained when the same reaction was conducted using stoichiometric amounts of the chiral reducing agent.

Haque and Roberts observed moderate enantioselectivities in the radical chain hydrosilylation of prochiral alkenes using catalytic amounts of an optically active thiol. As shown in Scheme 21, in the presence of 5 mol% of chiral thioglucose derivative **85**, hydrosilylation of alkene **84** gave the corresponding product **86** in good yield with 50% ee. In the key step of chirality transfer, hydrogen atom

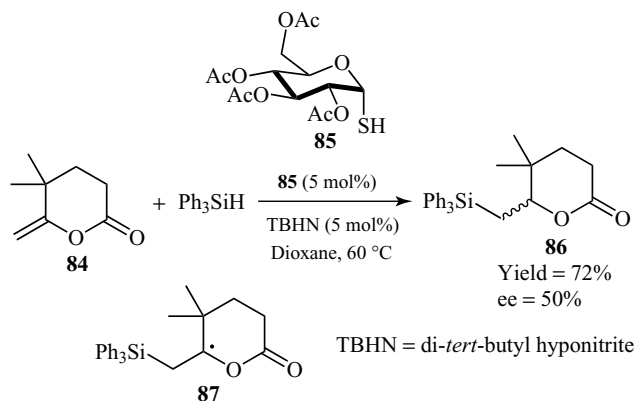
transfer occurs from chiral thiol to radical intermediate **87** with some enantioselectivity. The thiyl radical is reduced by Ph₃SiH to regenerate the chiral catalyst. Thus, chiral thiol works as the chiral hydrogen atom source in this process.^{55–57} Additional examples of reagent-based enantioselective hydrogen atom abstraction have also been reported, which involves chiral amine-boryl and silanethiyl radicals.^{58–60}

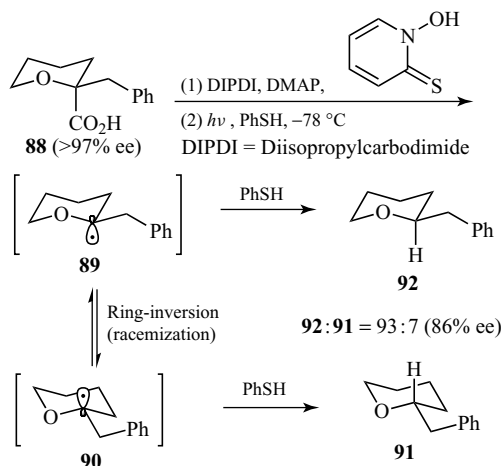
3.2 Memory of Chirality

Memory of chirality is a phenomenon in which the chirality of the starting material is preserved in a reactive intermediate for a limited time. The concept of “memory of chirality” was proposed during alkylation of certain enolates 10 years ago.⁶¹ Typically, alkyl radicals have very low barriers to inversion and application of the principles of memory of chirality to them is quite interesting.

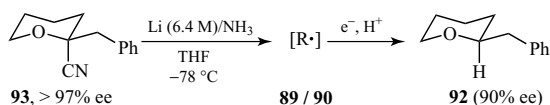
3.2.1 Memory of Chirality in Hydrogen Atom Transfer

Rychnovsky and coworkers observed high level of chirality preservation in the hydrogen atom transfer reaction of tetrahydropyran **88**.⁶² As shown in Scheme 22, the photo-decarboxylation of optically active Barton ester **88** leads to radical intermediate **89**, which can be trapped by PhSH as the hydrogen atom source to furnish product **92** in 86% ee.

**Scheme 21** Radical reduction using a chiral thiol as H-atom source.



Scheme 22 Memory of chirality in H-atom transfer.



Scheme 23 Memory of chirality in reductive decyanation.

Table 9 Memory of chirality in radical cyclization.

Precursor	R ¹	R ^E	R ^Z	X	Yield (%)	ee (%)
M-94a	Me	Me	H	I	73	89 (<i>R</i>)
M-94b	Me	Me	H	Br	60	92 (<i>R</i>)
M-94c	Me	Ph	Me	I	75	94 (<i>R</i>)
M-94d	Me	Me	Me	I	91	49 (<i>R</i>)
M-94e	Et	Me	I	I	93	90 (<i>R</i>)

Obviously, the hydrogen transfer process is faster than the ring inversion. It was pointed out that a slow conformational interconversion (5–10 kcal mol⁻¹) imposed a barrier to equilibration despite a very low barrier (< 0.5 kcal mol⁻¹) to radical inversion.

A memory effect was also observed in the reductive decyanation of optically active nitrile **93** (Scheme 23). Reductive decyanations of nitriles are stepwise reactions that proceed via a radical intermediate. Addition of **93** to a 6.4 M Li/NH₃ solution at –78 °C gave tetrahydropyran **92** in nearly complete memory of chirality.

3.2.2 Memory of Chirality in Cyclization

Curran *et al.*⁶³ reported a unique memory of axial chirality and its conversion to central chirality. As shown in Table 9, initiated by Et₃B/O₂, radical cyclization of *o*-haloarylanilides **94** to oxindoles **95** shows high-level chirality preservation (50–94% ee) with Bu₃SnH as the radical chain reagent. The reaction worked well for both aryl iodides and aryl bromides and the enantiomeric excesses are similar. However, cyclization of a dimethylacrylate substrate with a *Z*-alkene substituent as in **94d** gave reduced enantiomeric excess of about 50%. Higher enantiomeric excesses were obtained for **94c** with a R^E phenyl group most likely due to delocalization provided by conjugation with the phenyl ring. This stabilization of the radical intermediate increases the rate of the reaction.⁷

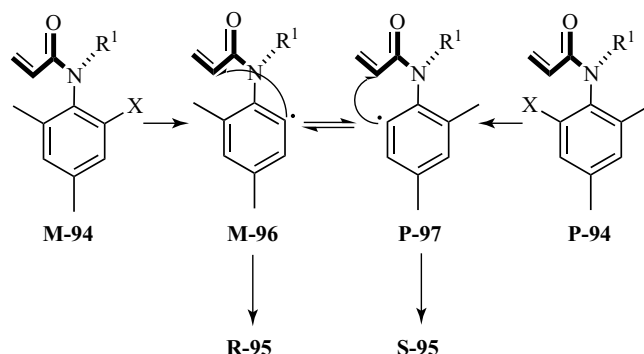
Although the energy barrier between **M-96** and **P-97** is not exactly known (M and P are helical chirality descriptors), high selectivity in the cyclization suggests that inversion between them is slower than radical cyclization (Scheme 24).

3.3 Chiral Lewis Acid-Mediated Enantioselective Radical Reactions

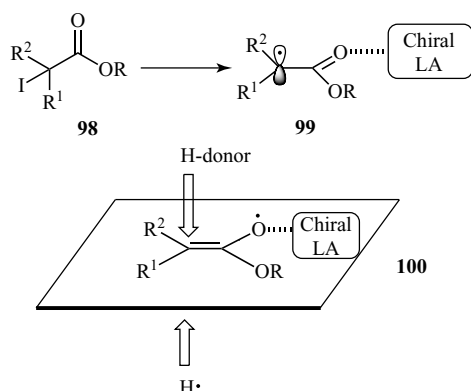
Chiral Lewis acids have been widely applied in a variety of transformations to access enantioenriched materials. Chiral Lewis acids can bind the substrate or other reacting components. Chiral Lewis acids have also been successfully utilized in radical reactions by either interaction with the substrate or the radical species.

3.3.1 Hydrogen Atom Transfer

Stereocontrol during chiral Lewis acid-mediated radical reduction at a carbon atom α to a carbonyl group can be visualized to occur in two potential



Scheme 24 Mechanism of memory of chirality in radical cyclization (cf. Table 9).

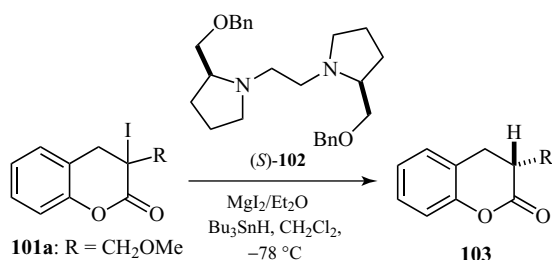


Scheme 25 Chiral Lewis acid controlled H-atom transfer.

pathways (Scheme 25). For both carbon-centered or an enol form of the radical generated in the presence of a chiral Lewis acid, the hydrogen atom donor can approach selectively to one face of either radical intermediate **99** or **100** leading to enantioenriched products.⁶⁴

Blumenstein *et al.*⁵⁴ reported an enantioselective hydrogen atom transfer reaction of α -alkyl- α -iododihydrocoumarin **101** using stoichiometric amounts of MgI_2 and a chiral diamine ligand **102** with Bu_3SnH as the hydrogen atom source (Table 10). In this study, the authors observed significant concentration effect for this reaction. At a higher concentration (around 36 mM), moderate enantioselectivities for **103** could be obtained (30–62% ee) with good chemical yields. Substrates **101a–c** gave higher selectivities than **101d**, which suggests that bidentate binding of the substrates is essential for higher enantiomeric excesses in this system.

Table 10 Enantioselective reduction of α -iodo lactones.



101a: R = CH_2OMe

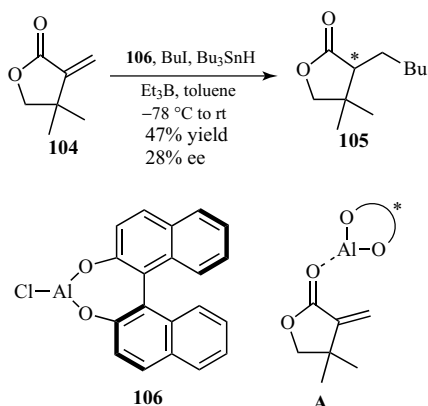
101b: R = CH_2OEt

101c: R = CH_2OBn

101d: R = Me

Entry	Substrate	Concentration of 102 (mM)	Yield (%)	ee (%)
1	101a	11	75	12 (R)
2	101a	36	88	62 (R)
3	101b	37	84	65 (R)
4	101c	38	89	58 (R)
5	101d	35	78	30 (S)

Alkyl radicals are frequently utilized in organic synthesis and are nucleophilic in character. Their addition to an olefin substrate is enhanced by electron-withdrawing substituents on the olefinic linkage. Sato and coworkers utilized conjugate addition to generate a C-centered radical intermediate for evaluating asymmetric hydrogen atom transfer.⁶⁵ As shown in Scheme 26, a strong chiral aluminum Lewis acid **106** could promote the conjugate addition of butyl radical to α -methylenebutyrolactone **104**. Modest enantioselectivity (28%) for **105** was observed in the ensuing hydrogen atom transfer process. This study represents the first example of asymmetric radical reaction controlled by a chiral Lewis acid, though the level of asymmetric



Scheme 26

induction was still low. The activation of the substrate occurs by monodentate coordination of the Lewis acid (see A).

Sibi *et al.*⁶⁶ reported a Lewis acid-promoted hydrogen atom transfer reaction using a bidentate dehydroalanine substrate **107**, which proceeds with high enantioselectivity. As shown in Table 11, in the presence of chiral Lewis acid derived from Mg(ClO₄)₂ and Ligand **109**, the radical intermediate obtained by the addition of a variety of nucleophilic radicals to **107** underwent H-atom transfer with good selectivity to furnish **108**. Reactions with primary alkyl radicals (α -alkoxyalkyl, ethyl, and *i*-butyl) and secondary radicals (*i*-propyl and *c*-hexyl) gave good enantioselectivities (55–85%). However, reaction with the bulky tertiary butyl radical was not selective and only gave 27% ee.

This decrease in selectivity was attributed to the *tert*-butyl group and the chiral Lewis acid shielding opposite faces resulting in reaction occurring from a mono-coordinated or noncomplexed substrate. The limitation for this hydrogen atom process is that 1.3 equiv of the chiral Lewis acid is necessary to ensure good yield and enantioselectivity.

Sibi and Sausker⁶⁷ have also evaluated another bidentate substrate **110** derived from commercially available 1,8-naphthosultam template for asymmetric hydrogen atom transfer using chiral Lewis acid. As shown in Table 12, in the presence of a combination of MgBr₂ ethyl etherate and the bisoxazoline ligand **109**, the hydrogen atom transfer process proceeded to yield **111** in high enantioselectivity (80–90% ee). The nucleophilic radical could be a primary, secondary, and a tertiary alkyl radical. Importantly, the reaction proceeded smoothly using substoichiometric amounts of the chiral Lewis acid. From entries 1 and 2 in Table 12, we can discern that 30 mol% of MgBr₂ gave similar enantioselectivity compared with stoichiometric amount of the chiral Lewis acid.

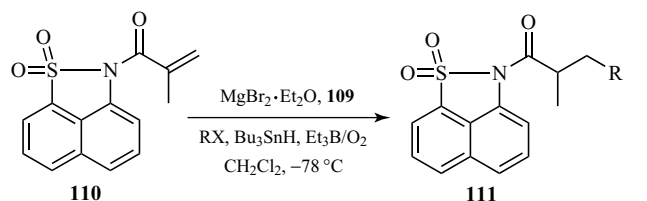
3.3.2 Halogen Atom Transfer

Halogen atom transfer reactions involve homolysis of a C–X or X–X bond in a neutral molecule, followed by the transfer of both components to an unsaturated functional group. There is atom economy in such processes and these reactions provide functionality for further transformations.⁶⁸ Mero and Porter⁶⁹ reported the first chiral Lewis acid

Table 11 Chiral Lewis acid-mediated hydrogen transfer to a bidentate dehydroalanine derivative.

107		108
RX	Yield (%)	ee (%)
AcBr	76	80
MeOCH ₂ Br	71	65
EtI	72	85 (<i>R</i>)
<i>i</i> -BuI	76	79
<i>i</i> -PrI	62	83 (<i>R</i>)
<i>c</i> -HexI	62	55 (<i>R</i>)
<i>t</i> -BuI	54	27 (<i>R</i>)

109

Table 12 Sultam templates in enantioselective H-atom transfer.


Entry	R	Lewis acid (equiv)	Yield (%)	ee (%)
1	<i>i</i> -Pr	MgBr ₂ ·Et ₂ O (1.0)	90	78
2	<i>i</i> -Pr	MgBr ₂ ·Et ₂ O (0.3)	55	80
3	<i>t</i> -Bu	MgBr ₂ ·Et ₂ O (0.3)	84	89
4	<i>c</i> -Hex	MgBr ₂ ·Et ₂ O (0.3)	71	82
5	MeOCH ₂	MgBr ₂ ·Et ₂ O (0.3)	89	90

catalyzed halogen atom transfer reaction of α -halo oxazolidinone imide **112** and 1-octene **113** using a combination of zinc triflate and phenyl bisoxazoline ligand **114** (Scheme 27). This intermolecular atom transfer process gave product **115a**. The crude product was reduced to **115b** and selectivity determined. Compound **115b** was formed in low yield (5–15%, over two steps) and modest enantioselectivity (40% ee).

In 2001, Yang *et al.*⁷⁰ described an intramolecular halogen atom transfer reaction catalyzed by a chiral Lewis acid. As shown in Table 13, using a combination of Zn(OTf)₂ and tertiary butyl bisoxazoline **117**, unsaturated β -keto esters **116a–d** underwent enantioselective bromide transfer reaction efficiently. The exocyclic products **118a–d** could be

obtained in as high as 95% ee. Interestingly, addition of 4-Å molecular sieves was very important for this reaction. Addition of molecular sieves not only led to a dramatic increase in yield and enantiomeric excess but also allowed for the use of substoichiometric amounts of the chiral Lewis acid.

Yang *et al.*⁷¹ designed diene substrates **119** and **121** for evaluating tandem bromine transfer (Scheme 28). Reaction of **119** using a stoichiometric amount of the chiral Lewis acid gave the corresponding 6-*endo* tandem cyclized product **120** in 84% ee. Although the yield was as low as 16%, this one-step reaction produces useful bicyclic ring skeleton with multiple stereocenters in an enantioselective manner. Each substrate required optimization of reaction conditions. For diene **121**, a combination

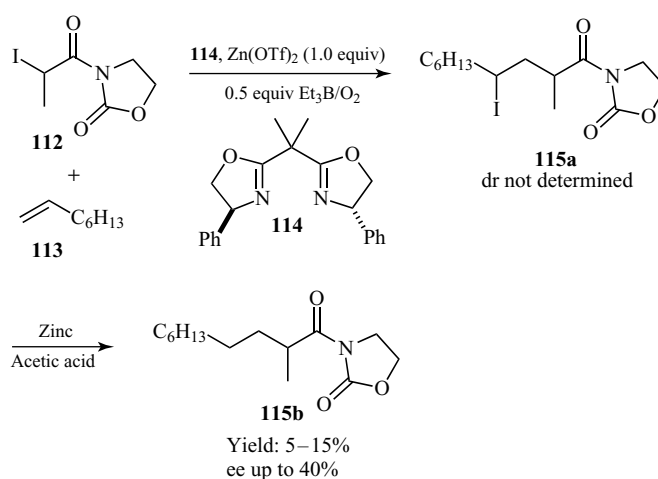
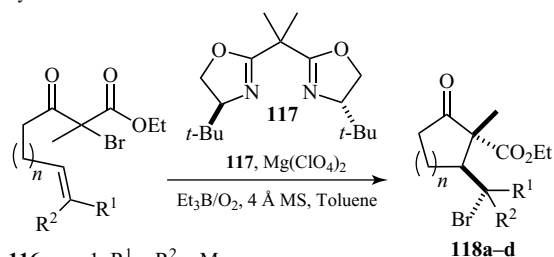
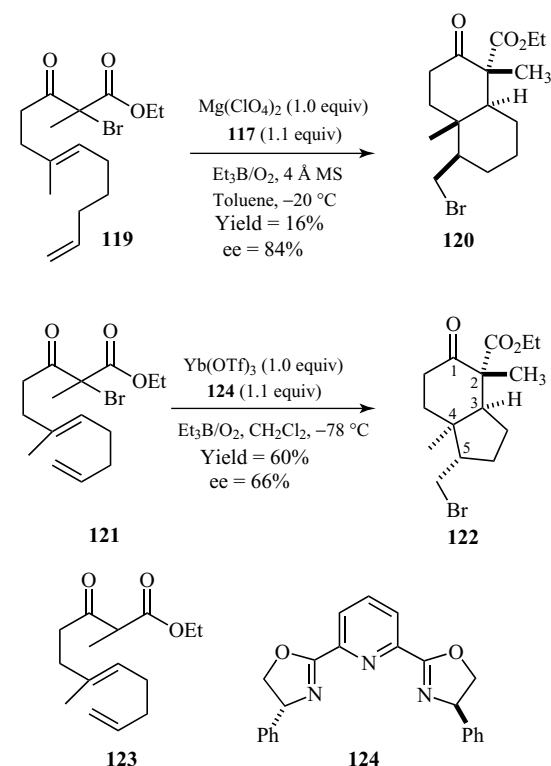
**Scheme 27** Chiral Lewis acid-mediated atom transfer addition of α -iodoimide.

Table 13 Chiral Lewis acid-mediated atom transfer cyclization.**116a** $n = 1$, $\text{R}^1 = \text{R}^2 = \text{Me}$ **116b** $n = 2$, $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{H}$ **116c** $n = 2$, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Et}$ **116d** $n = 2$, $\text{R}^1 = \text{R}^2 = \text{Me}$

Substrate	Catalyst (equiv)	Time (h)	Yield (%)	ee (%)
116a	0.3	7	68	92
116b	0.3	7	58 (1 : 1) ^a	74 : 87 ^b
116c	0.3	12	81 (1 : 1.4) ^a	74 : 95 ^b
116d	0.5	7.5	53	94

^aRatio of **118b** : **118c**^bEnantiomeric excesses for **118b** and **118c****Scheme 28** Chiral Lewis acid-mediated tandem atom transfer cyclization.

of $\text{Yb}(\text{OTf})_3$ and **PyBOX 124** proved to be optimal chiral Lewis acid and the cyclized product **122** could be obtained in 60% yield and 66% ee. Reductive debromination product **123** was always observed as the side product.

3.3.3 Reductive Alkylations

Reductive radical alkylation is a process that involves the addition of radicals to carbon–carbon or carbon–heteroatom multiple bonds followed by trapping with a hydrogen atom source. Generally, chiral Lewis acids are used to control the radical addition step in an asymmetric manner. Naito and coworkers investigated enantioselective radical additions to $\text{C}=\text{N}$ of oxime ether **125** derived from glyoxylate using chiral Lewis acids (Scheme 29).⁷² Several combinations of chiral ligands and Lewis acids were evaluated. Stoichiometric amount of MgBr_2 and phenyl bisoxazoline ligand **114** gave the best result and furnished product **126** with excellent yield and moderate enantioselectivity (52% ee). A tetrahedral model, **127**, was proposed to explain the stereochemical outcome of the reaction.

Friestad *et al.*⁷³ have also reported chiral Lewis acid-mediated reductive radical alkylation of carbon nitrogen double bond. In their study, a combination of copper triflate and bisoxazoline ligand **117** could promote the radical reductive alkylation of valerolactam-derived *N*-acyl hydrazone **128** with high enantioselectivity. As shown in Table 14, in the presence of stoichiometric amount of chiral Lewis

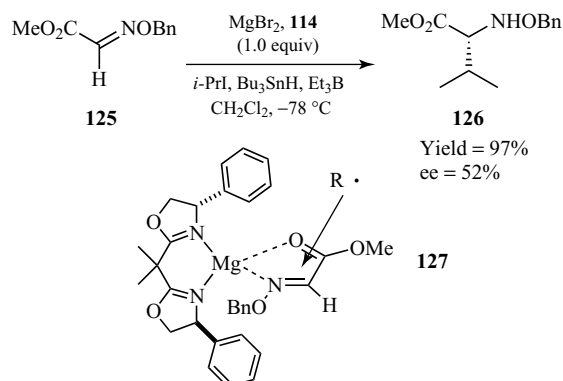
**Scheme 29** Chiral Lewis acid-mediated reductive radical alkylation of carbon nitrogen double bond.

Table 14 Chiral Lewis acid-mediated reductive radical alkylation of hydrazone.

Mol% CLA	Yield (%)	ee (%)
100	66	95
50	71	81
20	83	58
10	74	46

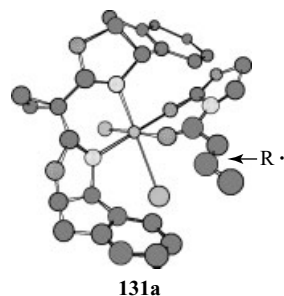
acid, the enantiomeric excess for the isopropyl radical adduct **129** could reach as high as 95%. However, the enantioselectivity decreases dramatically when the reactions are carried out with substoichiometric amount of the chiral Lewis acid. The lower catalyst loading did not impact the yield of the reaction.

Asymmetric conjugate radical addition to electron-deficient carbon–carbon double bond followed by hydrogen atom transfer is one of the most successful application of chiral Lewis acid radical chemistry. In order to reach high enantioselectivity, a bidentate substrate was generally necessary. Sibi and coworkers reported the first enantioselective radical conjugate additions using substoichiometric amount of a chiral Lewis acid (10 mol%). Conjugate addition of isopropyl radical to oxazolidinone-derived substrate **130** using MgI_2 /ligand **109** as a chiral Lewis acid gave the product **131** in 88% yield and excellent enantioselectivity (95% ee) (Table 15). It was observed that a substrate capable of bidentate chelation to the chiral Lewis acid was very important to activate it toward radical addition at low temperature. The chelation also helped the substrate adopt an *s*-cis orientation at the $\text{C}(\text{O})\text{--C}(\text{sp}^2)$ bond and provide optimal face shielding (see model **131a**).^{74,75}

Sibi and Shay⁷⁶ showed that achiral template played an important role in the outcome of enantioselective reductive radical alkylation to $\text{C}=\text{C}$ bond. By changing the oxazolidinone template of **130** to a 3,5-dimethylpyrazole in **132** resulted in a reversal of stereochemistry using the same chiral Lewis acid (Scheme 30). Radical addition in the presence of stoichiometric amounts of zinc triflate and ligand

Table 15 Chiral Lewis acid-mediated reductive alkylation of $\text{C}=\text{C}$ bond.

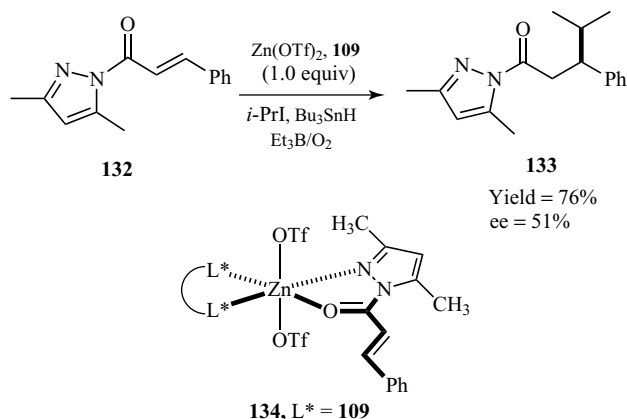
Lewis acid (equiv)	Yield (%)	ee (%)
MgI_2 (0.1)	88	95
$\text{Zn}(\text{OTf})_2$ (1.0)	—	53



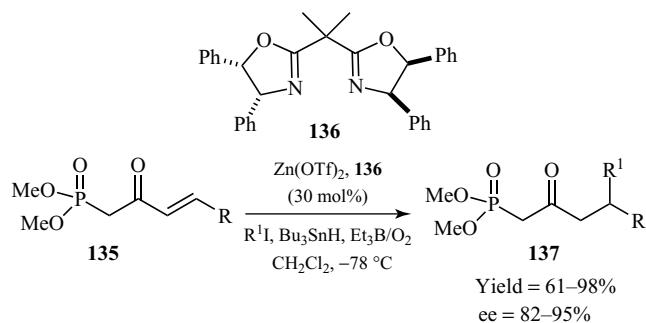
109 gave good yields and moderate selectivities for **133**. Chiral Lewis acid coordinates with acylated pyrazoles **132** and forms a five-membered chelate unlike the six-membered chelate formed with oxazolidinones **130** (vide supra). This change in chelate ring size, accompanied by a *trans*-octahedral geometry with **132** and **109**, has been proposed to account for the reversal of enantioselectivity (see **134**).

α' -Phosphoric enone has also been examined in enantioselective conjugate radical additions by Lee and Kim (Scheme 31).⁷⁷ Radical addition to **135** using $\text{Et}_3\text{B}/\text{O}_2$ as a radical initiator, Bu_3SnH as the hydrogen atom source, and a chiral Lewis acid (30 mol%) derived from zinc triflate and bisoxazoline **136** gave high yields for the conjugate addition product **137**. The chemical efficiency and level of enantioselectivities (82–95% ee) were excellent using a variety of primary, secondary, and tertiary alkyl radicals. Reaction with β -alkyl and aryl substrates were evaluated and found to be effective.

Radical addition to α,β -disubstituted enoates is difficult because the substrates are less reactive for both steric and electronic reasons. Sibi and coworkers have reported the use of tertiary butyl imide as the template in conjugate radical additions to α,β -disubstituted enoals. This template provided reactivity enhancements as well as the ability to control rotamers in α -substituted acrylates. Radical



Scheme 30 Template effect in chiral Lewis acid-mediated reductive radical alkylation.



Scheme 31 Chiral Lewis acid-mediated reductive alkylation of α -phosphoric enones.

addition to the tiglate substrate **138** in the presence of 30 mol% chiral Lewis acid derived from MgI_2 and bisoxazoline ligand **117** gave the radical addition/trapping products **139** with excellent diastereo- and enantioselectivities (Table 16). A variety of alkyl radicals could be used in this reaction (entries 1–3). This reaction system has a wide substrate scope and R^2 could vary from alkyl to aryl group. The anti diastereomer was formed as the major product in all cases and the level of enantioselectivity was also high for most of the reactions.⁷⁸

Castle and coworkers⁷⁹ have examined radical conjugate addition/trapping reaction using β -substituted α,β -unsaturated α -nitro ester and amide **140** as substrates (Table 17). The reaction was promoted by a chiral Lewis acid prepared from $\text{Mg}(\text{NTf}_2)_2$ and DBFOX (**141**). Reactions were efficient when a stoichiometric amount of chiral Lewis acid was employed yielding the product **142** in good yield and high enantioselectivity. The diastereomeric ratio was nearly 1 : 1. Reaction with 50 mol%

of the catalyst was equally efficient. However, lowering the catalyst loading to 30 mol% gave the diastereomeric products in low enantioselectivity. The products could be converted to β -substituted α -amino acids (**143**) in good yield and good enantioselectivity.

In all reported enantioselective radical addition/trapping reactions that proceed with high selectivity, detachable achiral auxiliaries play a pivotal role. These auxiliaries not only provide an extra donor atom that enables Lewis acid chelation, but they also allow for control of the rotamer geometry of the substrate. Sibi and Zimmerman⁸⁰ have examined radical addition/trapping reaction of hydroxypyrones using chiral Lewis acids. Since this substrate has a fixed s-trans geometry, no achiral auxiliary was needed to control rotamer geometry. Commercially available kojic acid proved to be a good substrate to evaluate chiral salen (salen = *N,N'*-bis(salicylidene)ethylenediamine dianion) Lewis acid **146** catalyzed radical

Table 16 Chiral Lewis acid-mediated radical reductive alkylation of α,β -disubstituted enoys.

Entry	R ¹	R ²	R ³	Yield (%)	dr	ee (%)
1	Et	Me	Me	63	87 : 13	92
2	<i>i</i> -Pr	Me	Me	79	99 : 1	92
3	<i>i</i> -Bu	Me	Me	83	99 : 1	94
4	<i>i</i> -Pr	Et	Me	37	95 : 5	80
5	<i>i</i> -Pr	Ph	Me	71	99 : 1	93
6	<i>i</i> -Pr	Me	Et	50	87 : 13	74

Table 17 Chiral Lewis acid-mediated radical alkylation/reduction of β -substituted α,β -unsaturated α -nitro amide.

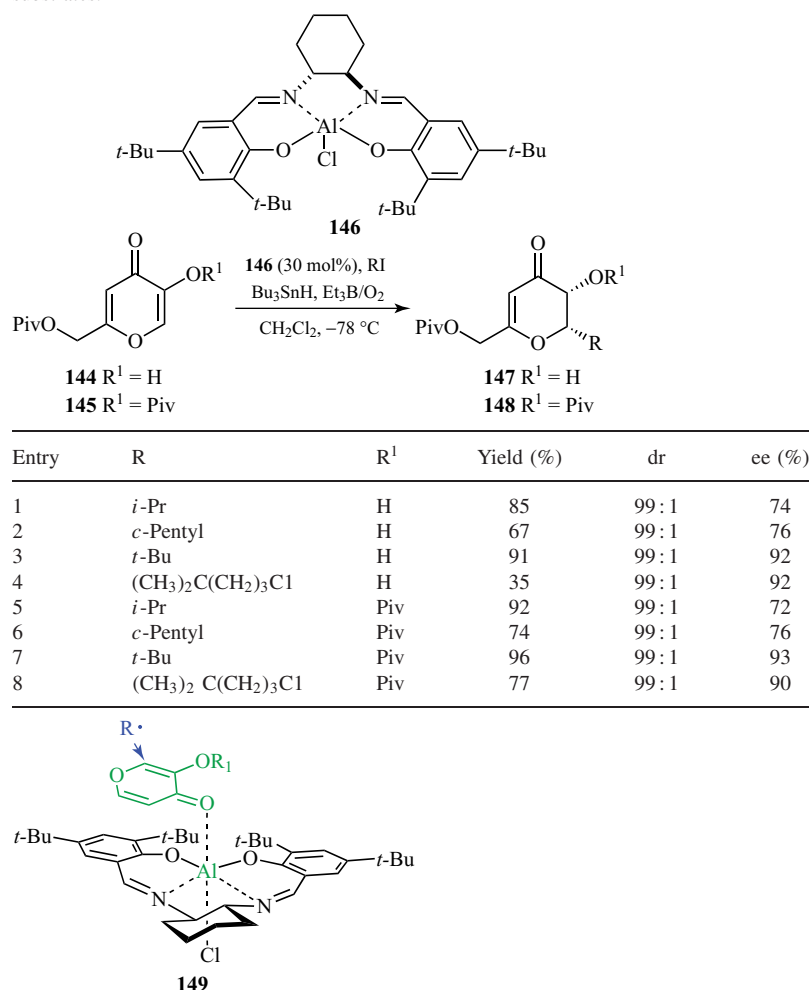
Mol% CLA	Yield (%)	<i>syn/anti</i>	ee (%) (<i>syn, anti</i>)
100	76	1.4 : 1	88, 76
50	70	1.4 : 1	84, 64
30	57	1.2 : 1	41, 30

addition/trapping reactions. Protection of the C-6 hydroxyl group increased substrate solubility and deactivated the C-6 position toward conjugate radical addition. Radical addition to either substrate

144 or **145** gave exclusively C-2 addition products **147** and **148** under standard reductive radical alkylation conditions. This condition was quite efficient for bulky tertiary radicals and excellent diastereo- and enantioselectivities were observed for all cases (entries 3–4 and 7–9, Table 18). On the other hand, secondary radicals examined in this study gave 72–76% ee for both substrates. A model **149** in which the pyrone carbonyl coordinates the Al-salen Lewis acid was proposed to explain the stereochemical outcome. The stereochemistry of hydrogen atom transfer step was believed to be controlled by the newly formed β -stereocenter with radical R group shielding the top face.

Sibi and Nad⁸¹ have evaluated the reductive radical alkylation of exo-methylene cyclohexanones **150** with fixed *s-cis* geometry (Scheme 32). As shown in Scheme 26, single-point bonding chiral salen-derived Lewis acid **146** was the best catalyst for the reaction. Excellent diastereo- and enantioselectivity could be obtained for isopropyl radical under standard conditions furnishing **151** in good yield (95% ee, dr $\geq$ 99 : 1). This reaction provides a method to synthesize enantioenriched cyclic aldols via radical reaction with the formation of two stereogenic centers in a single operation.

The use of tin reagents as a radical mediator is well known (see **Tin Hydrides and Functional Group Transformations**). Tin reagents are toxic and tin byproducts are difficult

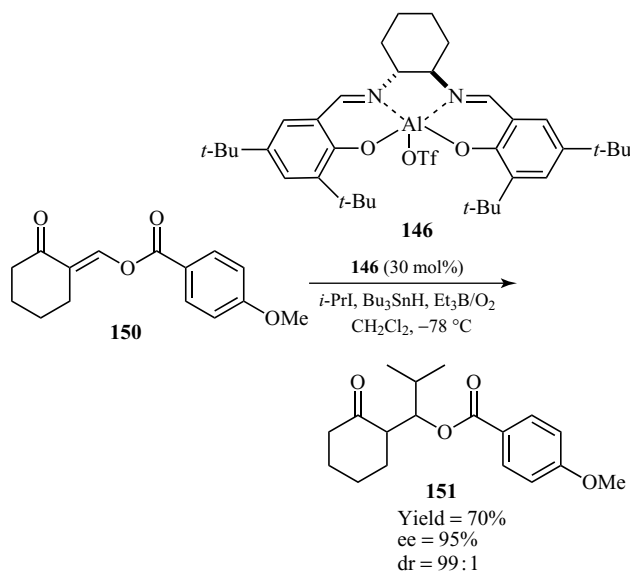
Table 18 Chiral Lewis acid-mediated radical reductive alkylation of single-point binding substrates.

to remove during purification. Several alternatives to tin reagents have been reported in the literature and these include silanes, thiols, phosphorus acids, indium hydrides, and cyclohexadienes. Generally, higher temperature is required if one uses a nontin reagent as the radical chain carrier. However, Lewis acid-mediated asymmetric radical reactions are generally conducted at low temperatures, which necessitate the use of an efficient radical chain carrier such as tin hydride. Sibi *et al.*⁸² have explored the possibility of chiral Lewis acid-mediated nontin radical conjugate addition/trapping process. A variety of nontoxic silanes were evaluated in enantioselective radical conjugate additions (Table 19). Radical addition to **152** in the presence of 30 mol%

of Mg(NTf₂)₂ and chiral bisoxazoline **109** using less toxic and inexpensive hexyl silane gave the addition product **153** in good yield and selectivity. The reactions were conducted at room temperature. Reactions with primary and secondary alkyl radicals gave ethyl radical adduct as a side product.⁸³

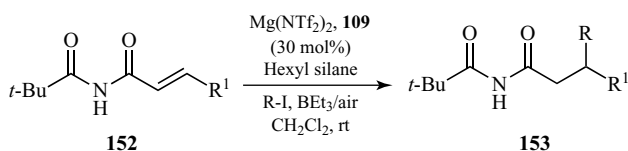
3.3.4 Fragmentations

Fragmentation reactions involve the addition of radicals to a neutral molecule followed by β -elimination from the resulting radical generating an olefin. Generally, allyl group transfer between electrophilic radicals and allylstannanes or allylsilanes has been



Scheme 32 Chiral Lewis acid-mediated reductive alkylation of an enone with a fixed *s*-cis geometry.

Table 19 The use of silanes in chiral Lewis acid-mediated radical reductive alkylation.



Entry	R	R ¹	Yield (%)	Prod/ethyl	ee (%)
1	Et	CH ₃	64	—	44
2	<i>i</i> -Pr	CH ₃	73	10/1	83
3	<i>t</i> -Bu	CH ₃	81	>50/1	85
4	<i>c</i> -Hexyl	CH ₃	60	2/1	70
5	(CH ₃) ₂ C(CH ₂) ₃ Cl	CH ₃	95	99:1	82
6	<i>t</i> -Bu	C ₆ H ₅	71	>50/1	91
7	<i>t</i> -Bu	4-Cl-C ₆ H ₄	89	>50/1	94
8	<i>t</i> -Bu	4-Me-C ₆ H ₄	88	>50/1	90

used frequently in organic synthesis. Chiral Lewis acid-promoted asymmetric fragmentations have also attracted attention. Porter *et al.*⁸⁴ reported highly enantioselective radical transformations involving reaction of α -halo oxazolidinones with allylsilanes using a chiral Lewis acid derived from MgI_2 or $\text{Zn}(\text{OTf})_2$ and a bisoxazoline ligand. Reaction of α -bromoacyl oxazolidinone **154** with allylstannane or allylsilane mediated by a bidentate chiral Lewis acid proceeded smoothly in good chemical yield to furnish the allylated product **155** in $\sim 90\%$ ee. With respect to enantioselectivity, allylsilanes worked better than allylstannanes in this particular reaction

for both substrates **154a** and **154b** (compare entries 1 and 3 with the entries 2, 4, and 5) (Table 20).

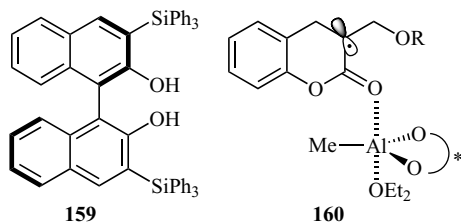
Chiral Lewis acid-mediated fragmentation has also been used to construct all carbon chiral quaternary centers. Hoshino and coworkers evaluated different chiral Lewis acids for radical allylation of α -substituted- α -iodolactones **156** and **157** using allylstannane.⁸⁵ As shown in Table 21, a chiral aluminum Lewis acid prepared from trimethylaluminum and ligand **159** could activate the substrates to provide the desired allylated products **158** in good yields with 27 and 3% ee, respectively. It was found that addition of diethyl ether (1 equiv with

Table 20 Chiral Lewis acid-mediated fragmentation.

Entry	R ¹	Mx ₂	Z	Yield (%)	ee (%)
1	154a , Me	Zn(OTf) ₂	SnBu ₃	84	42 (<i>S</i>)
2	154a , Me	Zn(OTf) ₂	Si(OEt) ₃	65	60 (<i>S</i>)
3	154b , <i>t</i> -Bu	Zn(OTf) ₂	SnBu ₃	63	74 (<i>R</i>)
4	154b , <i>t</i> -Bu	Zn(OTf) ₂	SiMe ₃	88	90 (<i>R</i>)
5	154b , <i>t</i> -Bu	MgI ₂	SiMe ₃	86	68 (<i>S</i>)

Table 21 Installation of chiral quaternary center by radical fragmentation reaction.

Entry	R	Me ₃ Al + 159 (equiv)	Additive	Yield (%)	ee (%)
1	Me, 156	1.0	—	72	27 (<i>R</i>)
2	Me, 156	1.0	Et ₂ O	84	81 (<i>R</i>)
3	CH ₂ OBn, 157	1.0	—	72	3 (<i>S</i>)
4	CH ₂ OBn, 157	1.0	Et ₂ O	76	91 (<i>R</i>)
5	CH ₂ OBn, 157	0.2	Et ₂ O	73	82 (<i>R</i>)



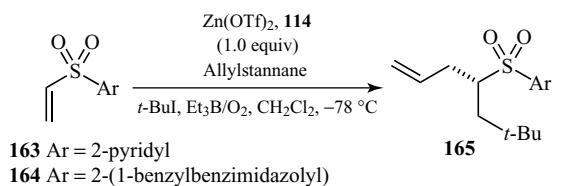
respect to Lewis acid and ligand) led to a dramatic increase in enantioselectivity to 81 and 92% for both substrates. More significantly, the catalyst loading could be lowered to 20 mol% without significant erosion in enantioselectivity. A single-point bonding model between lactone carbonyl oxygen and chiral aluminum Lewis acid was proposed to account for the selectivity, where aluminum exists as a five-coordination complex.

Table 22 Chiral Lewis acid-mediated radical conjugate addition/fragmentation.

Entry	R (equiv)	161 : M : L*	Yield (%)	ee (%)
1	<i>c</i> -Hexyl (1.5)	1 : 1 : 1.2	62	68 (<i>R</i>)
2	<i>t</i> -Butyl (5.0)	1 : 1 : 1.2	92	90 (<i>R</i>)

3.3.5 Tandem Radical Conjugate Addition–Fragmentation Reactions

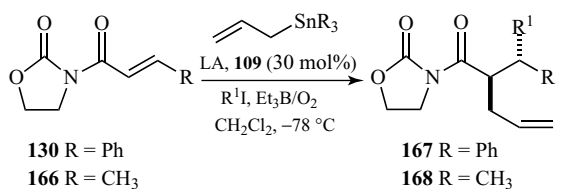
α -Acyl radicals are generally used for fragmentation reactions to access allylated products because of their electrophilicity. α -Acyl radicals can be generated not only from α -halo carbonyl compounds but also from radical conjugate additions to α,β -unsaturated carbonyl compounds. Porter and coworkers reported the first chiral Lewis acid-mediated asymmetric radical conjugate addition–fragmentation reaction (Table 22).⁸⁶ Radical addition to oxazolidinone acrylate **161** in the presence of Zn(OTf)₂/ligand **114** and allylstannane leads to the formation of the allylated product **162** in good yield and selectivity. This reaction shows strong solvent effect and a mixture of dichloromethane and pentane (4:6) proved to be the best solvent. For reaction with *t*-butyl radical, enantioselectivity as high as 90% ee could be obtained.

Table 23 Chiral Lewis acid-mediated radical conjugate addition/fragmentation with α,β -unsaturated sulfones.

Entry	Substrate	Allylstannane	Yield (%)	ee (%)
1	163	AllylBu ₃ Sn	36	46
2	164	AllylBu ₃ Sn	35	80
3	163	AllylBu ₃ Sn	82	50
4	164	AllylBu ₃ Sn	49	16
5	163	Allyl ₄ Sn	87	51
6	164	Allyl ₂ Bu ₂ Sn	74	50
7	164	Allyl ₂ Bu ₂ Sn	86	78
8	164	Allyl ₂ Bu ₂ Sn	80	84

Toru and coworkers investigated tandem radical addition–fragmentation reactions using α,β -unsaturated sulfones **163** and **164** attached to a pyridyl and benzimidazol template, respectively, to furnish **165** (Table 23).⁸⁷ The results showed that diallyldibutylstannane was the best allylation reagent for this fragmentation reaction. Reaction with benzimidazol sulfone **164** gave better enantioselectivity (up to 84% ee). Drawbacks to this reaction was the need for stoichiometric amount of the chiral Lewis acid and a large excess of stannane (10 equiv).

Using chiral Lewis acid-mediated radical addition/trapping strategy, Sibi and Chen⁸⁸ examined

Table 24 Chiral Lewis acid-mediated radical conjugate addition/fragmentation to construct two contiguous stereocenters.

Entry	Substrate	LA 0.3 equiv	R ¹	Yield (%)	dr	ee (%)
1	130	MgI ₂	Et	79	32 : 1	77
2	130	MgI ₂	<i>i</i> -Pr	93	37 : 1	93
3	130	MgI ₂	<i>t</i> -Bu	84	99 : 1	97
4 ^a	130	Cu(OTf) ₂	<i>t</i> -Bu	90	99 : 1	–96
5	166	Mg(ClO ₄) ₂	<i>c</i> -Hexyl	83	4 : 1	62

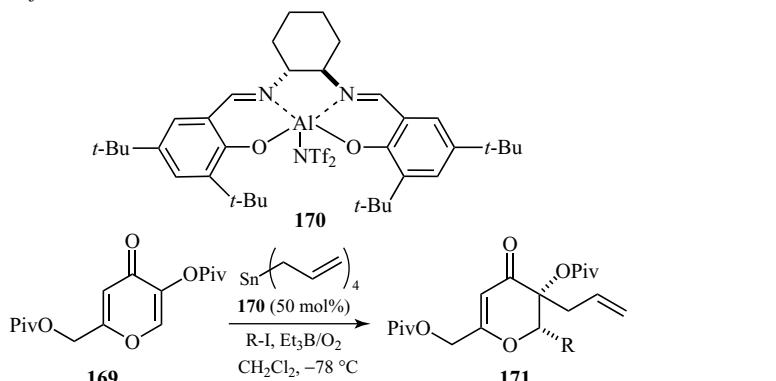
^a Allyltriphenyltin was used.

the potential for establishing two contiguous chiral centers with control over relative and absolute stereochemistry of the product (Table 24). Radical addition to **130** or **166** mediated by a chiral Lewis acid followed by allylation gave the corresponding radical adducts **167–168** with good to excellent enantioselectivities with predominant *anti*-stereochemistry. Enantiomeric products could be obtained by a simple change in the Lewis acid from magnesium to copper, while using the same ligand **109**.

The kojic acid derivatives discussed earlier are also excellent substrates for radical addition–fragmentation reactions. Sibi and Zimmerman⁸⁰ have evaluated radical addition/allylation to substrate **169** using salen-Al **170** as the chiral Lewis acid. Two contiguous stereocenters are established in one operation with one of them a quaternary center (Table 25). Catalyst modification with counter ion exchange from Cl to NTf₂ was required for successful execution of the reaction. The enantioselectivities are modest and similar to what was observed for reductive alkylation discussed earlier.

3.4 Organocatalysis in Radical Reactions

Organocatalysis, the use of small organic molecules to catalyze organic transformations, is relatively new and a very popular field within the domain of chiral molecule synthesis. Compared to well-established branches of catalysis (enzyme catalysis, Lewis acid catalysis, and organometallic catalysis), organocatalysis has some advantages. First, organic molecules are generally insensitive to oxygen and moisture in the atmosphere and there is no need to use special techniques to carry out the reactions. Second, a wide variety of organic reagents, such as amino acids, carbohydrates, and hydroxy acids, are available as single isomers from natural sources, and therefore, they are usually cheap and readily accessible. Third, small organic molecules are typically nontoxic and environment friendly. Several different types of organocatalyses have been developed, which includes enamine catalysis, hydrogen bonding catalysis, iminium ion catalysis, and counterion catalysts.⁸⁹ Organocatalysis for asymmetric free radical reactions is still in its infancy, although the future holds a lot of promise. Only a few examples have appeared in this area.

Table 25 Chiral Lewis acid-mediated radical conjugate addition/fragmentation of kojic acid derivatives.


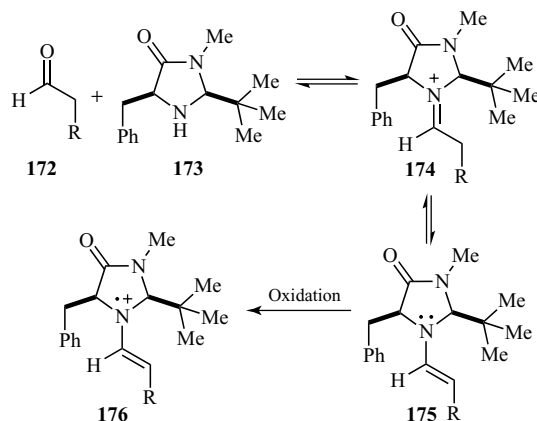
Entry	R	Yield (%)	dr	ee (%)
1	<i>i</i> -Pr	77	99 : 1	70
2	<i>c</i> -Pentyl	90	99 : 1	69

3.4.1 Organocatalysis

In 2007, MacMillan's group introduced a new concept called *SOMO catalysis*, which is based on one-electron oxidation of an electron-rich enamine. For example, reaction of aldehyde **172** with the chiral imidazolidinone **173** furnishes the enamine **175** via the iminium ion **174**. The enamine undergoes an oxidation to generate a reactive radical cation **176** with three π -electrons (Scheme 33). The electrophilicity of the SOMO of this radical intermediate allows it to react readily with a variety of weakly nucleophilic "SOMOphiles" at the α -position of the parent enamine.⁹⁰

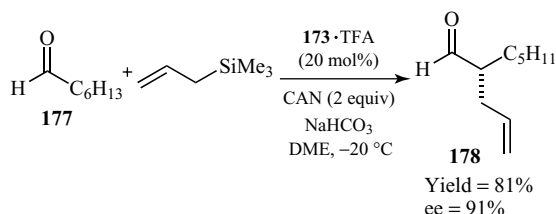
The SOMO catalysis was demonstrated by an allylation reaction using allyltrimethylsilane as the SOMO nucleophile. As shown in Scheme 34, treatment of aldehyde **177** with 20 mol% imidazolidinone catalyst **173** and 2 equiv of ceric ammonium nitrate as the oxidant, gave (*R*)-2-allyl-octanal **178** with excellent level of enantioinduction and in good yield (91% ee, 81% yield). Moreover, a variety of chemical functionalities were inert under this oxidative condition, including olefins, ketones, esters, and carbamates.

Sibi and Hasegawa⁹¹ independently reported another example of organocatalysis in radical chemistry (Scheme 35). In this study, commercially available stable radical TEMPO was used to trap the radical intermediate formed through oxidation

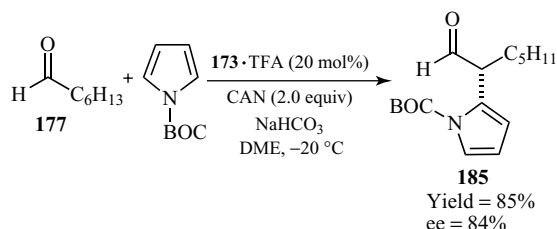
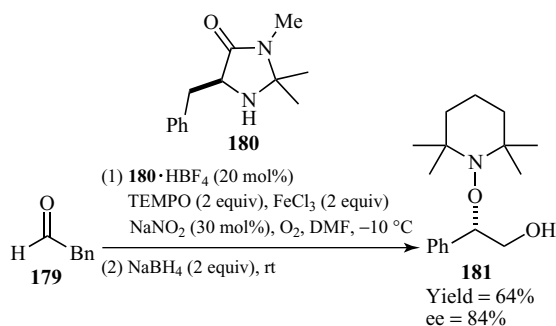
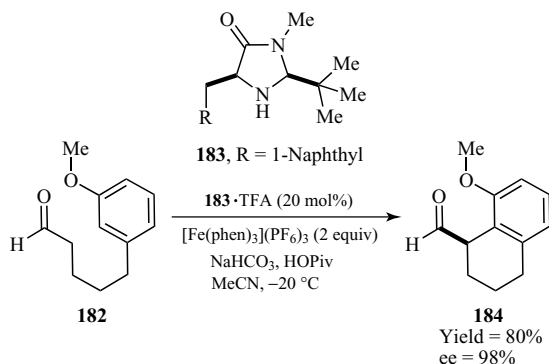
**Scheme 33** Radical reactions with organic catalysts.

of enamine prepared from aldehyde **179** and imidazolidinone catalyst **180**. High enantioselectivity for the α -oxyamination alcohol product **181** was obtained in good yield and high enantioselectivity after reduction of the intermediate aldehyde with NaBH₄. The reactions proceeded with good enantioselectivity with a variety of aldehydes. Furthermore, the authors demonstrated the use of catalytic amount of the SET reagent using a co-oxidant (NaNO₂/O₂) without compromising yield and selectivity.

MacMillan and coworkers and Nicolaou *et al.* independently demonstrated asymmetric α -arylation



Scheme 34 Enantioselective allylation via SOMO catalysis.

Scheme 37 Intermolecular α -arylation using SOMO catalysis.Scheme 35 Enantioselective α -oxyamination of aldehyde.Scheme 36 Intramolecular α -arylation using SOMO catalysis.

of aldehydes via SOMO catalysis.^{92–94} As shown in Scheme 36, in the presence of imidazolidinone catalyst **183** and 2.5 equiv of the oxidant $[\text{Fe}(\text{phen})_3]\text{PF}_6$, aryl-tethered aldehyde **182** underwent the designed cyclization process smoothly and gave formyl α -arylation product **184** in 80% yield with excellent enantioselectivity (98% ee). Moreover, a wide variety of aryl and heteroaryl ring systems were applicable in this intramolecular

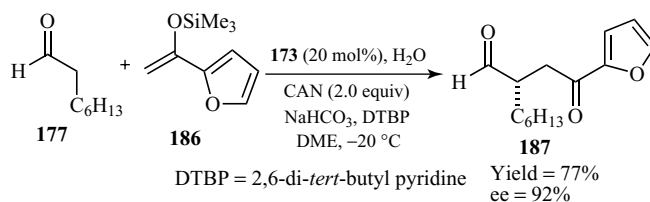
α -aldehyde arylation reaction. For example, anisole, naphthalene, indole, pyrrole, thiophene, and furan ring systems all function well in the ring-forming reaction.

An intermolecular arylation between aldehyde **177** and pyrrole mediated by catalyst **173** was also reported by MacMillan's group.⁹⁰ The reaction proceeds in good yield and selectivity to furnish the arylated product **185** (Scheme 37).

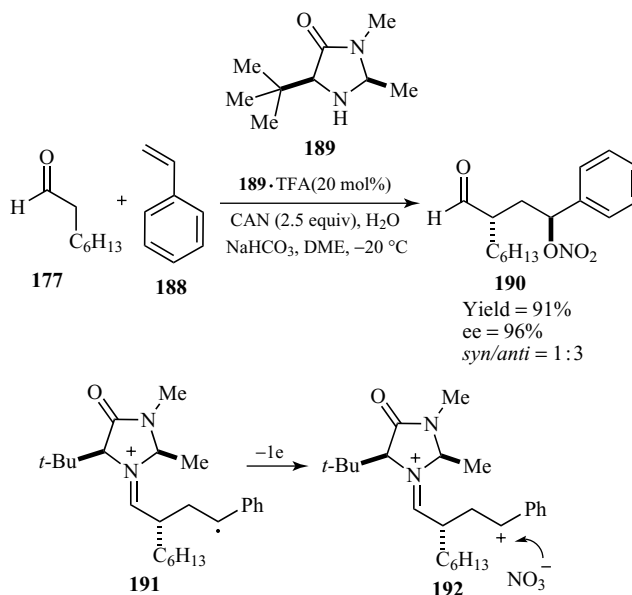
π -Rich enolsilanes are excellent reagents as “SOMOphiles” in another designed reaction from the MacMillan group that provides access to enantioenriched γ -ketoaldehydes from simple aldehydes (Scheme 38).⁹⁵ Reaction of aldehyde **177** with enol silane **186** using catalyst **173** gave the 1,4-dicarbonyl product **187**. The reaction shows broad scope for both the aldehyde and the enolsilane components.

The 3π -electron radical cation obtained after oxidation of enamines could also be trapped by simple styrene derivatives (Scheme 39). In this reaction, radical addition derived from **177** and **189** to styrene **188** results in a stable benzyl radical (**191**). A cationic intermediate (**192**) is formed after a second SET process. This is trapped by NO_3^- in the reaction mixture to form α -alkyl- γ -nitrate-aldehyde **190** as the product. The reaction described in Scheme 39 showed high enantioselectivity (96% ee) and moderate diastereoselectivity (*syn/anti* = 1 : 3) for the product aldehyde. Furthermore, β -substituted styrene was a competent substrate for SOMO catalysis resulting in the formation of a product with three stereogenic centers.⁹⁶

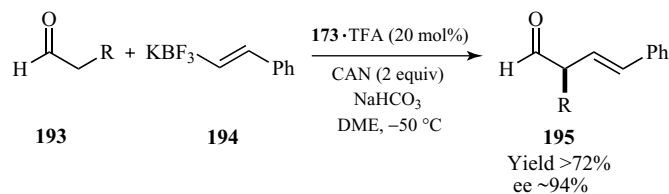
MacMillan and coworkers have developed a process that provides access to enantioenriched α -vinyl aldehydes. The process involves reaction of an aldehyde **193** with an (*E*)-alkene containing vinyl trifluoroborate salt **194**. The reaction is mediated by an imidazolidinone catalyst and an



Scheme 38 Synthesis of 1,4-dicarbonyl compounds via SOMO catalysis.



Scheme 39 Radical reaction with styrenes via SOMO catalysis.

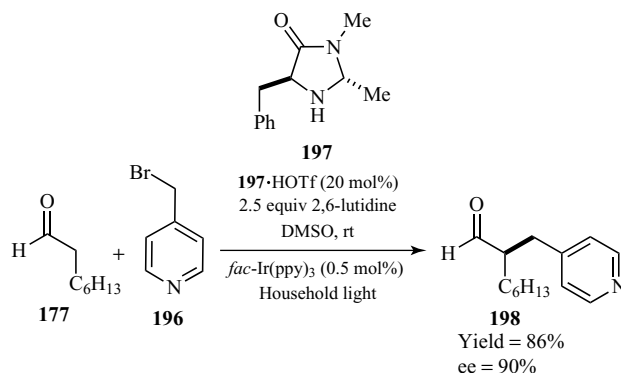


Scheme 40 α-Vinylation of aldehydes via SOMO catalysis.

oxidant. The product α-vinyl aldehydes **195** are formed in high enantioselectivity as *E*-isomers only (Scheme 40).⁹⁸ More importantly, epimerization and olefin isomerization to an α,β-unsaturated product were not observed under the reaction conditions. A wide variety of aldehydes and alkene components have been examined and enantioselectivities for all these cases were in the range of 89–96%.

MacMillan's group has also investigated the possibility of asymmetric trapping of electrophilic

benzyl radicals with a chiral enamine derived from aldehydes and a chiral amine catalyst (Scheme 41).⁹⁸ In this study, commercially available photocatalyst *fac*-Ir^{III}(ppy)₃ was used to generate benzyl radicals through an SET process using household fluorescent light (see **Synthetic Radical Photochemistry**). The benzyl radical adds to the chiral enamine to form an α-amino radical. The product *fac*-Ir^{IV}(ppy)₃ species formed after the first SET process functions as

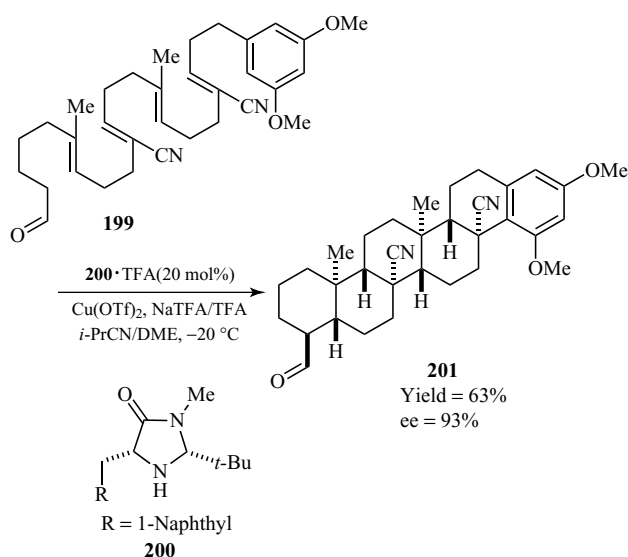


Scheme 41 α -Benzylation of aldehydes via SOMO catalysis.

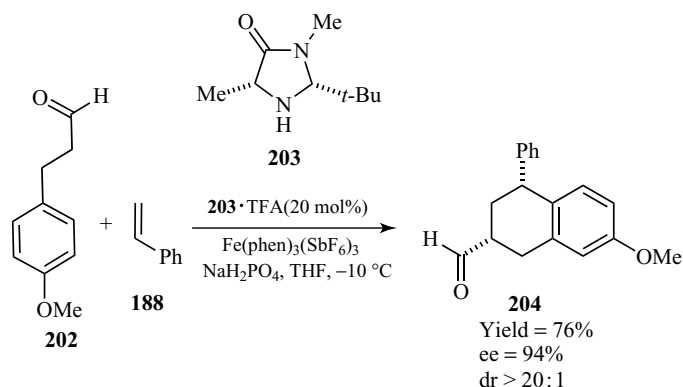
a reductant and transforms the α -amino radical intermediate to an iminium intermediate by a second SET process. This results in recovery of the photocatalyst. The iminium intermediate is hydrolyzed to the product. As shown in Scheme 41, in the presence of a modified imidazolidinone catalyst **197** and photocatalyst *fac*-Ir^{III}(ppy)₃, aldehyde **177** reacts smoothly with 4-(bromomethyl)pyridine to give **198** in high enantioselectivity (90% ee) and high yield. Further investigation showed that electron-deficient aryl and heteroaryl substrates were effective under the same conditions leading to a variety of enantioenriched α -benzylated aldehydes.

Tandem reactions have also been investigated using SOMO catalysis. Using this methodology, multiple bonds can be formed efficiently in an asymmetric manner leading to polycycles. As an example, MacMillan and coworkers reported the cyclization of an unsaturated aldehyde **199** under SOMO catalysis conditions using catalyst **200**. In this reaction, nine contiguous stereocenters are formed in one step including four all-carbon quaternary stereocenters to furnish **201** in 93% ee and excellent yield (Scheme 42).⁹⁹

A highly selective, radical-mediated (4 + 2) coupling of aldehydes and conjugated olefins has also been achieved through asymmetric SOMO catalysis



Scheme 42 Polycyclic product formation via SOMO catalysis.

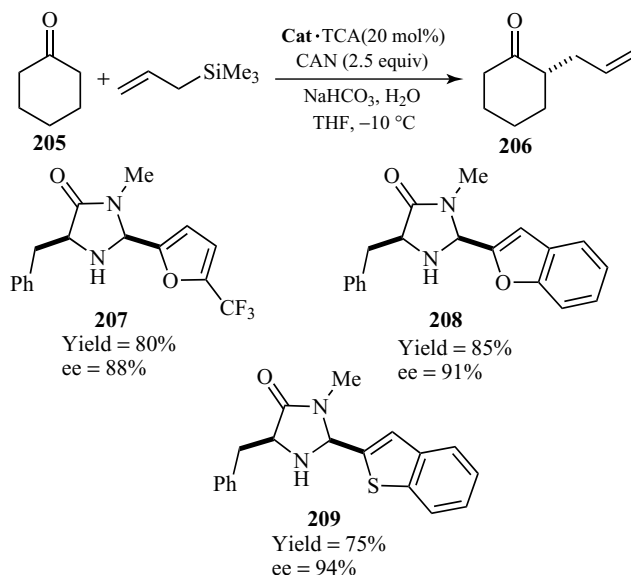


Scheme 43 Cascade cycloaddition via SOMO catalysis.

(Scheme 43).¹⁰⁰ A radical polar crossover mechanism was proposed wherein olefin addition to transient enamine radical cation and oxidation of the resulting radical furnishes a cation, which is vulnerable to nucleophilic addition. A variety of aromatic aldehydes (**202**) couple to styrenes and dienes to provide cyclic products (**204**) with high chemical efficiency, regioselectivity, and stereoselectivity.

Compared to aldehydes, ketones show lower reactivity under SOMO catalysis. Most of the widely used imidazolidinone catalysts decompose under

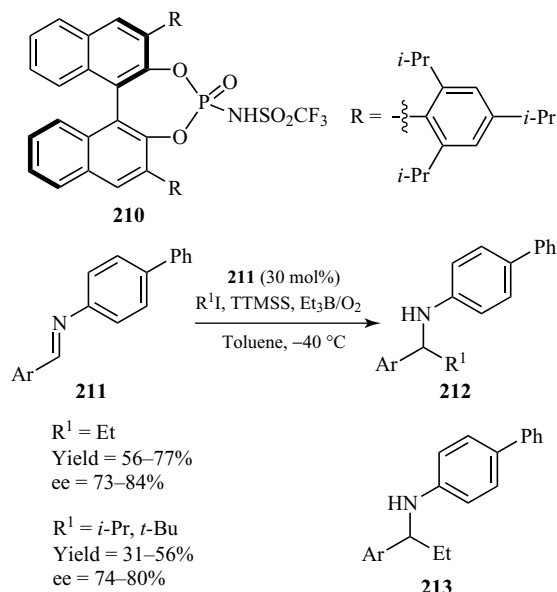
oxidative conditions when used in conjunction with ketone substrates. Newly designed imidazolidinone catalysts **207**, **208**, and **209** proved to be stable under oxidative conditions and could be used for reactions with ketones (Scheme 44).¹⁰¹ Using allyltrimethylsilane as the alkylation reagent, allylation of cyclohexanone **205** proceeded enantioselectively in good yield and selectivity to furnish **206** (74–80 and 88–94% ee). Moreover, these new catalysts could also be used in α -enolization and α -homobenzoylation of cyclohexanone in good enantioselectivities.



Scheme 44 Allylation of cyclohexanone via SOMO catalysis.

3.4.2 Chiral Brønsted Acid Catalysis in Radical Reactions

Recently, chiral BINOL-based phosphoric acid analogues **210** have been explored as organocatalysts in a wide variety of synthetic transformations.¹⁰² Among all these types of reactions catalyzed by chiral phosphoric acids, 1,2-addition of nucleophiles to imines has received greater attention from synthetic chemists.¹⁰³ Lee and Kim have investigated reductive radical additions to imine using chiral Brønsted acids as catalysts (Scheme 45).¹⁰⁴ In this study, nontin reagent TTMSS was chosen as radical chain carrier and hydrogen atom source. Phosphoramidate **210** proved to be the optimal catalyst for the radical addition. Under standard radical reaction conditions, primary, secondary, and tertiary alkyl radicals derived from the corresponding alkyl iodides gave 1,2-addition products **212–213** with imine substrate **211**. Although the enantioselectivities were good to high (73–84% ee) for all the reactions, secondary and tertiary alkyl radicals gave low yields and a byproduct from ethyl radical addition was also observed.



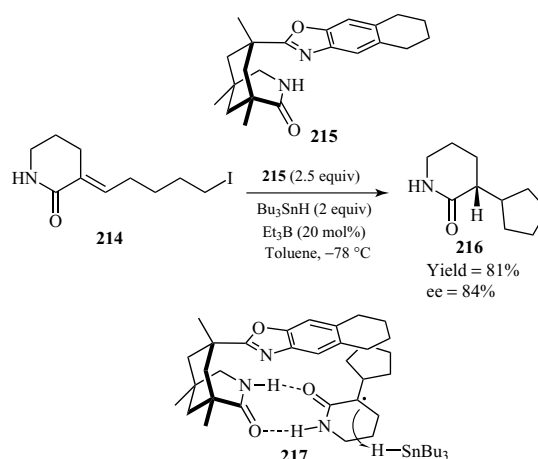
Scheme 45 Chiral Brønsted acid-catalyzed radical addition to imine.

3.4.3 Hydrogen Bonding Catalysis in Radical Reactions

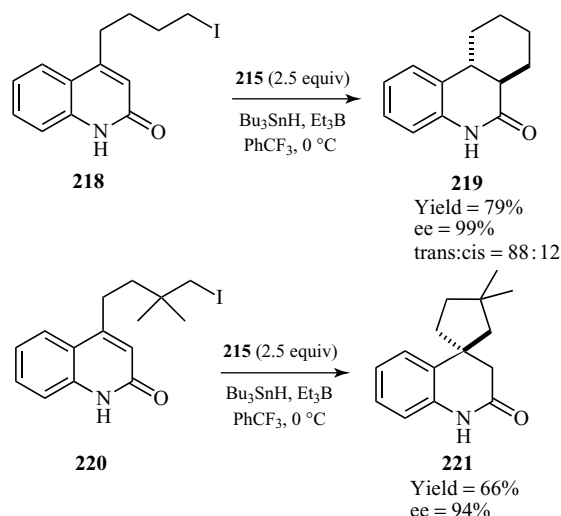
In 2004, Bach and coworkers reported the earliest example of a radical reaction using an organic activator. The reaction was an intramolecular radical cyclization followed by enantioselective hydrogen atom transfer mediated by a H-bonding catalyst **215** (Scheme 46).¹⁰⁵ The enantioselectivity for the reductive cyclization of 3-(ω -iodoalkylidene)piperidin-2-ones (**214**) was investigated and the observed selectivity for **216** could reach as high as 84% at -78°C . It should be noted that lower amounts of radical initiator (Et_3B) gave improved enantioselectivities and a large excess of the chiral source **215** (2.5 equiv) was necessary to obtain selectivity. The observed stereochemistry was explained using a model shown in **217**, where the substrate and the chiral reagent form two hydrogen bonds and provide an organized structure for selective H-atom transfer.

Organocatalyst **215** was also used to investigate radical cyclization of 4-(4'-iodobutyl)quinolinone **218** and **220** under similar conditions as described above.¹⁰⁶ When 2.5 equiv of the catalyst **215** was

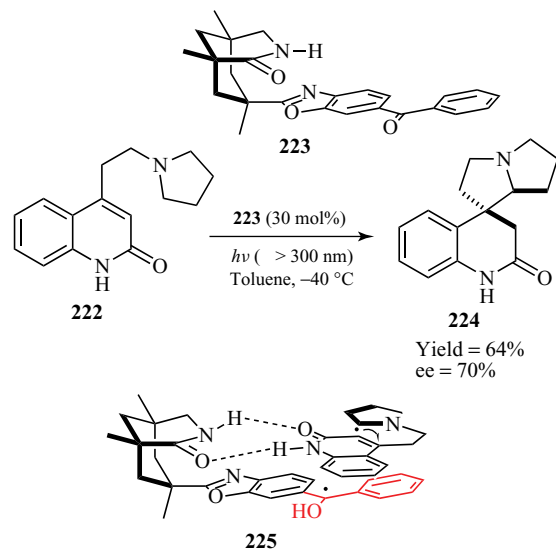
used, reaction of **218** gave the 6-endo product **219** in good yield and excellent selectivity (99% ee). Interestingly, cyclization of **220** substituted with a *gem*-dimethyl group gave the spirocyclic 5-*exo* product **221** exclusively in good yield and with high enantioselectivity (94% ee).



Scheme 46 Hydrogen bond-mediated asymmetric radical reaction.



Scheme 47 Asymmetric cyclization of 4-(4'-iodobutyl) quinolinones.



Scheme 48 Enantioselective photochemical radical cyclization.

Bach and coworkers modified the hydrogen bonding catalyst **215** and incorporated a benzoyl group that could function as a photon acceptor and evaluated it in radical cyclizations. Ultraviolet irradiation of a mixture of substrate **222** and catalyst **223** induced an electron transfer from the amine to the photoexcited catalyst.¹⁰⁷ Subsequent loss of a

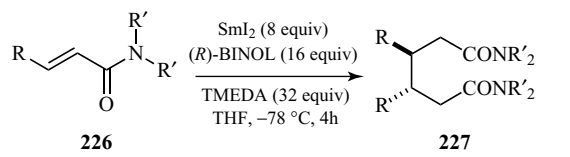
proton from the intermediate radical cation presumably led to an α -aminoalkyl radical, which added intramolecularly to C-4 of the quinolone substrate furnishing **224** (Scheme 48). The reaction gave 70% enantioselectivity and ~64% yield using substoichiometric amount of the catalyst. A stereochemical model for the reaction is shown in **225**.

3.5 Chiral Ligand-Assisted Asymmetric Electron Transfer Reactions

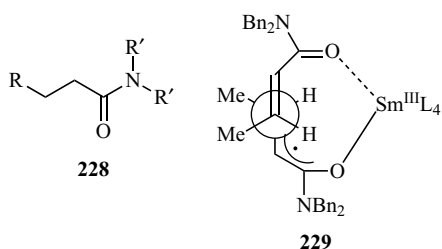
3.5.1 Samarium-Mediated Asymmetric Radical Reactions

Samarium iodide is a versatile reagent that is extensively used in radical chemistry (see **Organic Synthesis Using Samarium Diiodide**). Samarium iodide or samarium metal are excellent SET reagents. There are multiple reviews on the use of samarium iodide in radical reactions.^{108–110} As mentioned before, after SET process, the newly formed samarium(III) species has Lewis acidity that could affect diastereoselectivity in radical reactions. In principle, chirality could be achieved using a chiral ligand in samarium-mediated radical process. Ketyl radicals generated using samarium(II) iodide have found applications in asymmetric transformations. Inanaga and coworkers have applied chiral samarium(II) complex, derived from SmI_2 and (*R*)-BINOL, to promote reductive homo-coupling reaction of β -monosubstituted acrylic acid amides **226** to give the corresponding 3,4-*trans* disubstituted adipamides **227** in high enantioselectivities (up to 85% ee). The yield of **227** in this transformation was rather low and was accompanied by a byproduct **228**. Excess amount of SmI_2 and the chiral ligand were required for obtaining high selectivity.¹¹¹ A model **229** that accounts for the observed selectivity has been proposed (Table 26).

Mikami and Yamaoka¹¹² have investigated asymmetric addition of ketyl radicals to olefins. As shown in Table 27, SmI_2 -mediated reductive coupling of ketones **230** with α,β -unsaturated esters **231** proceeded enantioselectively using 2 equiv of (*R*)-BINAPO **232** as the chiral ligand. The products **233** were formed in good enantioselectivity, but the chemical efficiency was low (<50% yield).

Table 26 Hydrodimerization through ketyl radicals.


Entry	R	R'	Yield (%)	ee (%)
1	Me	Bn	70	71 (+)
2	Et	Bn	45	82 (+)
3	<i>n</i> -Pr	Bn	35	82 (+)
4	BnCH ₂	Bn	20	85 (+)
5 ^a	Me	Ph	55	44 (-)

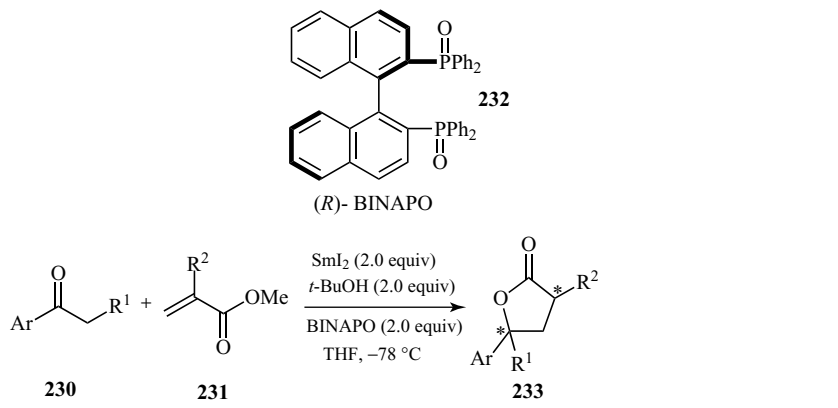
^a dl : meso = 63 : 37.

3.5.2 Titanium-Mediated Asymmetric Radical Reactions

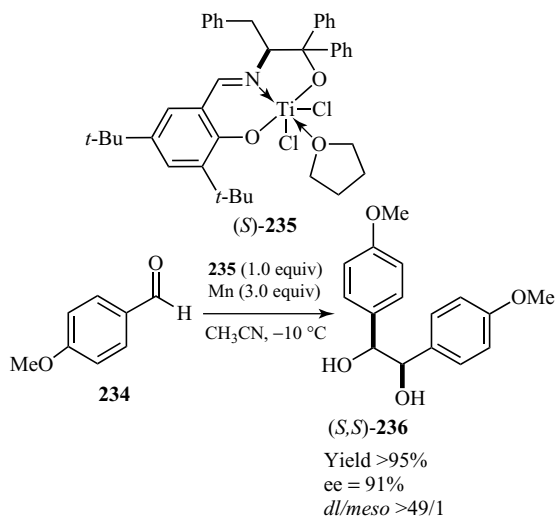
Titanium(III) catalysts are also good electron-transfer reagents to generate ketyl radicals

from carbonyl compounds. The enantioselective pinacol coupling of aldehydes has been achieved using a chiral titanium complex as the catalyst. Air-stable catalyst **235** derived from tridentate salen ligand and TiCl₄ could promote the pinacol coupling of *p*-methoxybenzaldehyde **234** to provide the diol **236** in high yield and selectivity (91% ee).¹¹³ A survey of reductants (Mn, Ce, SmI₂, and Zn) suggested manganese to be the ideal one for reactions at -10°C. Electron-deficient benzaldehydes gave poor enantiomeric excesses for the coupling products (Scheme 49).

Titanium(III) catalysts are also excellent electron transfer reagents in reactions with epoxides (see **Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**). The general procedure is to combine Ti(IV) with zinc metal to generate Ti(III) *in situ*, which coordinates to the epoxide and carries out an electron transfer to furnish an α -titanoxy radical. This radical intermediate could be reduced by trapping with hydrogen atom or allowed to react further with other radical acceptors. Gansäuer and coworkers have investigated ring-opening reactions of *meso*-epoxides using different chiral titanium catalysts.¹¹⁴ The results showed that *meso*-epoxide **237** in the presence of chiral titanium complex **239** or **240** underwent ring opening to give triol derivatives **238** in good yields and excellent enantioselectivities (74–94%). Importantly, the catalyst loading could

Table 27 Ketyl radical addition/cyclization.


Ar	R ¹	R ²	Yield (%)	cis : trans	ee (%) cis/trans
Ph	H	H	46		67
Ph	H	Me	42	66 : 34	89/55
Ph	Me	H	18		63



Scheme 49 Titanium-mediated pinacol formation.

be decreased to as low as 5% without impacting selectivity (Table 28).

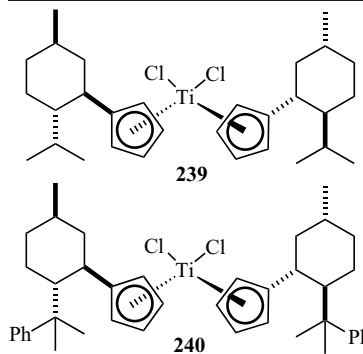
The same Ti(III) catalysts were also utilized in the ring opening of cyclic epoxides **241** followed by trapping of the intermediate radical with *t*-butyl acrylate **242** (Scheme 47). The *trans* : *cis* selectivities for the products were greater than 4 : 1 and good enantioselectivities for the *trans* isomer **243** was obtained. Ring size had minimal impact on selectivity (Table 29).¹¹⁵

3.5.3 Oxidative Coupling

SET takes place from metal to the organic substrate in samarium- and titanium-mediated radical

Table 28 Epoxide ring opening using titanocene catalysts.

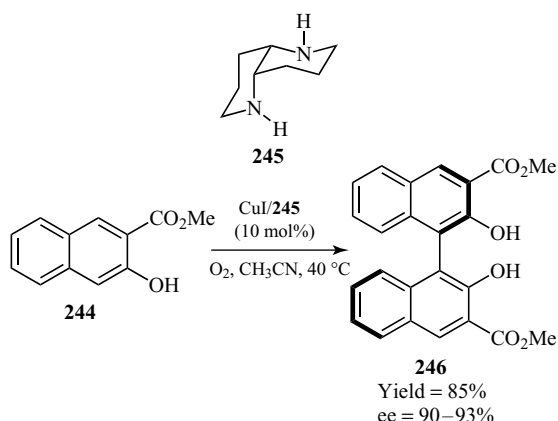
Entry	R	Catalyst	Yield (%)	ee (%)
1	Et	239	76	93
2	Et	240	72	94
3	<i>n</i> -Pr	240	60	92
4	<i>n</i> -Pr	239	70	91
5	<i>t</i> -Bu	240	68	74
6	<i>t</i> -Bu	239	66	86



reactions. The reverse scenario can also be used in radical reactions via oxidative generation of cationic radical species that can undergo coupling reaction. Asymmetric oxidative coupling has been achieved using a combination of metal with chiral ligands. For example, in the oxidative homo coupling (Scheme 50) of 2-naphthol derivative **244**, chiral 1,5-diaza-*cis*-decalin **245** proved to be an efficient ligand (Scheme 48). When CuI/O₂ was used as the oxidant, the corresponding BINOL derivative **246** could be obtained in high enantioselectivity

Table 29 Epoxide ring opening using titanocene catalysts followed by trapping with an α,β -unsaturated ester.

Entry	<i>n</i>	Catalyst	Yield (%)	ee (%)
1	1	240	69	74
2	1	239	72	81
3	2	240	61	82
4	3	240	65	82
5	3	239	78	80



Scheme 50 Asymmetric oxidative homo coupling via SET process.

(up to 93% ee).^{116–118} Under these conditions, Cu(I) is oxidized to Cu(II) *in situ* due to the presence of oxygen and enters the catalytic cycle.

4 CONCLUSION

In the past 25 years, it is safe to say that radical chemistry has reached its potential and can now compete effectively with ionic chemistry for the installation of C–C and C–X bonds with high enantioselectivity. Radical reactions generally proceed under neutral conditions and show a large functional group tolerance. The need for protecting groups is also minimized during radical reactions. A variety of chiral activators have been utilized for installing stereochemistry in radical reactions. Enantioselective radical reactions mediated by chiral Lewis acids still suffer from large catalyst loading and the need for toxic tin reagents. Organocatalysts have made a significant impact on enantioselective radical chemistry and a good fraction of them can be considered ecofriendly. The future looks very promising for the development of efficient and highly selective radical reactions using a variety of chiral activators with low catalyst loading.

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FURTHER READING

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Boron in Radical Chemistry

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1 INTRODUCTION

The tremendous development of radical chemistry has been triggered by the unique properties of tin derivatives that allow the design of a wide range of efficient chain reactions. However, application of this chemistry is severely hampered by the toxicity of triorganotin derivatives. The ability of organoboron compounds to participate in free-radical reactions has been identified since the earliest investigation of their chemistry.¹ Taming the radical reactivity of organoboranes was a slow process but, eventually, it led to an extremely valuable alternative to tin chemistry for a wide range of reactions. The low toxicity of boric acid derivatives that are usually formed at the end of the processes makes this chemistry particularly promising for synthesis and industrial applications can be envisaged. The distinctive properties of boron derivatives make them suitable for the achievement of some unique transformations. The use of organoboranes in radical reactions has been reviewed at several occasions in recent time.^{2–4} This article mainly focuses on recent developments but basic principles and key discoveries are briefly described to give a general picture of the field.

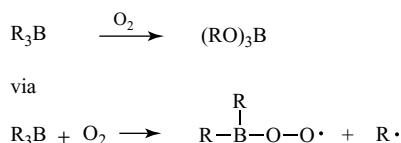
2 REACTIVITY OF ORGANOBORANES

The autoxidation of organoboranes (Scheme 1) is known for a long time to involve radical intermediates.^{5–7} This observation led to the use

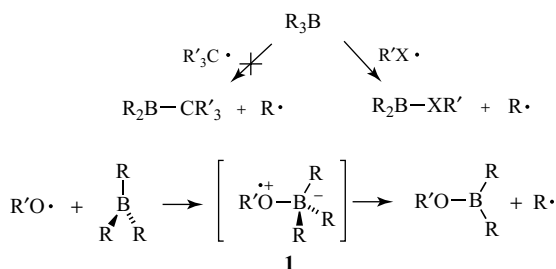
of triethylborane as a universal radical initiator operative under a very wide range of reaction conditions (temperature and solvent).^{8,9}

Interestingly, homolytic substitution at boron does not proceed with carbon-centered radicals.¹⁰ However, many different types of heteroatom-centered radicals, for example, alkoxyl radicals, react efficiently with organoboranes (Scheme 2).

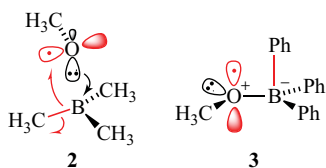
Bimolecular homolytic attack by free radicals at boron centers were extensively studied three decades ago.^{11–14} In a typical S_H2 reaction, an oxygen radical may displace an alkyl radical, as shown in Scheme 2. Species **1** has never been observed when R is aliphatic. However, it has been detected in the case of aromatic systems; the intermediate was identified by using laser flash photolysis techniques.¹⁵ Recently, Scaiano reported a theoretical investigation on the reaction mechanism for oxygen-centered radical attack on alkyl- and arylboranes.¹⁶ The model reveals how the mechanism, traditionally considered as an S_H2 reaction, involves instead nucleophilic attack of the oxygen lone pair on the empty boron p orbital. The single electron on the oxygen is not directly involved in the process. However, as a result of a stereoelectronic effect, the bond aligned with the singly occupied molecular orbital (SOMO) is deactivated and the corresponding ligand leaves promptly as a radical species. The overall mechanism can be described as a nucleohomolytic reaction that shares many characteristics with conventional nucleophilic substitution (Scheme 3, model **2**). In the case of triphenylborane, the intermediate **3** was located by DFT calculations



Scheme 1 Autoxidation of organoboranes.



Scheme 2 Reactivity of trialkylboranes toward carbon- and heteroatom-centered radicals.



Scheme 3 Proposed transition state (**2**) and intermediate (**3**) in the homolytic substitution of trimethylborane and triphenylborane by a methoxyl radical.

in agreement with experimental observations.¹⁵ The geometry at the boron center is a distorted tetrahedron, with a trigonal pyramidal component, because of the slightly stretched bond of the leaving phenyl group.

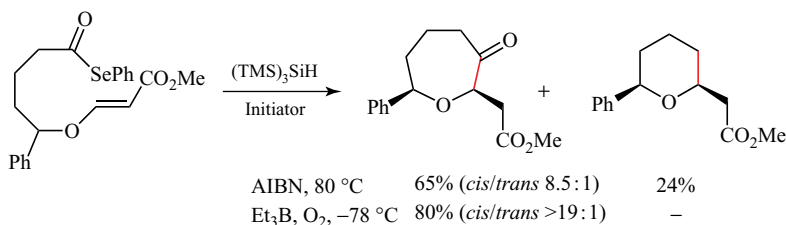
3 ORGANOBORANES AS RADICAL INITIATORS

Utimoto and Oshima were the first to apply the reaction of triethylborane with oxygen to initiate radical reactions (see **Overview of Radical Initiation**).^{8,17} The system Et₃B–O₂ offers over classical initiators the great advantage of being efficient even at low temperature (–78 °C). This aspect proved to be particularly important for the development of stereoselective radical reactions and for radical reactions involving thermally unstable adducts or products. Review articles describing the use of triethylborane as a radical initiator have appeared.^{3,9} A few selected examples, mainly from recent publications, are presented to highlight the borane initiation procedure. The use of trialkylboranes, such as tributylborane, is of growing importance in the field of polymer chemistry.¹⁸ Applications in unexpected fields, such as dental adhesives, have been reported.¹⁹

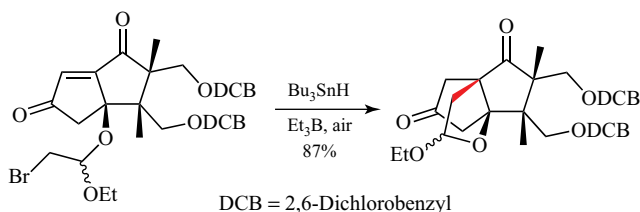
3.1 Reduction of Halides and Related Compounds

Evans reported the cyclization of acyl radicals to vinylogous carbonates in the presence of (TMS)₃SiH (TMS = Me₃Si). By using Et₃B–air initiation rather than azobisisobutyronitrile (AIBN), the *cis*-oxepanones are obtained in higher stereoselectivities and yields. Interestingly, the decarbonylation of the intermediate acyl radical is suppressed (Scheme 4).²⁰ Inoue and Hiram applied a similar acyl cyclization strategy using tributylgermanium hydride for the stereoselective preparation of polycyclic ethers related to ciguatoxin and brevetoxin.²¹

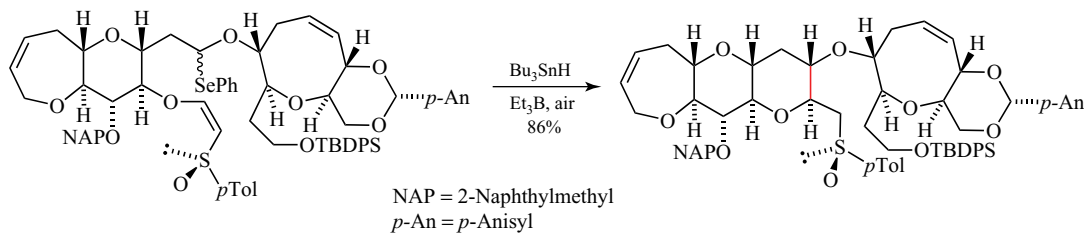
The use of acid-labile radical precursors is perfectly compatible with this initiation procedure



Scheme 4 Reductive cyclizations with silanes.



Scheme 5 Ueno–Stork cyclization involving an acid-sensitive allylic ether.



Scheme 6 Key cyclization in the synthesis of ciguatoxin CTX3C.

as shown by the Ueno–Stork cyclization used as a key step in the (+)-merrillactone synthesis of Inoue (Scheme 5).²²

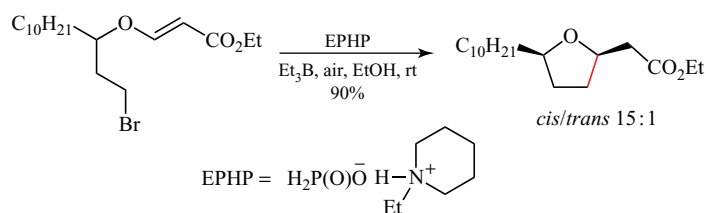
Another spectacular example of the efficiency of the Et_3B –air method is depicted in Scheme 6. This highly stereoselective cyclization of an O,Se-acetal is the key reaction of a practical synthesis of ciguatoxin CTX3C reported recently by Yamashita *et al.*²³

Interestingly, Et_3B –air initiation can be performed in aqueous solution.²⁴ A wide range of aryl and alkyl halides are reduced in water by water-soluble organosilanes using Et_3B –air initiation.²⁵ Tin-free radical reduction by organophosphites and phosphinic acid can also be initiated by Et_3B –air.²⁶ For instance, radical cyclizations using phosphinic acid neutralized with sodium carbonate and Et_3B –air as a radical initiator in aqueous ethanol are reported.²⁷ A similar stereoselective cyclization of a β -alkoxyacrylate with 1-ethylpiperidinium

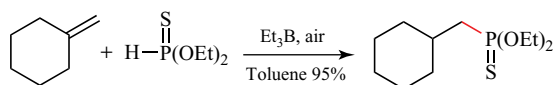
hypophosphite (EHP) at room temperature is described by Lee (Scheme 7).²⁸

3.2 Addition of RX-H to Alkenes and Alkynes

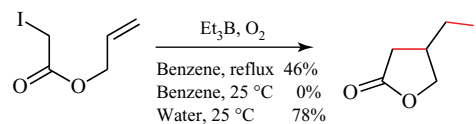
Tris(trimethylsilyl)silane (see **Silanes as Reducing Reagents in Radical Chemistry**),^{29,30} thiols,³¹ germanes,^{32–34} and gallium hydride³⁵ add easily to terminal alkynes in the presence of Et_3B –air.³⁶ The addition of hypophosphites to alkenes under Et_3B initiation is also reported.³⁷ Piettre described recently the addition of diethylthiophosphite to alkenes leading to the formation of thiophosphonates (Scheme 8).³⁸ Interestingly, this reaction can be used for cyclization of dienes and ring opening of strained alkenes such as α -pinene. Parson prepared an alkenylthiophosphonate by reaction of a chiral thiophosphite with phenylacetylene.³⁹



Scheme 7 Phosphinic-acid-mediated radical cyclization.



Scheme 8 Addition of diethylthiophosphite to alkenes.



Scheme 10 Lactone synthesis via iodine atom transfer, influence of water.

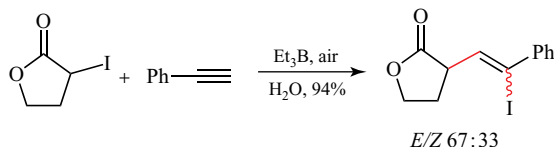
3.3 Atom-Transfer and Related Processes

3.3.1 Iodine Atom Transfer

Triethylborane proved to be a good initiator for iodine atom-transfer reactions (see **Halogen and Chalcogen Transfer Chemistry**).^{24,40,41} The ethyl radical, issued from the reaction of triethylborane with molecular oxygen, can abstract an iodine atom from the radical precursor to produce a radical $R^\bullet$ that enters into the chain process. The iodine exchange is fast and efficient when $R^\bullet$ is more stable than the ethyl radical. The efficiency of the whole process is also probably due to the high reactivity of Et_3B toward molecular iodine that results in an efficient removal of undesirable traces of I_2 in the reaction mixture. A similar effect has been put forward to explain the role of hexamethyl- and hexabutylditin in radical-mediated iodine atom transfer.⁴²

Et_3B -induced addition of perfluoroalkyl iodides,^{43,44} α -iodoesters,⁴⁵ α -iodoamides,⁴⁶ α -iodonitriles,⁴⁵ and simple alkyl iodides⁴⁷ to alkenes and alkynes are reported. Interestingly, these reactions are also performed with success in aqueous media^{24,48,49} demonstrating further the ability of Et_3B to act as an initiator in water (Scheme 9).⁵⁰

Triethylborane is also an excellent initiator for intramolecular iodine atom-transfer reactions. For example, cyclization of the propargyl α -iodoacetal gives the corresponding bicyclic vinyl iodide in high yield.⁴⁷ Allyliodoacetamide and allyliodoacetate (Scheme 10) cyclize cleanly under Et_3B -air initiation. In the case of the ester, the reaction has to be run in refluxing benzene in order to allow Z/E -ester isomerization before cyclization.^{51,52} No



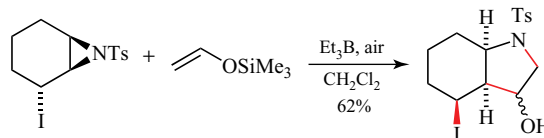
Scheme 9 Iodine atom transfer in water.

trace of cyclized product is detected when the reaction is carried out at room temperature. Interestingly, by running the same reaction in water, Oshima obtained the desired lactone in 78% yield.⁴⁸ It was suggested that water facilitates the Z/E isomerization. Efficient preparation of medium- and large-ring lactones in water is reported.^{48,49}

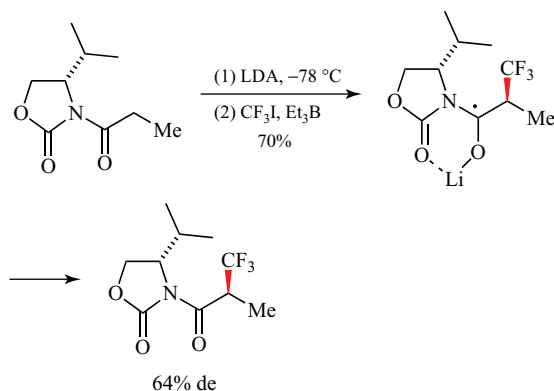
Examples of tandem intermolecular addition–cyclization under iodine atom-transfer conditions are reported.^{47,50} Et_3B -induced radical cascade reactions with 1,5-enynes and 1,5-dienes are applied to the synthesis of dioxatriquinanes and tricyclic glucoconjugates.^{53,54} Some of these elegant cascade cyclizations are performed under mild conditions at -50°C . Miyabe and Takemoto investigated the enantioselective formation of lactams by an addition–cyclization process involving hydroxamates and chiral Lewis acids.^{55,56}

Taguchi reported annulation reactions using acyclic and cyclic N -tosylated iodomethylaziridines.⁵⁷ The reaction with electron-rich alkenes, such as silylenol ethers, proceeds smoothly as illustrated in Scheme 11.

Silylenol ethers are also utilized as a trap for electrophilic radicals derived from α -haloesters⁴⁵ or perfluoroalkyl iodides.⁵⁸ They afford the α -alkylated ketones after acidic treatment of the intermediate silylenol ethers. Similarly, silyl ketene acetals are converted into α -perfluoroalkyl esters upon treatment with perfluoroalkyl iodides.^{58,59} The Et_3B -air initiated diastereoselective trifluoromethylation^{60,61} (Scheme 12) and (ethoxycarbonyl) difluoromethylation^{62,63} of lithium enolates derived from N -acyloxazolidinones were achieved. More recently,



Scheme 11 Preparation of pyrrolidine derivatives via annulation with iodomethylaziridine derivatives.



Scheme 12 Trifluoromethylation of a lithium enolate.

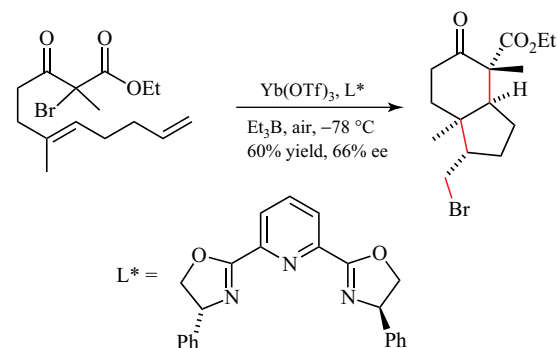
Mikami succeeded in the trifluoromethylation of ketone enolates.⁶⁴

3.3.2 Bromine Atom Transfer

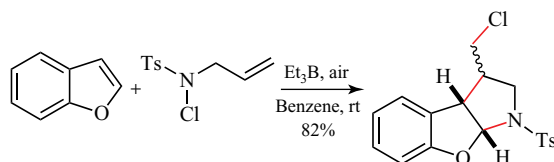
Bromides are less reactive than the corresponding iodides in atom-transfer processes (see **Halogen and Chalcogen Transfer Chemistry**). However, activated bromides such as diethyl bromomalonate⁴⁵ and bromomalonitrile react with olefins under Et_3B –air initiation.⁶⁵ Kharasch-type reactions of bromotrichloromethane with alkenes are also initiated by Et_3B –air.⁵⁰ A remarkable Lewis acid effect was reported by Porter. Atom-transfer reactions of an α -bromooxazolidinone amide with alkenes is strongly favored in the presence of Lewis acids such as $\text{Sc}(\text{OTf})_3$ or $\text{Yb}(\text{OTf})_3$; this reaction was employed for the diastereoselective alkylation of chiral oxazolidinone derivatives.⁶⁶ Yang reported a similar effect with bromomalonates⁶⁷ and was able to run an enantioselective cascade process involving a bromine atom transfer at -78°C (Scheme 13).⁶⁸ Interestingly, Oshima reported that bromine atom transfers take place at room temperature in ionic liquid media.⁶⁹

3.3.3 Chlorine Atom Transfer

Radical [3 + 2] annulation involving *N*-allyl-*N*-chlorotosylamide provides a route to pyrrolidine derivatives (Scheme 14).⁷⁰ The reaction of *N*-chlorosulfonyl derivatives with enol ethers initiated by Et_3B has also been reported.⁷¹



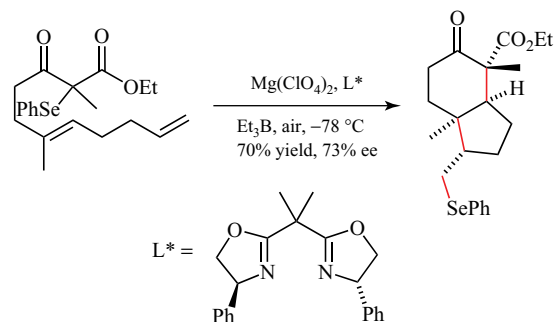
Scheme 13 Enantioselective cascade process involving a bromine atom transfer.



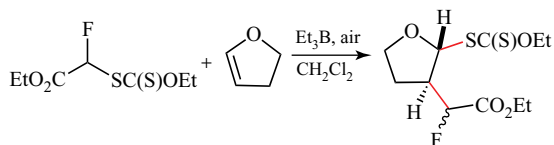
Scheme 14 Pyrrolidine preparation via a radical [3 + 2] annulation.

3.3.4 Phenylselenium Transfer

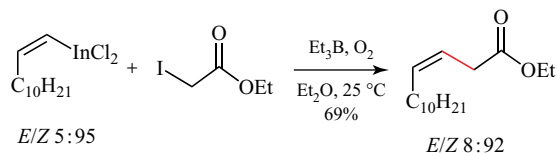
The transfer of phenylselenanyl group initiated by the system Et_3B –air works very efficiently in the presence of Lewis acids and promising enantioselectivities has been obtained in the presence of a box ligand (Scheme 15).⁷²



Scheme 15 Enantioselective cascade process involving a phenylselenanyl group transfer.



Scheme 16 Addition of α -xanthate- α -fluoroacetate to dihydrofuran.



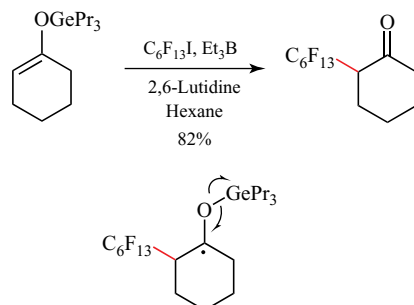
Scheme 17 Stereospecific styrylation reaction with an alkenylindium.

3.3.5 Xanthate-Transfer Reactions

The transfer of xanthates is a powerful method for C–C bond formation developed by Zard (see **Xanthates and Related Derivatives as Radical Precursors**).⁷³ Initiation is usually performed with the cheap and easy to handle dilauroyl peroxides (DLPs) at temperatures above 80 °C. When a lower temperature is desired, the use of Et_3B –air provides good results.^{74–77} For instance, the addition of xanthates to dihydrofuran affords the desired adducts in good yields when the reaction is performed in dichloromethane (Scheme 16).⁷⁵ Addition of xanthates derived from ketones requires carefully controlled reaction conditions to avoid the formation of a transient boron enolate leading to simple reduction of the xanthate.⁷⁶ A xanthate-transfer process initiated by Et_3B –air has been employed to perform an elegant addition–substitution sequence leading to selenochromanes.⁷⁸

3.4 Alkenylation, Allylation, and Related Processes

Oshima reported radical alkenylation and allylation of α -halo carbonyl compounds under mild conditions by utilizing vinyl and allyl organometallic radical traps and Et_3B as a radical initiator.^{35,79–81}

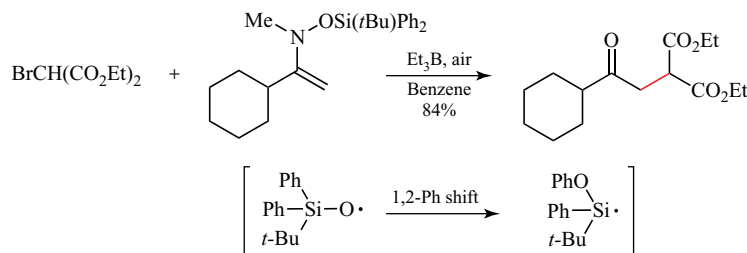


Scheme 18 Perfluoroalkylation of ketones via germynol ethers.

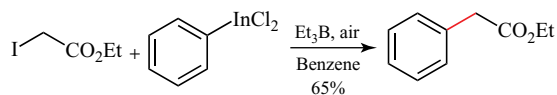
Styrylation reaction shows retention of the stereochemistry of the starting alkenylindium (Scheme 17).

Germynol ethers react with perfluoroalkyl iodides under Et_3B initiation to give α -perfluoroalkyl ketones. The intermediate radical adduct decomposes readily via β -elimination and provides the α -perfluoroalkyl ketone and a trialkylgermyl radical as a chain carrier (Scheme 18).⁵⁸

Kim reported a metal-free approach for the α -alkylation of ketones via *N*-siloxyenamine (Scheme 19).⁸² In this reaction, Et_3B is supposed to act as an initiator since fragmentation of the intermediate radical adduct affords a siloxy radical that undergoes a 1,2-phenyl shift to produce a silyl



Scheme 19 α -Alkylation of ketones with an *N*-siloxyenamine.



Scheme 20 Radical phenylation of an α -iodoester.

radical that propagates the chain. However, since 0.5 equivalent of Et_3B is used, the efficiency of the chain process is questionable and Et_3B may well be acting as a chain transfer reagent (see Section 5).

3.5 Arylation Processes

Intramolecular arylation processes initiated by Et_3B –air system are reported. They involve a radical 1,4-aryl migration from tin to a carbon.⁸³ An intermolecular α -arylation of a ketone with phenylindium dichloride is reported. The reaction requires the presence of triethylborane (Scheme 20). A mechanism involving an addition–fragmentation process may be operative but an electron transfer process cannot be ruled out.

Miranda reported the Et_3B -mediated arylation of ester and amide α -xanthates with pyrrole and indole derivatives in the presence of iron(II) sulfate (Scheme 21). The reaction is not a chain process and it requires a stoichiometric amount of the initiator. The iron(II) salt is probably oxidized to iron(III) by borane peroxides that insures rearomatization via oxidation of the transient radical adduct.

4 ORGANOBORON COMPOUNDS AS A SOURCE OF C-CENTERED RADICALS

Radicals generated from diverse organoboron derivatives can be used for carbon–carbon and carbon–heteroatom bond formation. Efficient chain reactions have been observed with trialkylboranes

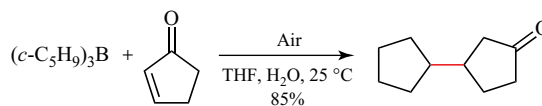
and alkylcatecholboranes. More stable organoboron derivatives, such as boronic acid and trifluoroborates, can also be used as a source of radicals under oxidative conditions.

4.1 Trialkylboranes

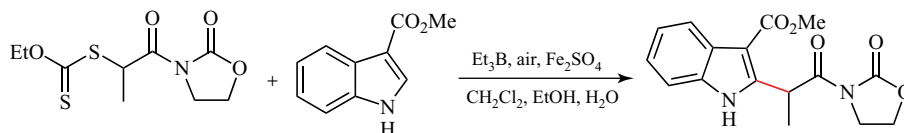
4.1.1 Trialkylboranes in Conjugate Addition

One of the first synthetic application of organoboranes in radical chemistry is the conjugate addition to enones (Scheme 22) and enals reported by Brown.^{84–87} Addition to β -substituted enones and enals are not spontaneous and initiation with the oxygen,⁸⁸ diacetyl peroxide,⁸⁹ or under irradiation⁸⁹ is necessary.

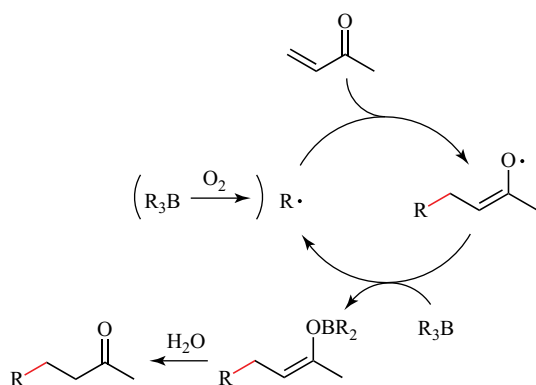
Brown proposed a mechanism where the enolate radical resulting from the radical addition reacts with the trialkylborane to give a boron enolate^{90,91} and a new alkyl radical that can propagate the chain (Schemes 23).⁸⁷ Water present in the system hydrolyzes the boron enolate and prevents degradation by undesired free-radical processes involving the enolate. This hydrolysis step is essential when alkynones⁹² and acrylonitrile⁸⁴ are used as radical traps since the resulting allenes or keteneimines react readily with radical species. On the basis of the spectroscopic evidences, Maillard and Walton proposed that the reaction of triethylborane with radical traps, such as methyl vinyl ketone (MVK), acrolein, and 3-methylbut-3-en-2-one, involves complexation of the trap by the Lewis acidic borane prior to conjugate addition.⁹³



Scheme 22 The Brown conjugate addition.



Scheme 21 Radical arylation of axanthate.



Scheme 23 Brown mechanism for the conjugate addition of organoboranes to methyl vinyl ketone.

The reaction between trialkylboranes and enones has found some interesting synthetic applications. An example is the preparation of prostaglandin precursors from *exo*-methylene cyclopentanone, generated *in situ* from a Mannich base. After dehydrogenation, a second conjugate addition of trioctylborane is used to introduce the ω -chain (Scheme 24).⁹⁴ Radical addition to benzilidene Meldrum's acid⁹⁵ and benzilidenemalonitrile⁹⁶ have been reported. Simple unsaturated esters, lactones, and amides do not react under these conditions because of the inefficiency of the chain propagation. Initiation of the chain reaction using *tert*-butylperoxide under microwave irradiation provides interesting opportunities for scale-up.⁹⁷

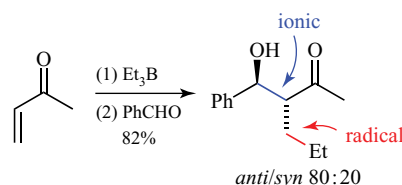
A serious drawback of the trialkylborane reactions is that only one of the three alkyl groups is transferred. The more sophisticated *B*-alkylboracyclanes have been introduced to overcome this limitation.^{98,99} However, this method, referred later as the Brown–Negishi reaction, is not suitable for primary alkyl radicals (yield < 35%)

and for traps substituted at the β -position. Similar results are obtained with cyclohexyldiethylborane (easily prepared from Et₂BH and cyclohexene). The efficient addition to MVK is possible. However, the same limitation as the Brown–Negishi reaction was observed with other radical traps.¹⁰⁰ Recently, the use of alkyldiphenylborane and alkyldimethylborane was reported for addition to benzoquinone.¹⁰¹

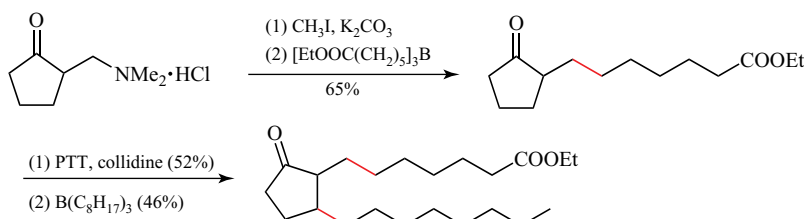
Several attempts to take advantage of the intermediate boron enolate to achieve tandem conjugate addition–aldol reaction are published.¹⁰² Chandrasekhar reported the addition of triethylborane to MVK followed by the *in situ* trapping of the enolate by reaction with benzaldehyde (Scheme 25).¹⁰³

Toru investigated the stereoselectivity of the conjugate addition of trialkylboranes to 2-arylsulfinylcyclopentenones.^{104–107} Excellent stereocontrol is achieved with different alkyl radicals (Scheme 26). The lack of diastereoselectivity and a competitive Pummerer rearrangement has limited the synthetic potential of this reaction in acyclic systems.¹⁰⁸

The reaction of trialkylboranes with 1,4-benzoquinones to give 2-alkylhydroquinones in quantitative yield was the first reaction of this type occurring without the assistance of a metal mediator.^{109,110} An ionic mechanism was originally proposed but rapidly refuted since the

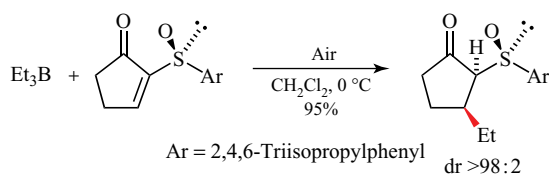


Scheme 25 Tandem conjugate addition–aldol reaction.

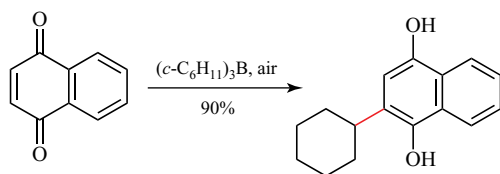


PTT = Phenyl trimethylammonium perbromide

Scheme 24 Conjugate addition of a functionalized trialkylborane.



Scheme 26 Stereoselective addition to 2-arylsulfinylcyclopentenones.



Scheme 27 Addition of alkyl radicals to quinones using trialkylboranes.

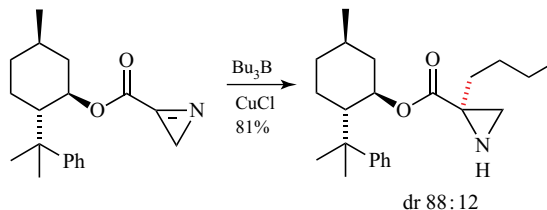
reaction is inhibited by radical scavengers such as galvinoxyl and iodine.¹¹¹ This procedure is in many cases superior to the more widely used organometallic additions. Primary and secondary alkyl radicals afford the addition products in high yield (Scheme 27).¹¹²

4.1.2 Trialkylboranes in Addition to Imines

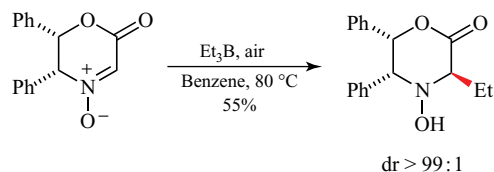
Intramolecular addition of trialkylboranes to imines and related compounds have been reported and the main results are part of review articles.^{113,114} Addition of ethyl radicals generated from Et₃B to aldimines affords the addition products in fair to good yield but low diastereocontrol.¹¹⁵ Similar reactions with aldoxime ethers,¹¹⁶ aldehyde hydrazones,¹¹⁶ and *N*-sulfonylaldimines¹¹⁷ and ketimines¹¹⁸ are published. Addition of triethylborane to 2*H*-azirine-3-carboxylate derivatives was investigated¹¹⁹ and Somfai extended this reaction to the addition of different alkyl radicals generated from trialkylboranes to a chiral ester of 2*H*-azirine-3-carboxylate under Lewis acid activation with CuCl (Scheme 28).¹²⁰ Multicomponent reactions are also possible.¹²¹

Naito reported a radical addition to nitrones that occurs with high stereocontrol (Scheme 29).¹²²

Interestingly, most of the reactions reported with imines and related products such as oximes, oxime



Scheme 28 Addition of trialkylboranes to a chiral ester of 2*H*-azirine-3-carboxylate under Lewis acid activation with CuCl.



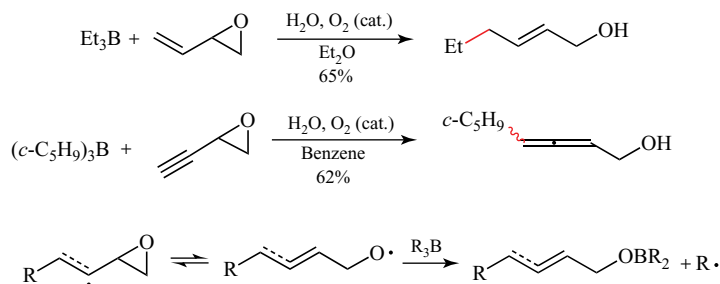
Scheme 29 Addition of triethylborane to nitrones.

ethers, hydrazones, and nitrones can be performed in aqueous media.¹²³

4.1.3 Trialkylboranes in β -Fragmentation Processes

Brown and Suzuki showed that the treatment of trialkylboranes with ethenyl- and ethynylloxiranes in the presence of a catalytic amount of oxygen, affords the corresponding allylic or allenic alcohols (Scheme 30). The mechanism involves addition of alkyl radicals to the unsaturated system leading to 1-(oxiranyl)alkyl and 1-(oxiranyl)alkenyl radicals followed by rapid fragmentation to give alkoxy radicals that finally complete the chain process by reacting with the trialkylborane.^{124–126}

According to Yao, the free-radical substitution of β -nitrostyrene (2-nitroethenylbenzene) by trialkylboranes provides *E*-alkenes.¹²⁷ It involves a radical addition to the β -position (α to the nitro group) followed by fragmentation of NO₂[•]. Nozaki reported the reaction of trialkylboranes with styrylsulfoxides and sulfones. Alkyl radicals generated from trialkylboranes add at the β -position of β -styrylsulfoxides and sulfones (α - to the sulfur atom). The resulting radicals fragment and deliver the β -styryl adducts.¹²⁸ Interestingly, the sulfoxides eliminate very rapidly leading to partial retention of the olefin configuration.



Scheme 30 Reaction of trialkylboranes with ethenyl- and ethynyloxiranes.

4.2 B-Alkylcatecholboranes

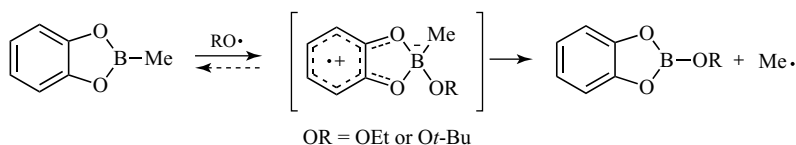
B-Alkylcatecholboranes have been introduced in order to circumvent the lack of selectivity in the cleavage of trialkylboranes and they proved to be an excellent source of alkyl radicals. They are extremely sensitive toward oxygen and they react readily with alkoxy radicals. Davies and Roberts demonstrated by electron spin resonance (ESR) that a perboranyl radical intermediate resulting from the complexation of *B*-methylcatecholborane with the alkoxy radical is involved in the substitution reaction.¹²⁹ Interestingly, this intermediate is stabilized by delocalization onto the aromatic ring (Scheme 31).

B-Alkylcatecholboranes are more reactive than trialkylboranes and they are easily prepared from olefins via hydroboration with catecholborane with or without a catalyst. However, the most attractive

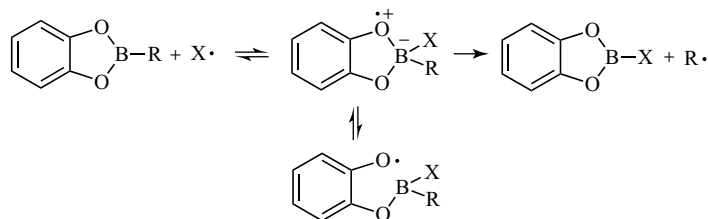
feature of *B*-alkylcatecholboranes is the possibility to generate selectively one alkyl radical from an olefin. Indeed, reaction of *B*-alkylcatecholboranes with a heteroatom-centered radical leads exclusively to alkyl radicals since the cleavage of B–X and B–O bonds are reversible (Scheme 32).¹³⁰

4.2.1 B-Alkylcatecholboranes in Conjugate Additions

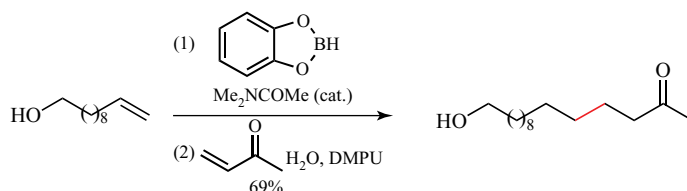
A modified version of the Brown–Negishi reaction using *B*-alkylcatecholboranes is reported.¹⁰⁰ This method is based on a simple one-pot procedure involving the hydroboration of various substituted alkenes with catecholborane, followed by treatment with catalytic amount of oxygen/*N,N'*-dimethylpropyleneurea (DMPU)/water and a radical trap. Efficient radical additions to α,β -unsaturated ketones and aldehydes are



Scheme 31 Reaction of *B*-methylcatecholborane with alkoxy radicals.



Scheme 32 Irreversible formation of alkyl radicals from *B*-alkylcatecholboranes.

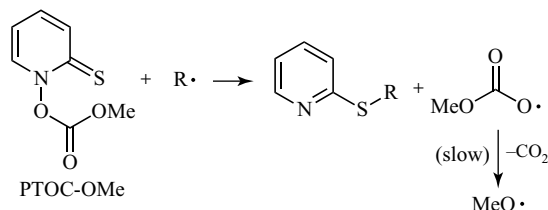


Scheme 33 *B*-Alkylcatecholborane-mediated addition of organoboranes to enones.

described. Primary alkyl radicals are efficiently generated by this procedure and the reaction was employed for a 0.3-mol scale synthesis of the γ -side chain of (–)-perturasinic acid (Scheme 33).¹³¹ The reaction is also amenable to radical addition to β -substituted enones and enals as well as to cyclization and annulation reactions.¹⁰⁰

The addition of *B*-alkylcatecholboranes to quinones was investigated.¹³² Good yields of the expected conjugate addition products are obtained with primary and most secondary radicals. However, hindered secondary radicals and tertiary alkyl radicals afford an unexpected product resulting from a radical addition to the oxygen atom of the quinone (Scheme 34).

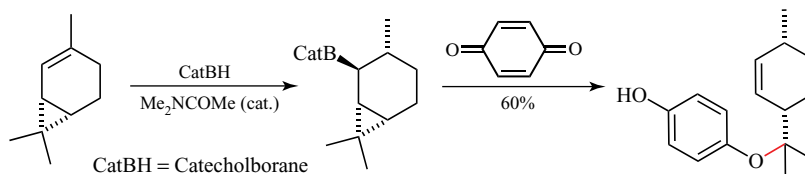
The modified Brown–Negishi reaction with *B*-alkylcatecholborane (Scheme 33) is mostly limited to enones and enals. Other radical traps such as unsaturated esters, amides, and sulfones fail to react under these conditions. This failure was interpreted as a consequence of an inefficient reaction of the radical adduct and *B*-alkylcatecholboranes. The use of a chain transfer reagent, which is able to convert a carbon-centered radical into an oxygen-centered radical, allows solving this problem. The Barton carbonate PTOC-OMe (PTOC, pyridine-2-thione-*N*-oxycarbonyl)^{133,134} proved to be an excellent radical chain transfer reagent (Scheme 35).¹³⁵ Interestingly, the same reagent is an excellent radical initiator under irradiation with a standard 150-W tungsten lamp. The PTOC-OMe is a stable reagent easily obtained by the reaction



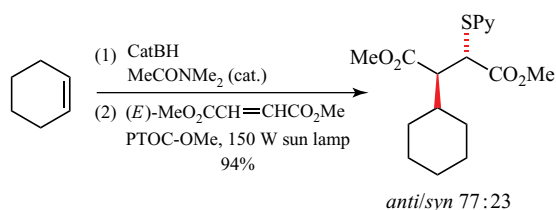
Scheme 35 Barton carbonate PTOC-OMe, a radical chain transfer reagent able to convert a C-centered radical into an O-centered radical.

of the commercially available sodium salt of *N*-hydroxypyridine-2-thione with methyl chloroformate. A related strategy has been developed by Dalko and Cossy using the Barton ester PTOC-Ph as chain transfer reagent.¹³⁶

In a preliminary study, *in situ* generated *B*-alkylcatecholboranes were allowed to react with PTOC-OMe under irradiation with a standard 150-W lamp. The *S*-pyridyl products coming from primary, secondary, and tertiary alkyl radicals were isolated in moderate to good yields.¹³⁵ On the basis of these initial results, a procedure for conjugate addition to various activated alkenes was developed. A one-pot procedure involving hydroboration of an alkene with catecholborane followed by irradiation in the presence of 5 equivalents of an activated alkene and 3 equivalents of the chain transfer reagent PTOC-OMe was developed (Scheme 36).¹³⁵ In contrast to the tin hydride-mediated reaction (Giese reaction),¹³⁷ no slow addition of the chain carrier is necessary.



Scheme 34 Addition of *B*-alkylcatecholboranes to quinones: C- versus O-addition.



Scheme 36 PTOC-OMe-mediated conjugate addition of *B*-alkylcatecholborane to activated alkenes.

B-Alkylcatecholboranes, prepared by rhodium(I)-catalyzed hydroboration of alkenes, are suitable radical precursors for conjugate addition to activated olefins. This procedure is particularly useful for the control of the regio- and chemoselectivity of such tandem processes.¹³⁸ A one-pot enantioselective hydroboration–radical conjugate addition was successfully performed. For example, the reaction between norbornene and methyl methacrylate as radical trap affords the product of conjugate addition in 68% yield and 85% enantiomeric excess (after desulfurization) (Scheme 37). The rhodium-catalyzed hydroboration also opens the way to cyclization reactions starting from dienes.¹³⁹

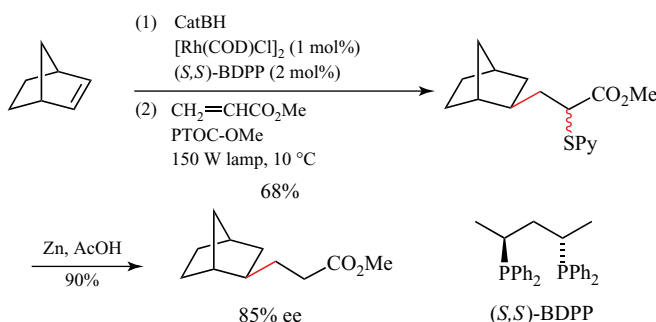
A one-pot procedure involving radical conjugate addition of *B*-alkylcatecholboranes to enones followed by intramolecular aldol reaction was reported recently.¹⁴⁰ This reaction was used to prepare

stereoselectively monocyclic and bicyclic products with up to four contiguous stereogenic centers (Scheme 38).

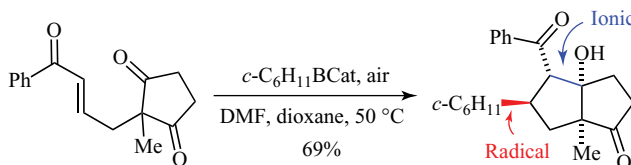
4.2.2 *B*-Alkylcatecholboranes in β -Fragmentation Processes

Radical allylation of *B*-alkylcatecholboranes using easily available allylsulfones has been described.^{141–143} By using phenylsulfones, the fragmentation produces a stable phenylsulfonyl radical that reacts with *B*-alkylcatecholborane to sustain the chain reaction (Scheme 39). The allylated products are obtained in satisfactory to excellent yields by using only 1.2 equivalents of the allylsulfones with primary, secondary, and tertiary alkyl radicals. Many different types of allylic sulfones bearing an ester group, a sulfonyl group, and a bromine atom react equally well. The whole transformation represents formally a reductive allylation or hydroallylation of alkenes.

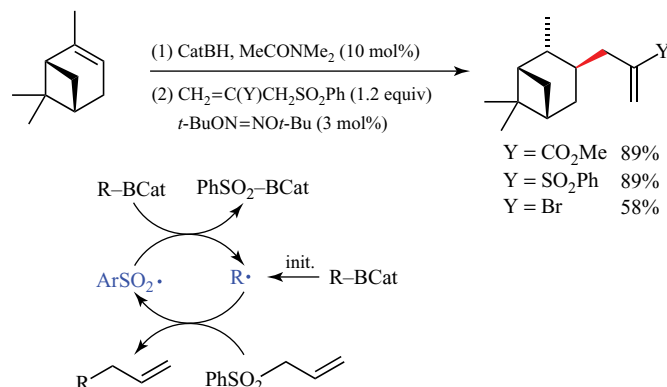
An extension of this reaction, that is, the coupling of *B*-alkylcatecholboranes with ethyl 2-(benzenesulfonylamino)acrylate is reported (Scheme 40).¹⁴⁴ In this reaction, fragmentation of an *N*-SO₂Ph bond is taking place during the propagation step. Using this procedure, various α -ketoesters (alkylated pyruvates) were prepared



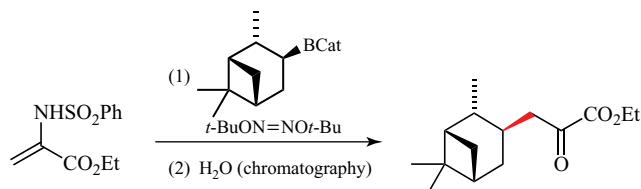
Scheme 37 Control of the enantioselectivity via rhodium(I)-catalyzed hydroboration.



Scheme 38 *B*-Alkylcatecholborane-mediated tandem radical conjugated addition-aldol cyclization.



Scheme 39 Alkylation of *B*-alkylcatecholboranes with allylsulfones.



Scheme 40 Alkylation of ethyl pyruvate via reductive coupling of alkenes and ethyl 2-(benzenesulfonylamino)acrylate.

in a straightforward manner. It also demonstrates the generality of the radical-mediated C–C bond formation starting from organoboranes and allylicbenzenesulfonyl derivatives.

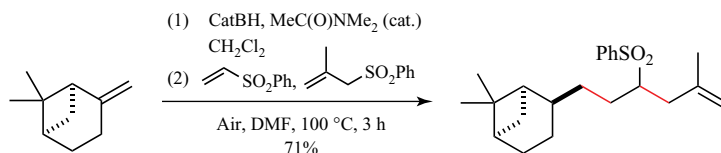
The cascade conjugate addition–allylation takes place efficiently when a good matching of polarity of the two radical traps is provided. For instance, addition of the primary radical generated from β -pinene to a mixture of phenyl vinyl sulfone and 2-methylallyl phenyl sulfone affords the product of addition–allylation in good yield (Scheme 41).¹⁴⁵

The allylation process was extended to several other related reactions that take advantage of the β -fragmentation of arenesulfonyl radicals. For instance, *B*-alkylcatecholboranes prepared *in situ* by hydroboration of olefins with catecholborane, undergo efficient coupling reactions with vinyl and alkynylsulfones. This procedure was extended to

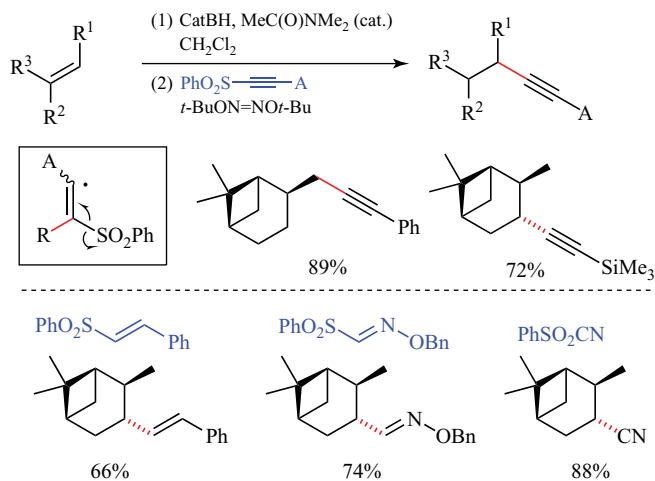
formylation and cyanation reactions of organoboranes (Scheme 42).¹⁴⁶

4.2.3 Oxygenation, Halogenation, and Chalcogenation of *B*-Alkylcatecholboranes

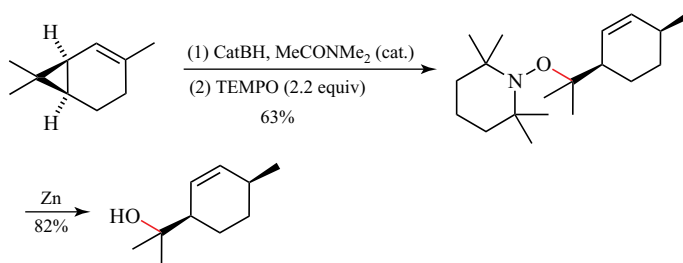
Owing to the specificity of radical processes (unusual rearrangements, mildness of the reaction conditions), radical hydroxylation of organoboranes represents an interesting alternative to the classical oxidative workup to convert alkenes into alcohols. The conversion of *B*-alkylcatecholboranes, prepared by hydroboration of the corresponding alkenes, is easily performed by treatment with 2 equivalents of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), a stable persistent radical (see **Nitroxides in Synthetic Radical Chemistry**),¹⁴⁷ or by treatment with



Scheme 41 Cascade addition–allylation.



Scheme 42 Vinylation, alkynylation, formylation, and cyanation of *B*-alkylcatecholboranes generated *in situ* from alkenes.



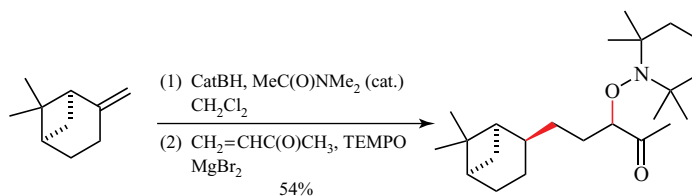
Scheme 43 Oxygenation of *B*-alkylcatecholborane using TEMPO.

oxygen. The reaction with TEMPO affords in good to excellent yield the corresponding alkoxyamines (Scheme 43).^{147,148} The first equivalent of TEMPO is used to generate the alkyl radical from the organoborane, the second equivalent is acting as a radical trap to form an alkoxyamine that can be reduced using standard methods to the desired alcohol. Studer reported the use of this reaction with various nitroxides for chemical modification of macromolecules containing multiple double bonds

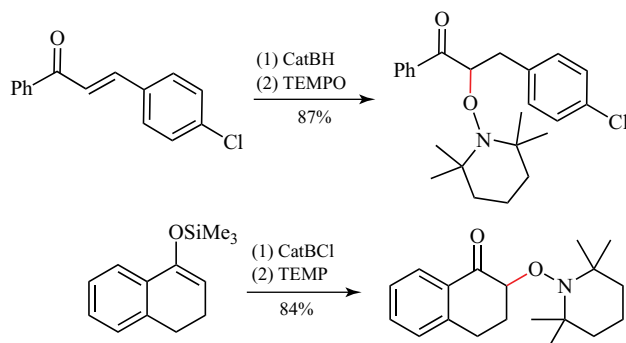
such as poly(butadiene) and of perallylated polyglycerol.¹⁴⁹

This reaction was also used for a conjugate addition–alkoxy amination process.¹⁴⁸ Very recently, Studer described the beneficial use of a Lewis acid ($\text{MgBr}_2 \cdot \text{Et}_2\text{O}$) for this reaction (Scheme 44).¹⁵⁰ This chemistry was used to prepare macro(alkoxyamines) that are initiators of polymerization.

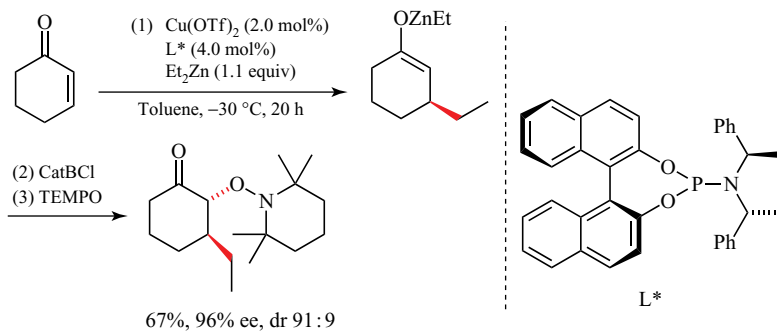
Interestingly, the generation of α -carbonyl radicals from catecholboron ketone enolates by reaction with TEMPO is also possible. The boron enolates



Scheme 44 Formation of α -(aminyl)oxyketones via radical addition–alkoxy amination.



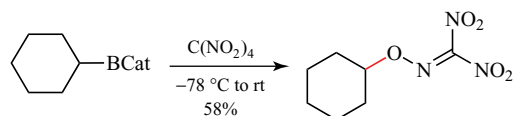
Scheme 45 Generation of radicals from boron enolates.



Scheme 46 Tandem enantioselective conjugate addition–radical alkoxyamination.

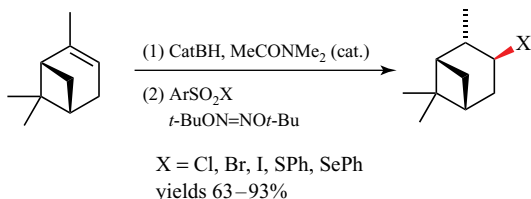
are readily obtained via reduction of linear enones with catecholborane or via “transmetalation” of silylenol ethers and zinc enolates with chlorocatecholborane. *In situ* trapping of the α -carbonyl radicals with TEMPO provided the corresponding alkoxyamines in high yields (Scheme 45). An *in situ* generated enantiomerically enriched chiral boron enolate reacted with TEMPO with very good diastereoselectivity (Scheme 46). Application of this chemistry for polymerization of vinyl ketones has been recently reported.¹⁵¹

The reaction of tetranitromethane with *B*-alkylcatecholboranes leads to the formation of unusual dinitrooxime ethers (Scheme 47).¹⁵² The mechanism involves an extremely fast addition of alkyl radicals to tetranitromethane. The substitution of one of the nitro groups by nucleophiles such as secondary amines, halogens, and styrene, and by radicals generated from *B*-alkylcatecholboranes is reported.



Scheme 47 Reaction of *B*-alkylcatecholborane with tetranitromethane.

The hydroboration of alkenes with catecholborane was used to develop an efficient formal anti-Markovnikov addition of HX (X = Cl, Br, I, SR, and SeR) to olefins (Scheme 48).¹⁵³ The conversion of the intermediate *B*-alkylcatecholboranes to the corresponding halides, sulfides, and selenides is based on a common process, that is, generation of a radical from the alkylborane followed by abstraction of a heteroatom from an aromatic sulfonyl reagent. The mildness of the reaction conditions is well illustrated by the preparation of iodoalkanes. Despite the notorious reactivity of iodoalkanes under radical reactions, no degradation product is observed.



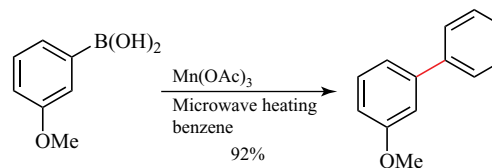
Scheme 48 Halogenation and chalcogenation of *B*-alkylcatecholboranes.

4.3 Modified *B*-Alkylcatecholboranes

In order to facilitate the separation of the final products from catechol derivatives generated during the workup procedure, a modified system involving dihydroxytetrahydroisoquinoline instead of catechol was used.¹⁵⁴ The desired organoborane is prepared *in situ* by hydroboration with BH₃·Me₂S followed by reaction of the monoalkylborane with the modified catechol. The modified alkylcatecholborane can be used in all previously reported radical reactions. Interestingly, the catechol residues are easily eliminated by simple extraction under acidic conditions. This reaction is particularly useful to run radical addition to benzoquinones since the separation of catechol from product hydroquinones is problematic (Scheme 49).

4.4 Boronic Acids and Derivatives

The oxidation of arylboronic acids offers an interesting approach for the generation of aryl radicals. Demir reported the preparation of biaryls resulting



Scheme 50 Mn(III)-assisted synthesis of biaryls.

from the oxidation of arylboronic acid by Mn(III) acetate in benzene or thiophene (Scheme 50).^{155,156}

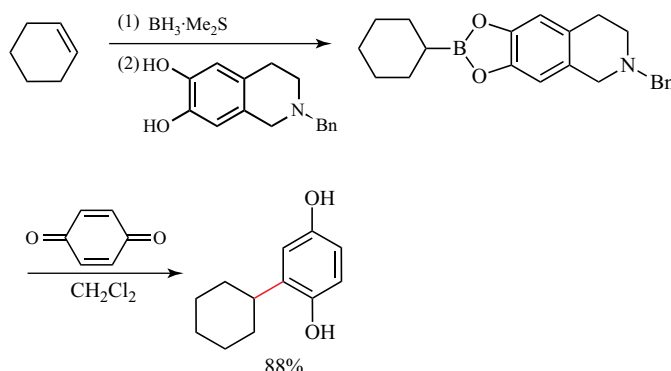
Studer extended this work to intermolecular addition to alkenes¹⁵⁷ and observed products that resulted from double olefin addition followed by aromatic substitution leading to tetrahydronaphthalene derivatives (Scheme 51). In the presence of oxygen, monoaddition followed by hydroxylation occurs (Scheme 52).

Fensterbank reported the oxidation of the organotrifluoroborate by copper(II) salts or by the Dess–Martin periodinane (DMP) generates alkyl radicals that are either trapped by the excess of TEMPO or by radical traps such as MVK (Scheme 53).¹⁵⁸

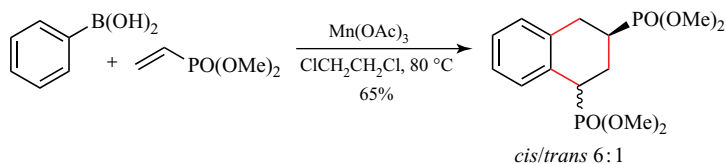
A ruthenium-catalyzed coupling reaction of propargylic alcohols via hydroboration with pinacolborane was described. Its mechanism may possibly involve the formation of radicals via an oxidative process.¹⁵⁹

5 ORGANOBORANES AS CHAIN TRANSFER REAGENTS

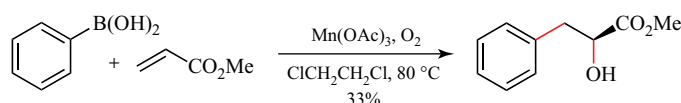
An important application of organoboranes in radical chemistry is their use as chain transfer reagents.



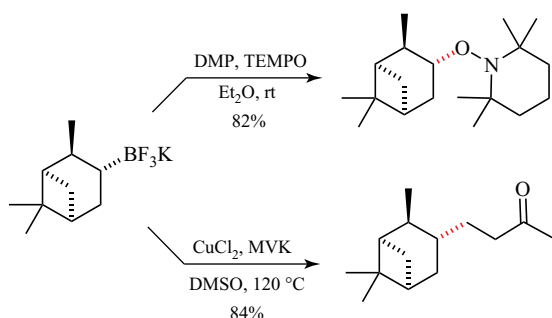
Scheme 49 Modified *B*-alkylcatecholborane for facilitated purification.



Scheme 51 Synthesis of tetrahydronaphthalene derivatives.



Scheme 52 Oxidative radical hydroxyarylation.



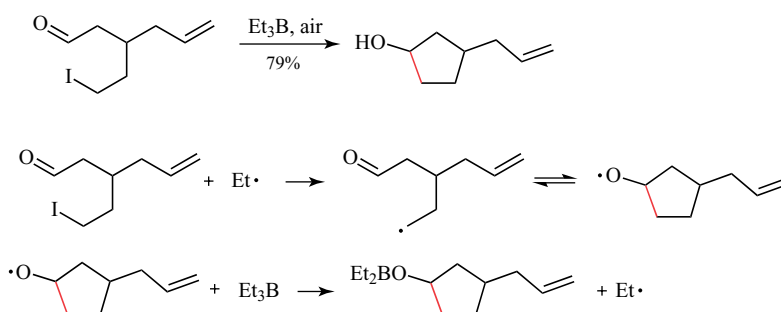
Scheme 53 Generation of radicals from potassium organotri-fluoroborates.

Chain transfer reagents are used when the chain reaction between the radical precursor and the radical trap cannot proceed owing to an unfavorable step. Alkyl radicals generated from the organoboranes are not involved in product formation but they serve to produce the radicals that lead to products. In contrast to reactions where the borane acts as an initiator, a stoichiometric amount of the organoborane is necessary for the reaction to

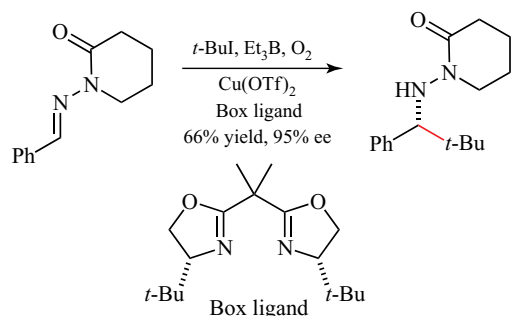
go to completion. This is best illustrated by the cyclization of alkyl radicals onto aldehydes reported by Malacria (Scheme 54).¹⁶⁰ Upon reaction with the alkoxyl radical, Et₃B generates an ethyl radical that can propagate the chain. In the absence of Et₃B, the alkoxyl radical would not be able to propagate the chain and the reaction would either stop or lead to side products. In this example, the reactive alkyl radical is generated via an iodine atom-transfer process. Reaction is classified here according to the type of reaction and iodine or hydrogen atom transfer used for the generation of the reactive radical.

5.1 Via Iodine Atom Transfer

Bertrand *et al.*^{113,161} and Naito^{114,116} reported the use of triethylborane for the tin-free addition of alkyl iodides to imines. This reaction was extended to 2*H*-azirine-3-carboxylates.^{119,120} Enantioselective radical additions to *N*-acyl hydrazones using triethylborane as chain transfer reagent are reported by Friestad. Enantiomeric excesses up to 95% are



Scheme 54 Triethylborane as a chain transfer reagent for the cyclization of iodoaldehydes.

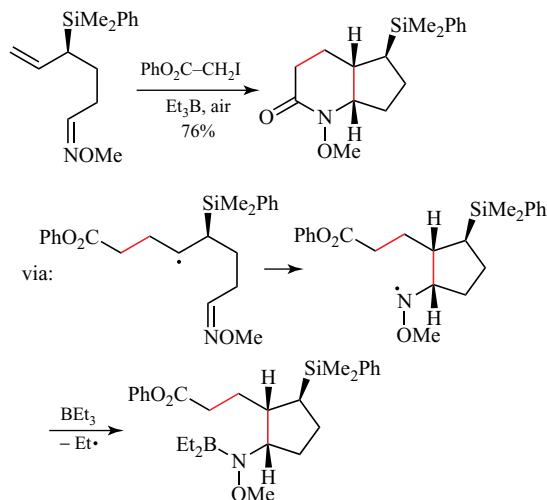


Scheme 55 Enantioselective addition to *N*-acyl hydrazones.

obtained in the presence of copper(II)-bisoxazolines Lewis acid (Scheme 55).¹⁶² Enantioselective cyclizations onto oxime ethers were examined by Miyabe and Takemoto.^{56,163}

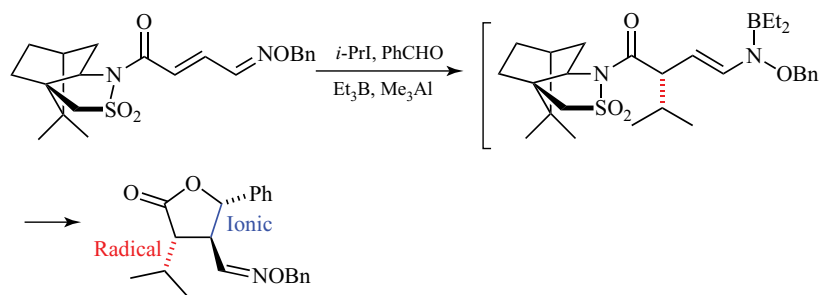
Tandem processes mediated by triethylborane involving conjugate addition of alkyl iodides to enones followed by aldol reaction are reported.¹⁰² A tandem process involving addition of an isopropyl radical to an α,β -unsaturated oxime ether affords an azaenolate intermediate that reacts with benzaldehyde in the presence of trimethylaluminum. The aldol product cyclizes to afford an isopropyl-substituted γ -butyrolactone in 61% overall yield (Scheme 56).¹⁶⁴ Triethylborane is acting as a chain transfer reagent that delivers the azaenolate necessary for the aldolization process. A related hydroxyalkylation process involving oxygenation of the intermediate azaenolate was reported by Myata and Naito.¹⁶⁵

Landais reported the efficient synthesis of piperidinone through a radical cascade mediated by Et_3B (Scheme 57).^{166,167}

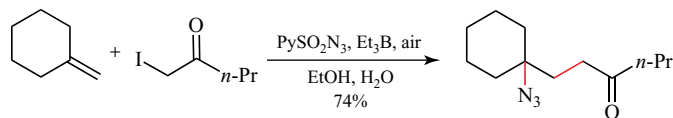


Scheme 57 Radical cascade leading to fused bicyclic piperidinones.

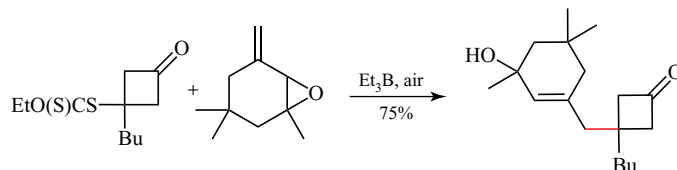
Alkenylation of alkyl iodides with β -nitrostyrene derivatives was reported.¹⁶⁸ The reaction is, however, not strictly a chain process since a stoichiometric amount of oxygen is necessary to run the reaction. The radical $\text{NO}_2^\bullet$ is presumably not sufficiently reactive toward triethylborane to sustain the chain process. A similar situation is occurring during the Et_3B -mediated radical carboazidation of alkenes.¹⁶⁹ This efficient process is complete in 1 hour at room temperature in an open to air reaction vessel but an excess of triethylborane (3 equiv) is required to obtain good yields. This may be an indication that the chain process, more precisely the reaction between the benzenesulfonyl radical and Et_3B , is not efficient. Recently, this reaction was applied to the reactions involving α -iodoketones (Scheme 58).¹⁷⁰



Scheme 56 Tandem radical addition-aldol reaction-lactonization process.



Scheme 58 Triethylborane-mediated carboazidation with α -iodoketones.



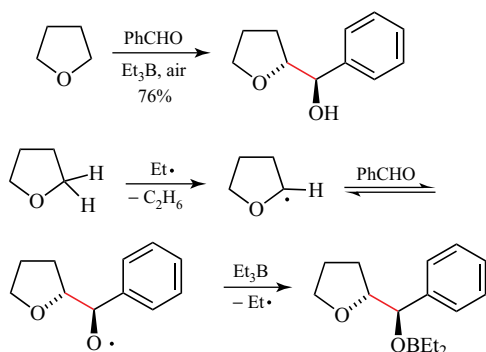
Scheme 59 Addition of xanthates to vinyl epoxides.

5.2 Via Xanthate Transfer

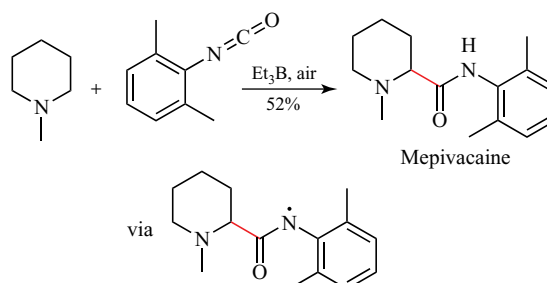
The radical addition of xanthates to vinyl epoxides has been described by Zard and has proved to be an efficient method for quaternary carbon formation (Scheme 59).¹⁷¹

5.3 Via Hydrogen Atom Transfer

Ethers and acetals undergo direct intermolecular addition to aldehydes under treatment with Et_3B –air (Scheme 60).¹⁷² A plausible mechanism is depicted in Scheme 60 and involves addition of the 2-tetrahydrofuryl radical to the aldehyde followed by a rapid reaction of the alkoxy radical with Et_3B . Triethylborane has a crucial role because



Scheme 60 Radical hydroxyalkylation of C–H bonds adjacent to oxygen.



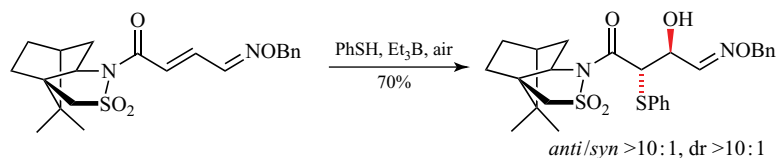
Scheme 61 One-step synthesis of mepivacaine.

by reacting with the alkoxy radical, it favors the formation of the condensation product relative to the β -fragmentation process (back reaction). Similar reactions with tertiary amines, amides, and urea are also reported¹⁷³ and applied for the synthesis of ($\pm$)-aphanorphone.¹⁷⁴

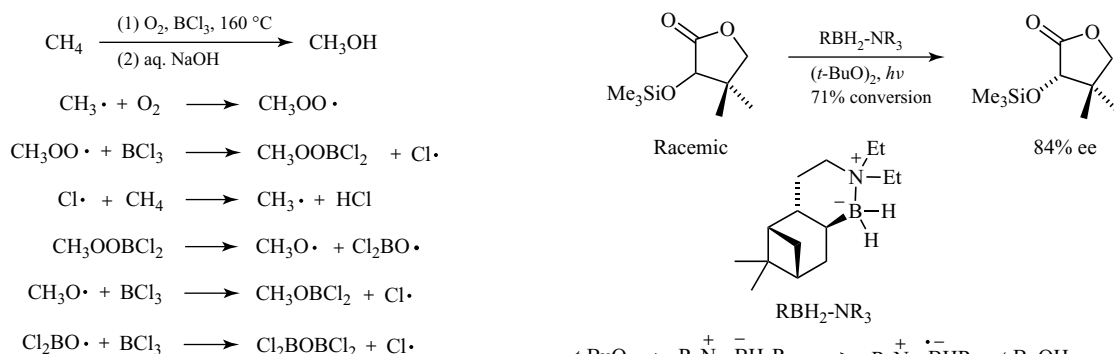
Yoshimitsu and Tanaka reported a novel carbamoylation of tertiary amides involving isocyanate radical traps.¹⁷⁵ This reaction was applied for a short synthesis of the local anesthetic mepivacaine (Scheme 61).

The regioselective hydroxysulfenylation of α,β -unsaturated imines was developed by Naito (Scheme 62).¹⁷⁶ It is not clear if the reaction involves the formation of a boron azaenolate (= *N*-borylenamine) or the direct reaction of the radical adduct with oxygen.

An interesting method for the production of methanol from methane was recently developed.¹⁷⁷ In this process, boron trichloride acts as a chain transfer reagent. The key steps of this process are shown in Scheme 63.



Scheme 62 Stereoselective hydroxysulfenylation.



Scheme 63 Conversion of methane to methanol mediated by boron trichloride.

6 BORON DERIVATIVES IN REDUCTIVE PROCESSES

6.1 Complexes of Boranes with Tertiary Amines

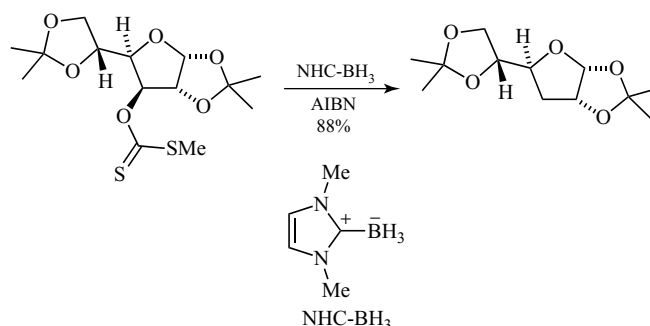
The B–H bond dissociation energies (BDEs) of boranes are strongly influenced by complexation with Lewis bases (see **Radical Stability—Thermochemical Aspects**).¹⁷⁸ This offers an opportunity for the development of a new class of reagents that are able to transfer hydrogen to radical intermediates. Roberts investigated the use of amine–borane complexes as hydridic polarity-reversal catalysis.¹⁷⁹ A slow hydrogen atom abstraction step caused by a mismatched polarity can be replaced by two rapid steps with matched polarity. For example, the slow abstraction of an hydrogen atom from acetonitrile by a *tert*-butoxyl radical (mismatched polarity) is replaced by a rapid reduction of the electrophilic *tert*-butoxyl radical with an amine–borane complex (matched polarity) and by the abstraction of an hydrogen atom from acetonitrile by the nucleophilic amine–boryl radical (matched polarity).^{180,181} Application of this concept to the kinetic resolution of chiral

Scheme 64 Kinetic resolution of a γ -lactone.

esters and lactones by using chiral amine–borane complexes lead to interesting enantioselectivities (Scheme 64).^{182–184} More recently, Lalevée showed that *N*-heteroarylboranes exhibit low B–H BDE's and could become useful reagents for the reduction of radicals.¹⁸⁵

6.2 Complexes of Borane with *N*-Heterocyclic Carbenes (NHC boranes)

The use of NHC boranes as hydrogen atom donor was recently investigated.^{186,187} Remarkably, complexation by NHC leads to a very effective decrease of B–H BDEs making these complexes suitable for the reduction of carbon-centered radicals.¹⁸⁸ Barton–McCombie deoxygenation of various xanthates is initiated by AIBN and provides the reduced products in moderate to good yield.¹⁸⁶ The rate constant for the reduction ranges from 1 to $8 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.¹⁸⁹ Interestingly, the best results so far have been obtained with NHCs possessing low

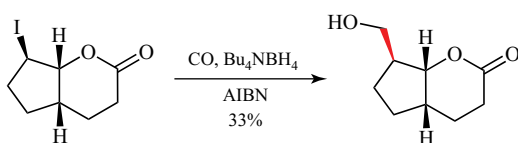


Scheme 65 Reduction of a xanthate with a low molecular weight NHC borane.

molecular weights (Scheme 65).¹⁹⁰ The reactivity of the intermediate NHC boryl radical has been investigated and based on these results further optimization and generalization of this system is expected.^{188,191}

6.3 Borohydride

Ryu recently provided experimental indications that tetrabutylammoniumborohydride may also act as a source of hydrogen atom in the hydroxymethylation of alkyl iodides (Scheme 66).¹⁹² Sodium cyanoborohydride is also used to run conjugate addition to acrylates (Giese reaction). In this case, a mechanism implicating an iodine atom-transfer process followed by hydride reduction of the carbon–iodine bond is operative.¹⁹³



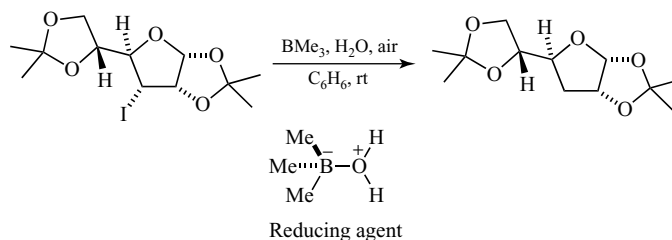
Scheme 66 Hydroxymethylation of alkyl iodides.

6.4 Complexes with Water and Alcohols

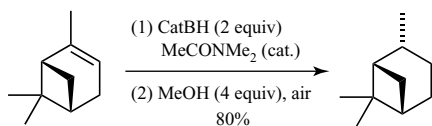
Wood reported an innovative development of the Barton–McCombie deoxygenation of alcohols allowing to work under tin-free conditions.¹⁹⁴ Trialkylborane–water complexes prove to be efficient reagents for the reduction of xanthates^{194–196} and iodides (Scheme 67).¹⁹⁷ The typically high barriers for hydrogen abstraction from water are lowered dramatically on complexation with BMe₃. The barrier lowering is found to be a consequence of the unique properties of trialkylboranes, acting as Lewis acids toward the closed-shell solvent, but as electron donors toward the evolving oxygen-centered radicals.¹⁹⁸ The rate constant for the hydrogen atom transfer has been measured by Newcomb and a relatively low value of $3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 20 °C has been found.^{199,200}

6.5 The Borane–Catechol System

A similar observation was made by Pozzi *et al.* who reported a mild and efficient radical-mediated reduction of *B*-alkylcatecholboranes in the presence



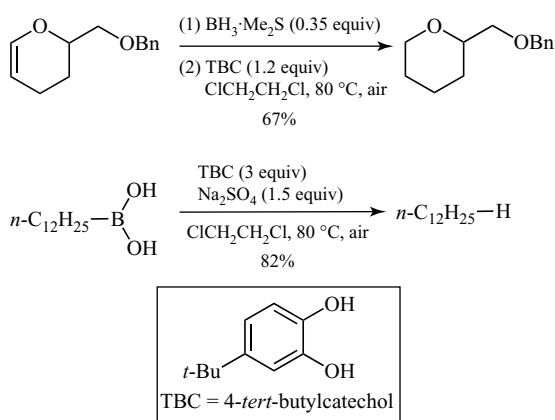
Scheme 67 Barton–McCombie deoxygenation with Me₃B–water complex.



Scheme 68 The reduction of *B*-alkylcatecholboranes by methanol.

of methanol and a radical initiator.²⁰¹ The radical nature of the process was demonstrated by using (+)-2-carene as a radical probe and an *in situ* generated *B*-methoxycatecholborane–methanol complex was suggested as a reducing agent (Scheme 68). Recently, this mechanism was revised based on ¹H- and ¹¹B-NMR studies.²⁰² A mechanism involving catechol as a reducing agent is proposed. Catechol, a chain breaking antioxidant, becomes a source of hydrogen atom in a highly efficient radical chain process.

On the basis of these results, a mild radical procedure for the transformation of organoboranes to alkanes was developed.²⁰³ 4-*tert*-Butylcatechol (TBC), a well-established radical inhibitor and antioxidant, is acting as a source of hydrogen atom. An efficient chain reaction is observed owing



Scheme 69 Reduction of organoborane with 4-*tert*-butylcatechol.

to the exceptional reactivity of phenoxyl radicals toward alkylboranes. The reaction has been applied to a wide range of organoboron derivatives such as *B*-alkylcatecholboranes, trialkylboranes, pinacolboronates, and alkylboronic acids (Scheme 69). Furthermore, the so far elusive rate constants for the hydrogen transfer between secondary alkyl radical and catechol derivatives have been experimentally determined ($\text{TBC} : \text{KH} = 1.3 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$). Interestingly, they are less than one order of magnitude slower than tin hydride at 80 °C making the catechols particularly attractive reagents for a wide range of transformations involving C–C bond formations.

7 BORON-CONTAINING RADICALS AND RADICAL TRAPS

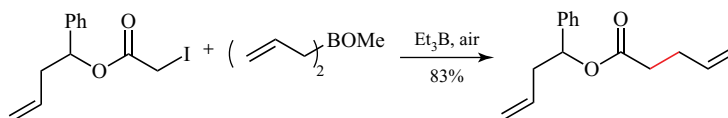
7.1 Allylboron Derivatives

The addition of α -iodoesters to several allylboron derivatives was investigated by Oshima.⁸¹ Diallylmethoxyborane affords the allylation product in good yield but the reaction is limited to iodide radical precursors (Scheme 70). No reaction is observed with the corresponding bromide suggesting that the mechanism involves an iodine atom-transfer process followed by ionic elimination of the iodoboron derivatives. A conjugate addition–allylation process is reported.

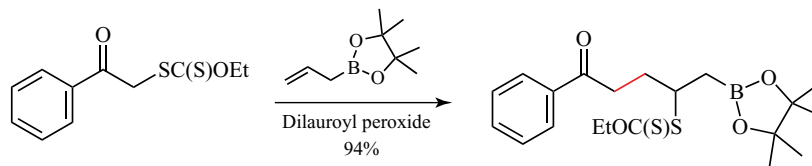
The addition of an ester α -xanthate to allylpinacolborane affords the simple addition product resulting from a xanthate transfer in good yields (Scheme 71).^{76,204}

7.2 Alkenylboron Derivatives

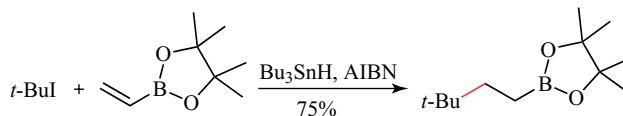
The use of alkenylboranes as radical trap has been pioneered by Matteson *et al.*²⁰⁵ and Carboni.²⁰⁶ Interestingly, nucleophilic radicals generated from iodides (Scheme 72) and Barton esters add



Scheme 70 Radical allylation with diallylmethoxyborane.



Scheme 71 Xanthate-transfer addition to allylpinacolborane.



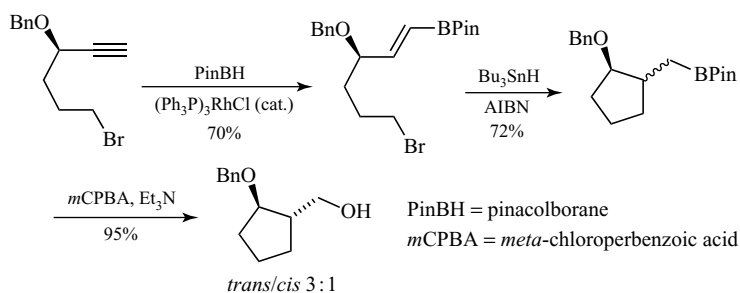
Scheme 72 Giese-type addition to vinylpinacolborane.

efficiently to vinylpinacolborane. Zard reported the addition of alkyl²⁰⁴ and acyl radicals via xanthate transfer to vinylpinacolborane.²⁰⁷ This last reaction proved to be an efficient procedure for the preparation of β -borylatedenones.

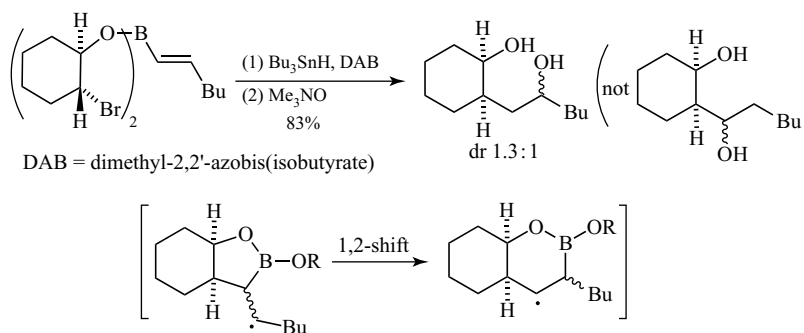
Cyclization reactions involving alkenylboranes represent an efficient approach for the preparation of alcohols.^{206,208,209} Lee reported an interesting

approach to cyclic diols from easily available starting materials (Scheme 73).²⁰⁸

Batey developed boron-tethered radical cyclizations and observed an unexpected 1,2-shift (Scheme 74).¹⁰ The mechanism of this rearrangement is not clear but a homolytic substitution at boron via a three-membered ring transition state was proposed.



Scheme 73 Preparation of cyclic diols via radical cyclization.



Scheme 74 Boron-tethered radical cyclization: an unexpected 1,2-shift.

7.3 Diboron Radical Traps

A Sandmeyer-type reaction involving bis(pinacolato)diboron has been recently reported (Scheme 75).²¹⁰ This metal-free process involves most probably aryl radicals that are trapped by the diboron species. This mechanism is supported by the observation that phenylpinacolborane is generated when dibenzoyl peroxide is heated in the presence of the bis(pinacolato)diboron.

7.4 Alkylborane Radical Traps

The radical addition of alkylboranes to α,β -unsaturated ketone and aldehyde produces transient boron enolates that are usually hydrolyzed (see Section 4.1.1). Interestingly, these boron enolates have been used in aldol reactions as shown previously (Scheme 25). The generation of boron enolates from α -iodocarbonyl compounds represents an interesting alternative to the use of bases.¹⁰² This approach is illustrated by the work of Danishefsky who has treated an α -iodolactam in the presence of the aldehyde with triethylborane at -78°C to effect a rapid, quantitative, and completely stereoselective aldol coupling (Scheme 76). This reaction provides the full skeleton of the naturally occurring alkaloid UCS1025A.²¹¹ This remarkable process, which presumably passes through the intermediacy of a boron enolate,

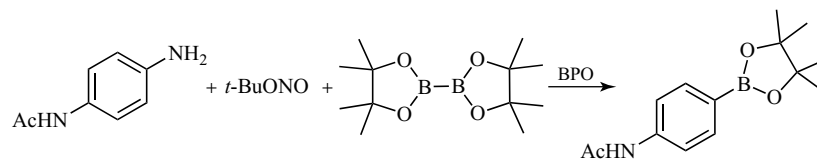
produces no β -elimination product and excess aldehyde may be recovered intact.

7.5 α -Boryl Radicals

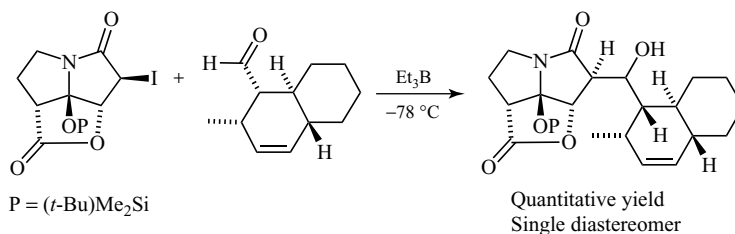
The cyclization of radicals substituted by a boron atom was reported by Carboni.²⁰⁶ More recently, Batey reported inter-²¹² and intramolecular²¹³ reactions involving α -boryl radicals. The radicals are easily generated from the corresponding iodides and possess an ambiphilic character.

8 CONCLUSIONS

The tremendous development of the use of radicals in organic synthesis and the necessity to avoid the use of tin derivatives because of their toxicity has led to a revival of the radical chemistry of organoboranes. The use of triethylborane as an initiator for radical chain reactions is now part of the classical arsenal of organic chemists. Generation of more complex and functionalized radicals from organoboranes is of great interest since a large variety of olefins become a potential source of radicals. Interestingly, organoboranes could also play the role of chain transfer reagents in radical processes. Owing to the particularly rich reactivity of boron derivatives, the design of tandem processes involving radical and nonradical



Scheme 75 Sandmeyer borylation.



Scheme 76 Key aldol process in the synthesis of UCS1025A.

reactions is possible. Boron derivatives are also at the origin of some of the most promising reagents to replace tin hydride in radical-reductive processes. Spectacular developments in this particular field are expected in a near future.

ACKNOWLEDGMENTS

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Unusual Cyclizations

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1 INTRODUCTION

The ability to create cyclic structures from acyclic precursors in a regio- and stereocontrolled manner is indispensable for the construction of complex organic molecules. Radical cyclizations, in particular those which form five- and six-membered cycles, are well documented and reliable elements of modern synthetic designs. However, some cyclization patterns remain underrepresented. In this article, we analyze several factors that render such cyclizations unusual.

The first factor, which is well recognized and discussed in detail in two earlier reviews by Srikrishna¹ and Walton,² is the ring size. The formation of smaller three- and four-membered rings is disfavored by the strain effects in the products, whereas the formation of medium-size 7+-membered rings is disfavored by entropic factors. Owing to the presence of two excellent reviews on these particular types of underrepresented radical cyclizations, this discussion mostly concentrates on the new, post-2006, developments in this area.

The second factor that makes certain cyclizations unusual is stereoelectronics. A ring closure proceeds rapidly only when efficient overlap of the bond-forming orbitals is possible. Guidelines based on the favorability of these interactions, allowing for the rational design of cyclization reactions, are based on “the Baldwin rules”³ and, for the radical processes, on a set of fundamental principles offered by Beckwith.^{4,5} It is well recognized that stereoelectronic factors favor exocyclizations in tetragonal

and trigonal systems, while for digonal closure, the principles of Baldwin and Beckwith diverge (*vide infra*). The (3,4,5,6)-*endo*-tet and (3,4,5)-*endo*-trig processes are unfavorable according to *both* Baldwin and Beckwith rules. Although the *endo*-tet reactions proceed through a cyclic transition state, they do not lead to cyclic products and, thus, are not included in this article (Figure 1).

Thermodynamics is the third factor that can influence how common a cyclization pattern is. Although endothermic ring closures are less common in the literature, such closures can be rendered efficient when they are coupled to a subsequent thermodynamically favorable step. Recent literature includes a number of such cyclizations that occur efficiently when the higher energy intermediate is trapped by a fragmentation or a fast exothermic cyclization.

Finally, the choice of functional group and the type of bond formed at the point of ring closure remains relatively limited. Attack at a double bond is the most common choice for a cycle-forming process. Attack at the single or triple bond (-tet or -dig cyclizations, respectively) remains relatively underrepresented. Similarly, the formation of a C–C bonds are the most prominent in radical cyclizations. The two ways in which C–heteroatom bond is formed include either addition of a heteroatom radical to an olefin/alkyne or addition of a carbon radical to the heteroatom of a C=X bond. Both of these unusual forms of cyclic closure are discussed with respect to both nitrogen and oxygen species.

Taking into account these considerations, this article is organized as follows. We begin with a

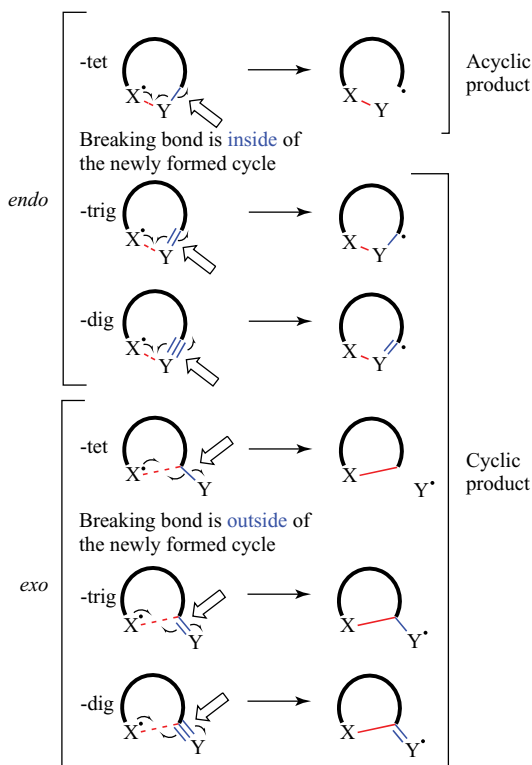


Figure 1 Comparison of the six possible patterns for intramolecular radical reactions. All but the *endo*-tet paths lead to cyclic products.

short discussion of the recent developments in the formation of small cycles (Section 2). We continue with stereoelectronically unfavorable modes of cyclic closure in the formation of five-membered rings (the 5-*endo* cyclizations). In the latter case, we pay special attention to such processes that involve alkynes (the 5-*endo*-dig cyclization). These processes are particularly unusual as the first example of an efficient 5-*endo*-dig radical cyclization at ambient conditions was reported only in 2002⁶ and an efficient C–C bond formation via a 5-*endo*-dig radical closure was first achieved only in 2008 (Section 3).⁷ We then discuss an unusual type of cyclization reaction where *two* radical centers are formed *simultaneously* from a closed-shell reactant in the construction of five- and six-membered rings (Section 4). In Section 5, we briefly summarize the post-2006 developments in the formation of larger cycles not covered in the recent review of Walton.² In Section 6, we discuss radical cyclizations that involve the formation of carbon–heteroatom bonds.

A selection of unusual cyclizations discussed in this work along with the relevant kinetic information are presented in Figure 2.

2 UNUSUAL CYCLIZATIONS LEADING TO THE FORMATION OF SMALL CYCLES

The formation of small cycles is difficult owing to the intrinsic strain energy accumulated in the small rings. As a result, thermodynamic factors usually favor the reverse reaction—the radical ring-opening. For example, both 3-*exo* and 4-*exo* cyclization modes are stereoelectronically favorable because the orbital overlap needed to form the bond closing the cycle is easily achieved. However, owing to the microscopic reversibility principle, the same stereoelectronic factors make the cyclopropylmethyl or cyclobutylmethyl ring-opening favored as well. In fact, the cyclopropylmethyl radical opening is so fast and reliable that it serves as a “radical clock” to determine the rate of other radical reactions (see **Radical Kinetics and Clocks**).^{22,23} The kinetics of this ring-opening has been studied extensively.^{24,25} Strategies for shifting these equilibria are based on increasing the thermodynamically favorability of cyclic product formation. Several approaches have been used to overcome the unfavorable strain effect of these small rings (19.2 kcal mol^{−1} in cyclopropane, 21.0 kcal mol^{−1} in cyclobutane)^{26,27}: (i) conjugative stabilization of the radical center, (ii) destabilization of acyclic reactants with strain, (iii) coupling cyclization steps with exothermic and irreversible fragmentation steps.

2.1 Three-Membered Rings

Although the rate constant for ring-opening in the parent cyclopropylmethyl radical is approximately 3 orders of magnitude greater than that of 3-*exo*-trig cyclization at 27 °C (9×10^7 vs 2×10^4 s^{−1}), this equilibrium can be shifted by the use of radical-stabilizing groups on the olefin. In 1990, Ingold *et al.* reported a rate constant for 3-*exo*-trig cyclization of 1,1-dideutero-4-phenyl-3-butenyl radical to be 1.2×10^7 s^{−1} at 42 °C, where the ring-closed form had become thermodynamically preferred.⁹ Beckwith and Bowry found that ester substitution also favorably shifted the equilibrium

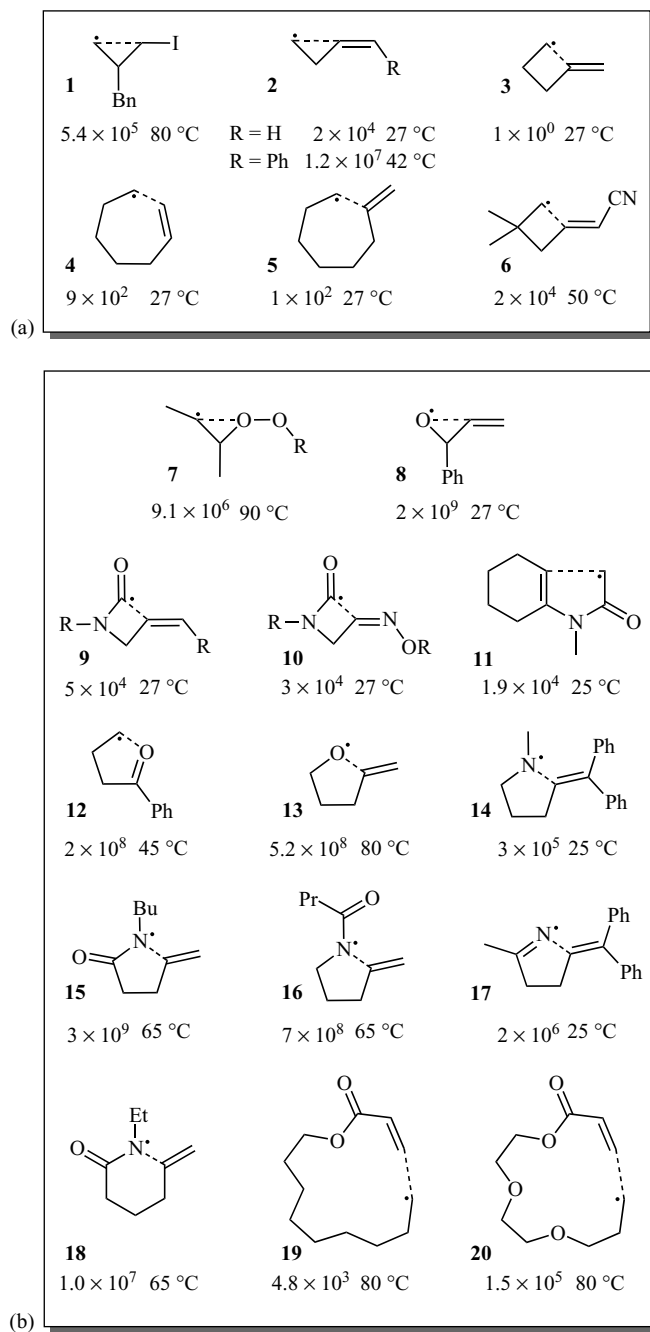


Figure 2 Rate constants (k_c , s^{-1}) of unusual cyclizations discussed in this work forming carbocycles (a) and heterocycles (b) (**1** Ref. 8, **2** Ref. 9, **3** Ref. 10, **4** Ref. 11, **5** Ref. 11, **6** Ref. 12, **7** Ref. 13, **8** Ref. 14, **9** Ref. 15, **10** Ref. 15, **11** Ref. 16, **12** Ref. 17, **13** Ref. 18, **14** Ref. 19, **15** Ref. 20, **16** Ref. 20, **17** Ref. 19, **18** Ref. 20, **19** Ref. 21, **20** Ref. 21).

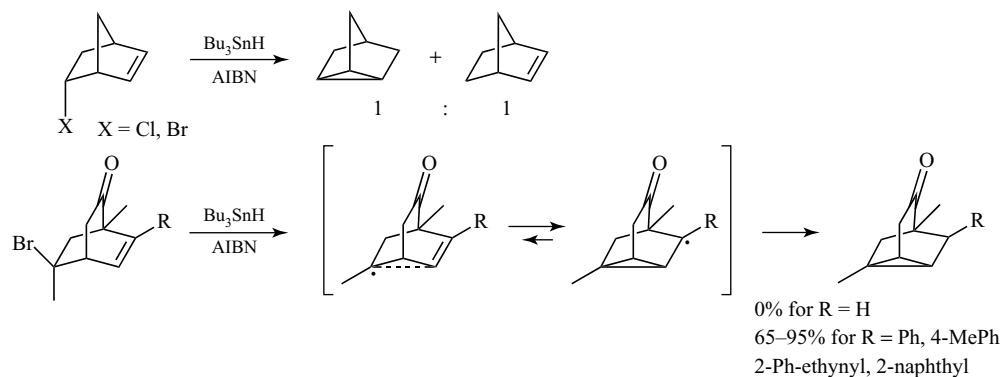
toward cyclic products (Ph k_c/k_{ro} = 17.5, CO₂^tBu k_c/k_{ro} = 1.3).^{23,28}

The relative magnitude of strain and conjugation effects on the thermodynamically controlled efficiency of 3-*exo*-trig cyclization is illustrated by comparison of data by Kuvila and coworkers on the cyclizations of bicyclic[2.2.1] and [2.2.2] halides. Reaction of the more strained [2.2.1] system resulted in a 1 : 1 mixture of cyclopropane and reduced products without the need for radical-stabilizing groups. When the strain of the reactant was decreased, no cyclopropyl products were observed. However, upon introduction of radical-stabilizing aromatic or ethynyl groups, the 3-*exo*-trig product could be trapped efficiently in 65–95% yields (Scheme 1).²⁹

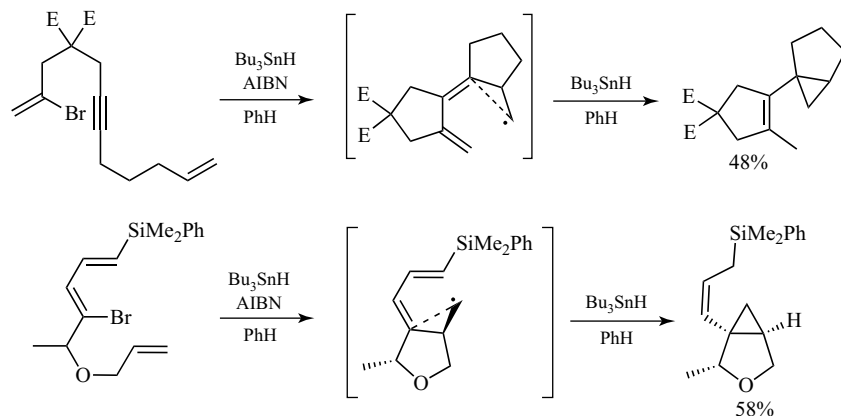
Allylic stabilization can also tip the balance in favor of the ring-closed product. Journet and Malacria,³⁰ as well as Weng and Luh,³¹ have

observed a regioselective 3-*exo*-trig closure to terminate cascades, forming an allylicly stabilized cyclopropylmethyl radical (Scheme 2). Although a 6-*endo*-trig closure would also give an allylic radical, no product derived from this path was observed.

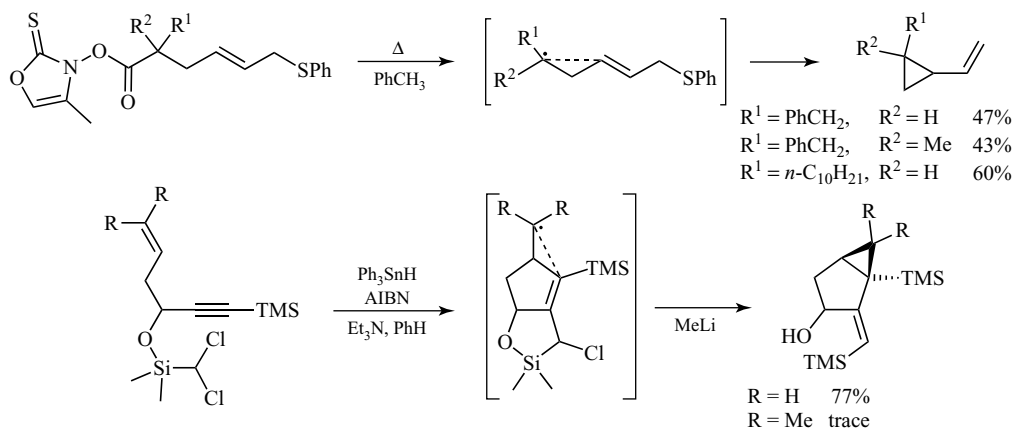
Čeković and Saičić have shown that cyclopropylcarbinyl radicals can also be trapped through an exothermic β -scission.^{32,33} Introduction of an allylic phenylthio group in the fifth position (with respect to the site of initial radical formation) was sufficient to obtain vinyl cyclopropanes in 43–60% yields (Scheme 3). Recently, this strategy has been adopted by Fensterbank, Malacria, and coworkers, who utilized the elimination of a chlorine atom to terminate a radical cascade of cyclizations, using the (dichloromethyl)dimethylsilyl ether functionality as both a site for initiation (loss of the first chlorine



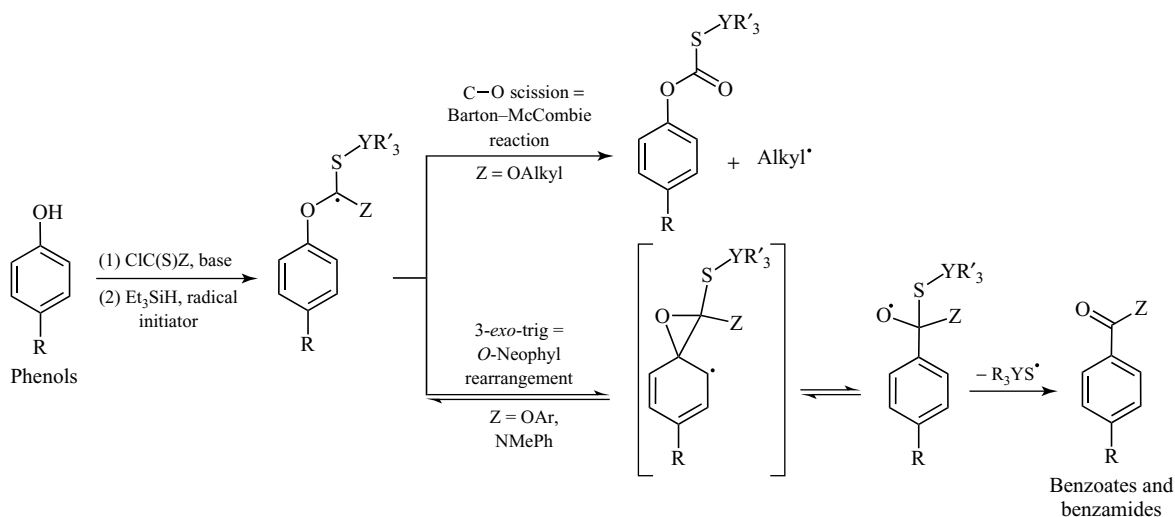
Scheme 1 3-*Exo*-trig cyclizations facilitated by strain in the starting material and conjugative stabilization of the cyclopropylcarbinyl radical.



Scheme 2 3-*Exo*-trig closures forming stabilized allylic radicals.



Scheme 3 3-Exo-trig closure trapped by an exothermic β -scission reaction.



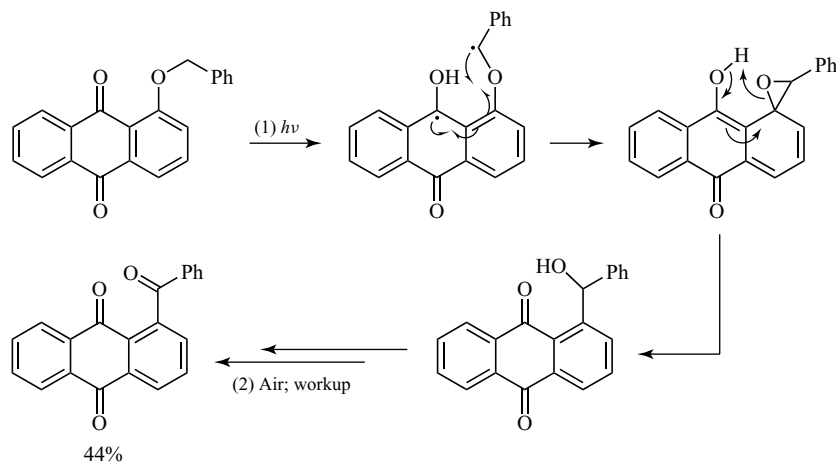
Scheme 4 3-Exo-trig closure onto an aromatic ring as a key step in a phenol-benzoate conversion via *O*-neophyl rearrangement/fragmentation cascade.

atom) and termination (loss of the second chlorine atom).³⁴ The stability of the intermediate radical was found to be critical to the success of the full cascade. While primary radicals underwent 3-*exo*-trig closure efficiently (77%), the tertiary radical did not afford the desired tricyclic product (Scheme 3).³⁴

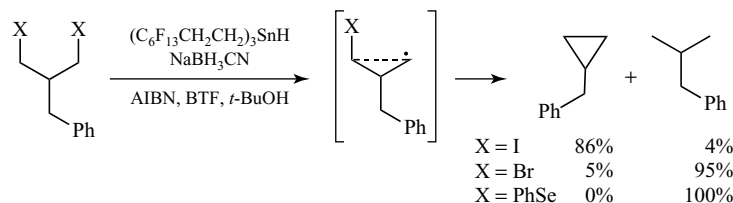
Baroudi and Alabugin have shown that the competition between scission of a $\text{O}-\text{C}_\beta$ bond^{35–39} and 3-*exo*-trig cyclization on aromatic rings (*O*-neophyl rearrangement) is shifted in favor of cyclization when C_β is sp^2 -hybridized.^{40–47} For these systems, the 3-*exo*-trig product does not always correspond to an energy minimum and, even if formed, reversibly

opens to establish a transient equilibrium between the *O*- and *C*-centered radicals, usually favoring the more stable *C*-centered radical.^{48–56} The direction of this reaction was controlled via incorporation of a delayed fragmentation step, cleaving the weak $\text{C}-\text{S}$ bond (Scheme 4). This procedure can be used for metal-free transformation of phenols into benzoates and benzamides.

Jones and coauthors reported a 3-*exo*-trig cyclization on an allylic radical⁵⁷ in the process of photochemical isomerization of 1-benzoyloxy-9,10-anthraquinones (Scheme 5). In contrast to other *O*-neophyl radical rearrangements



Scheme 5 The photochemical isomerization of 1-benzyloxy-9,10-anthraquinones, where the 3-*exo*-trig closure is coupled with radical recombination.



Scheme 6 3-*Exo*-tet radical cyclizations.

(see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**), the energy cost for the formation of a strained, dearomatized three-membered intermediate is in this case partially compensated by the coupling of the two radicals and return to the ground state hypersurface.

In contrast to the 3-*exo*-trig cyclization, their 3-*exo*-tet counterparts (intramolecular S_H2 reaction) are essentially irreversible. Curran and Gabarda found that the reductive radical cyclizations of simple 1,3-diiodopropane derivatives are efficient (86%) with less than 5% of doubly reduced product observed (Scheme 6). The rate for cyclic closure was determined to be $\sim 5 \times 10^5 \text{ s}^{-1}$.⁸ Togo and coworkers have shown that 1,3-dibromopropanes also undergo efficient 3-*exo*-tet closure in the presence of SmI_2 or In powder. The possible ionic mechanism, via reduction of the carbon radical prior to cyclization, was ruled out when only cyclopropyl products were obtained upon reaction in aqueous media and no products of protonation of the putative anion was observed.^{58,59} Peroxide bonds have also

been shown to be good platforms for 3-*exo*-tet closure (*vide infra*).

2.2 Four-Membered Rings

As discussed above, exocyclic closure is stereo-electronically favored. However, even under kinetic control, thermodynamic contributions can modify selectivity and relax intrinsic stereoelectronic preferences in two ways. First, in accordance with the Hammond–Leffler postulate,^{60,61} exothermic reactions have early, reactant-like transition states and consequently require less distortion from the reactant geometry in order to reach the transition state (TS).⁶² Decreased distortions often alleviate geometric requirements needed to reach the optimal bond-forming trajectories. Second, thermodynamic contributions directly lower the activation barriers in exothermic reactions relative to the barriers of the analogous thermoneutral or endothermic processes. Unlike other ring closures (3-*exo*/4-*endo*,

5-*exo*/6-*endo*) where both products have a similar amount of strain, the competition between 4-*exo* and 5-*endo* closure onto both olefins and alkynes is delicately balanced because the aforementioned thermodynamic contributions favor the formation of 5-*endo*-products. In this section, we discuss several examples where the interplay of sterics and electronics can be adjusted to efficiently afford the cyclobutyl product.

Similar to the 3-*exo*-trig closures discussed above, 4-*exo*-trig reactions are reversible and, in the absence of sufficient stabilizing groups, the isomerization equilibrium is shifted to the acyclic radical. For example, while 2-bromo-3,3-dimethylpentene gives only reduction product under standard tin radical conditions,⁶³ a cyano group provides enough stabilization to the cyclobutylcarbiny radical to yield an approximately 1 : 1 mixture of cyclic and reduced products.¹² The combined effects of methylthio and *p*-tolylsulfonyl groups provide slightly higher cyclic : reduced product ratios,⁶⁴ whereas ester substitution was sufficient to exclusively obtain the 4-*exo*-trig product in 72% (Scheme 7).⁶⁵

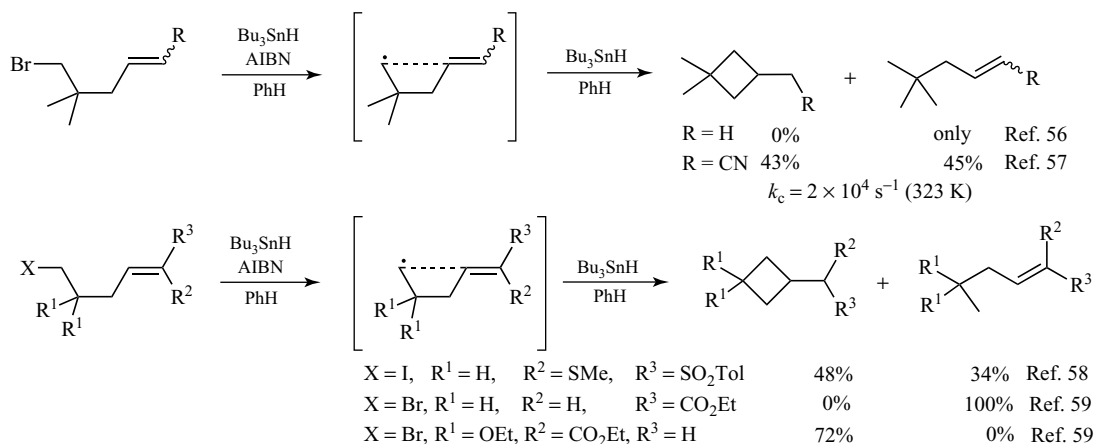
The majority of 4-*exo* radical cyclizations in the literature are focused on the synthesis of β -lactams from carbamoylmethyl radicals, a process that was thoroughly covered by the recent review of Walton.² The factors that influence the regioselectivity of cyclic closure of these systems have been reviewed by Ishibashi.⁶⁶ The results indicate that 4-*exo*-trig closure of carbamoylmethyl radicals proceeds under kinetic control⁶⁶ as the authors observed the 4-*exo*-

to 5-*endo*- switch in regioselectivity when the temperature was increased from room temperature to 110 °C.^{67,68}

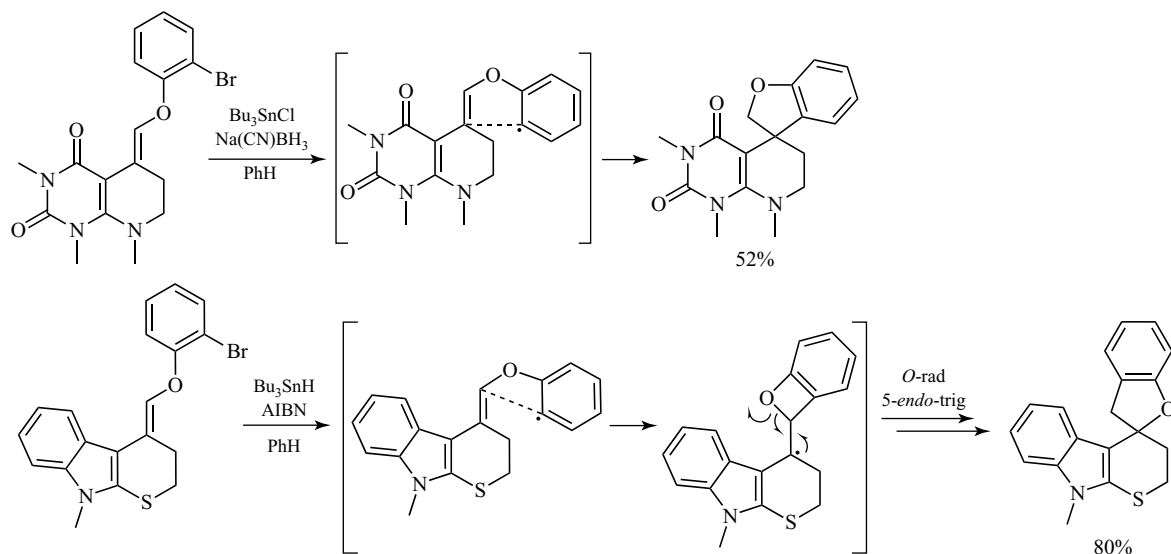
Control over the delicate balance in this pair of reactions can be challenging. While conjugation with an olefin provided sufficient stabilization to afford cyclopropanes (*vide supra*), Majumdar and coworkers found that it was not enough to prevent a 5-*endo*-trig closure where an anomeric radical was formed.⁶⁹ However, when the cyclobutylcarbiny radical was conjugated to an indole ring, the initial ring closure was selective for the 4-*exo*-trig pathway (Scheme 8).⁷⁰

As shown by Clark *et al.*, the regioselectivity can also be controlled through steric effects at the site of attack (Scheme 9). When the enamine was *exo* to the cyclohexane ring, the carbamoylmethyl radical (generated using a resin-bound CuBr catalyst) selectively attacked the less-hindered position in a 4-*exo*-trig fashion, yielding the β -lactam. When an *N*-cyclohexenyl group was employed, attack again occurred at the least hindered position, this time producing a mixture of 5-*endo*-trig products.⁷¹

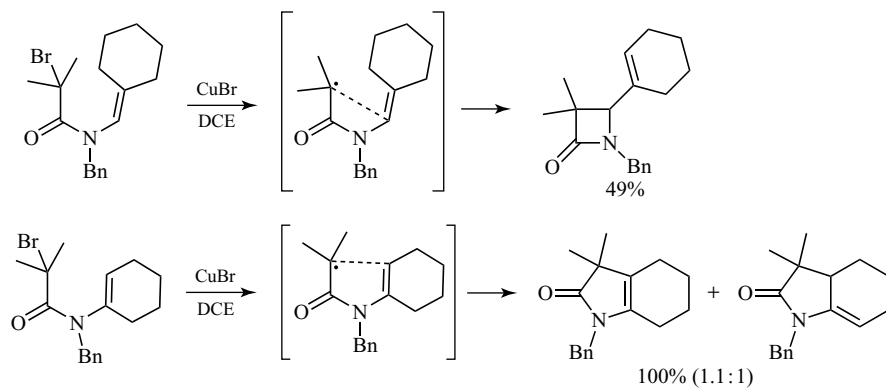
Another way to facilitate 4-*exo*-trig closure is through the restriction of conformational flexibility and trapping of the cyclobutylmethyl radical in a subsequent cyclization. After an initial 5-*exo*-trig cyclization, Gharpure and Porwal found that the product of 4-*exo* closure onto the internal olefin could be successfully trapped in a final 5-*exo*-trig closure (Scheme 10).⁷² However, attack at an exocyclic vinyl ether in the absence of an intramolecular



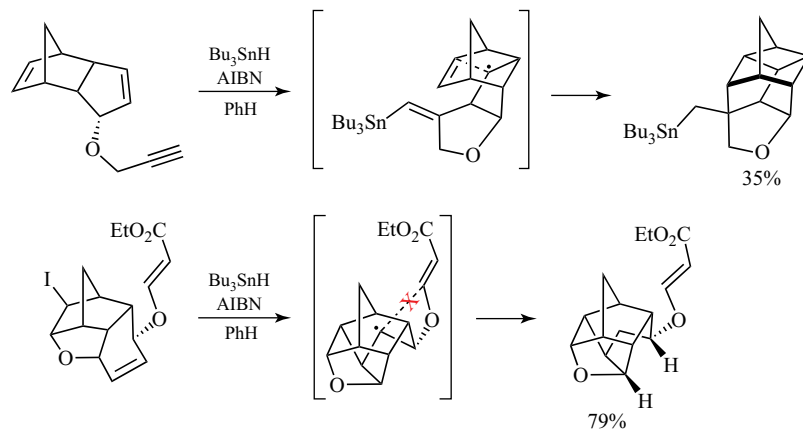
Scheme 7 Both the Thorpe–Ingold effect and stabilization of the cyclic radical are necessary to promote 4-*exo*-trig closure of primary carbon radicals.



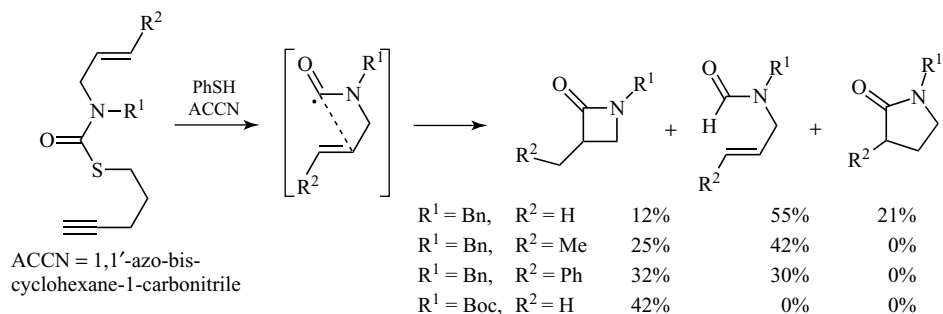
Scheme 8 Effect of cyclic radical stability on 4-*exo*-trig/5-*endo*-trig regioselectivity.



Scheme 9 Effect of alkene substitution on the 4-*exo*-trig/5-*endo*-trig regioselectivity.



Scheme 10 Trapping of the cyclobutylcarbonyl radical in a strained system via fast 5-*exo*-trig closure.



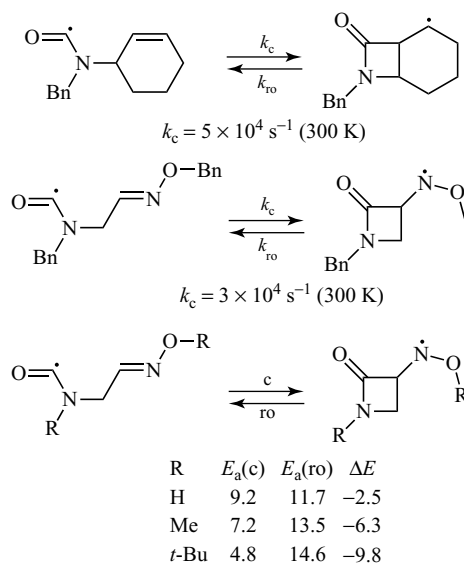
Scheme 11 Control of efficiency and regioselectivity by substituents on both the olefin and nitrogen.

radical trap, produced no cyclobutyl product.⁷³ This is in contrast to Jung's results (Scheme 7) where a carbon radical adjacent to two alkoxy groups underwent 4-*exo*-trig closure onto an α, β -unsaturated ester in 72% yield.⁶⁵

As mentioned previously, the synthesis of β -lactams has been a major focus of the 4-*exo*-trig literature. As discussed by Walton, the less common retrosynthetic disconnection in their formation involves a carbamoyl radical.² A recent example detailed the substituent effects on both the olefin and the nitrogen. For the *N*-benzyl derivatives, high regioselectivity was only observed for substituted olefins. However, the acyclic reduced product was a significant by-product, even when R^2 was a phenyl group. When the benzyl group was replaced with an electron-withdrawing Boc group, the carbamoyl radical closed efficiently onto a terminal olefin in a 4-*exo*-trig fashion without the formation of products derived from 5-*endo*-trig closure or reduction of the carbamoyl radical (Scheme 11).⁷⁴

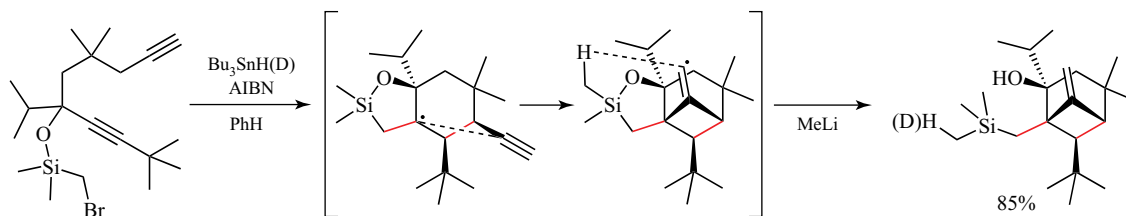
The facilitating effect of the N-substituent on the 4-*exo*-trig process has been examined by Walton *et al.* for carbamoyl radical closure onto oximes. The rate of these cyclizations is comparable to the analogous closures onto a 2-cyclohexenyl group ($k_{\text{C}=\text{C}} = 5 \times 10^4 \text{ s}^{-1}$, $k_{\text{C}=\text{NOR}} = 3 \times 10^4 \text{ s}^{-1}$ at 300 K).¹⁵ The authors performed DFT calculations (B3LYP/6-31+G** level) and found that the activation barrier for 4-*exo* closure dropped from 9.2 to 4.8 kcal mol⁻¹ in parallel with an increase in the exothermicity of cyclic closure (−2.5 to −9.8 kcal mol⁻¹) when the size of the N-substituent was increased from H to *t*-Bu (Scheme 12).

Although 4-*exo*-trig cyclizations are well documented, the literature examples of regioselective 4-*exo*-dig radical closures are scarce. A single

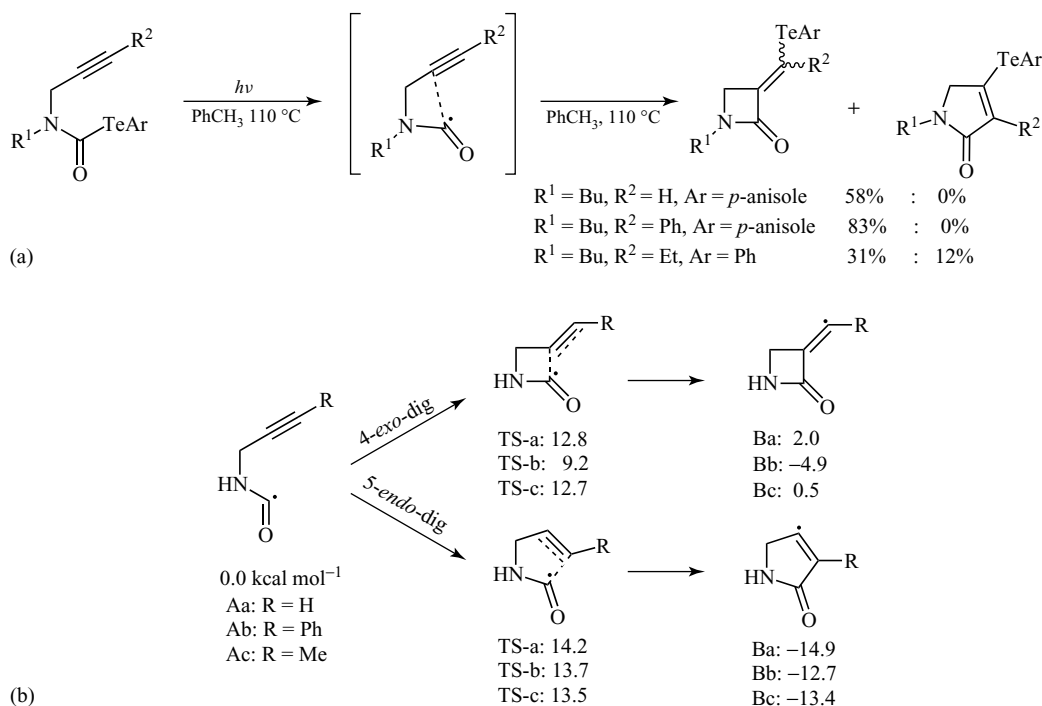


Scheme 12 Comparison of the rates of 4-*exo*-trig closure of carbamoyl radicals onto olefins and oximes. Activation barriers and exothermicities of 4-*exo*-trig closure onto an oxime, varying the nitrogen substituent (kcal mol⁻¹, B3LYP/6-31+G** level).

example of 4-*exo*-dig closure of an alkyl radical has been observed experimentally (Scheme 13). This transformation has been reported by Malacria *et al.* as part of radical cascade leading to the formation of bicyclo[3.1.1]heptanes.^{75,76} The overall yield for the product is 85% yield after reaction with MeLi, which can serve as a lower boundary estimate for the 4-*exo*-dig step. The surprising efficiency of this unprecedented transformation has been attributed to fast intramolecular trapping of the exocyclic vinyl radical via 1,6-*H* transfer (Scheme 13) from a SiCH₃ moiety.



Scheme 13 4-Exo-dig cyclization of an sp^3 carbon with a fully saturated linker as part of a cascade. Bonds formed in the initial 5-*exo*-dig/1,6-*H* transfer/6-*endo*-trig cascade steps occurring before the 4-*exo*-dig closure are shown in red.



Scheme 14 (a) Regioselective 4-*Exo*-dig cyclization of *N*-acyl radicals onto terminal and phenyl-substituted alkynes. (b) Relative energies (in kcal mol⁻¹) of the radical intermediates calculated at UB3LYP/6-311G(d,p) and UB3PW91/cc-pVTZ (in parentheses) levels. [Reproduced from Ref. 77. © Elsevier, 2009.]

Fujiwara *et al.* have reported that the cyclizations of carbamoyl radicals, generated via photolysis of carbamotelluroates, proceed with high 4-*exo*-selectivity for terminal- and phenyl-substituted alkynes in up to 83% yield.⁷⁷ Only when R^2 was an ethyl group did 5-*endo*-dig closure becomes competitive (4-*exo*:5-*endo* ratio = 2.5:1). In accordance with the experimental findings, DFT calculations found that the 4-*exo* pathway is strongly preferred kinetically over the 5-*endo* process for $R^2 = \text{Ph}$ but by a much smaller margin (0.8 kcal mol⁻¹) when $R^2 = \text{Me}$

(Scheme 14). This important work suggests that efforts into these unusual radical cyclizations (4-*exo*-dig) should be continued.

The above experimental results fully agree with the first comprehensive computational analysis of 4-*exo*-dig radical cyclizations by Alabugin and Manoharan.⁷⁸ The calculated 4-*exo*-dig barriers were predicted to be slightly lower than the barrier for competing 5-*endo*-dig cyclization for several parent radicals. These results regarding the competition between 4-*exo*/5-*endo* closure are discussed in detail in the subsequent section (Figure 4).

3 FIVE-MEMBERED RING FORMATION DISFAVORED BY STEREOELECTRONIC FACTORS

Although strain is no longer an issue in the formation of five-membered rings, there are other factors that can make their formation unusual. While exocyclizations are favorable stereoelectronically, the orbital overlap necessary to form the bond closing the cycle is not easily achieved for endocyclic closures of less than six atoms. However, owing to the generally greater thermodynamic stability of five-membered rings, 5-endo cyclizations can often compete successfully with 4-exo closures. We outline the stereoelectronic factors that influence this delicate equilibrium and those that can be efficiently tuned to afford the endocyclic product.

3.1 5-Endo-trig

The two popular set of guidelines proposed by Baldwin³ and Beckwith^{4,5} for the design of cyclizations agree that 5-endo-trig cyclizations are unfavorable but disagree regarding the feasibility of 5-endo-dig cyclizations. While Beckwith's guidelines state that all exoclosures are generally favorable, the Baldwin rules suggest that the 5-endo-dig closure should be more favorable than the competing 4-exo-dig cyclizations. These guidelines are based upon stereoelectronic and steric factors pertaining to the transition state structures of the respective ring closures. As such, knowledge regarding the angle of approach of the attacking species is critical.³ The ideal attack trajectory for trigonal systems was defined based on the well-established Bürgi *et al.*⁷⁹ angle of attack on sp^2 carbon atoms ($\sim 105^\circ$ – 109°). This trajectory optimizes the overlap of incoming nucleophiles with the trigonal $\pi_{C=Y}^*$ orbital. As a consequence, 5-endo-trig cyclizations were considered unfavorable owing to the strained transition state in achieving this approach angle. However, there are a plethora of examples of the respective trigonal closure. Several excellent reviews thoroughly cover the wide variety of literature on this topic through 2002.^{80,81}

Chatgililoglu, Guerra *et al.* examined the competition between 4-exo-trig and 5-endo-trig closures of carbamoyl radicals via competitive kinetic studies as well as a detailed theoretical study (UB3LYP/6-31G* level).¹⁶ They found that,

contrary to previous beliefs, 5-endo-trig closure is kinetically favored, exhibiting lower activation barriers than 4-exo-trig in almost every case. Although the angle of attack for 4-exo closure (111° – 118°) is closer to the angle of intermolecular addition of a methyl radical to ethylene⁸² compared to that of 5-endo (87° – 89°), there is a significant amount of strain energy in attaining the transition state for exocyclic closure ($6.1 \text{ kcal mol}^{-1}$ vs $0.8 \text{ kcal mol}^{-1}$ for 5-endo). However, these data should not be taken as an evidence of intrinsic stereoelectronic preference for the endo-attack, because the 5-endo-trig cyclizations are much more exothermic than the 4-exo-trig alternative. When the thermodynamic contribution is removed using Marcus theory,⁸³ the intrinsic barriers reveal the inherent preference for 4-exo-trig closure of both the parent and carbamoyl radicals (Figure 3). (K. Gilmore and I. V. Alabugin, unpublished work.)

The 5-endo-trig regioselective closure of carbamoylmethyl radicals has been exploited for the formation of saturated bicyclic γ -lactams.⁶⁸ The yield of the 5-endo-trig product can be improved by stabilizing the acyclic radical, for example, the primary versus benzylic example in Scheme 15.⁸⁴ Ikeda and coworkers⁸⁵ have improved the efficiency of γ -lactam formation of a primary carbamoylmethyl radical via polarization of the olefin.⁸⁴ This 5-endo-trig/radical conjugate addition (RCA) strategy was later utilized by El Bailly in the synthesis of (–)- γ -lycorane alkaloid.⁸⁶

5-endo-trig RCAs^{87,88} have also been used within domino transformations. In particular, Ishibashi and coworkers have reported a number of unusual cascades. An aryl radical was generated with the intention of trapping via regioselective 6-endo-trig closure onto an enamine followed by 5-endo-trig closure onto the pendent α,β -unsaturated carbonyl.⁸⁹ The parent system, however, gave only an 11% yield of the 6-endo closure with no trace of the cascade product. Introduction of a methyl group α to the carbonyl, to stabilize the 5-endocyclic radical, afforded 26% of the bicyclic product and an equal amount of the bicyclic reduced product (no 5-endo, Scheme 16).⁹⁰ As seen with Ikeda's work above (Scheme 15),⁸⁴ stabilization of the pre-5-endo radical also increases the overall reaction yield. In this example, a tertiary intermediate radical was trapped to yield the tricyclic product in 22–36% yield, without the need for added stabilization at the olefin.⁸⁹ Ishibashi *et al.* have published

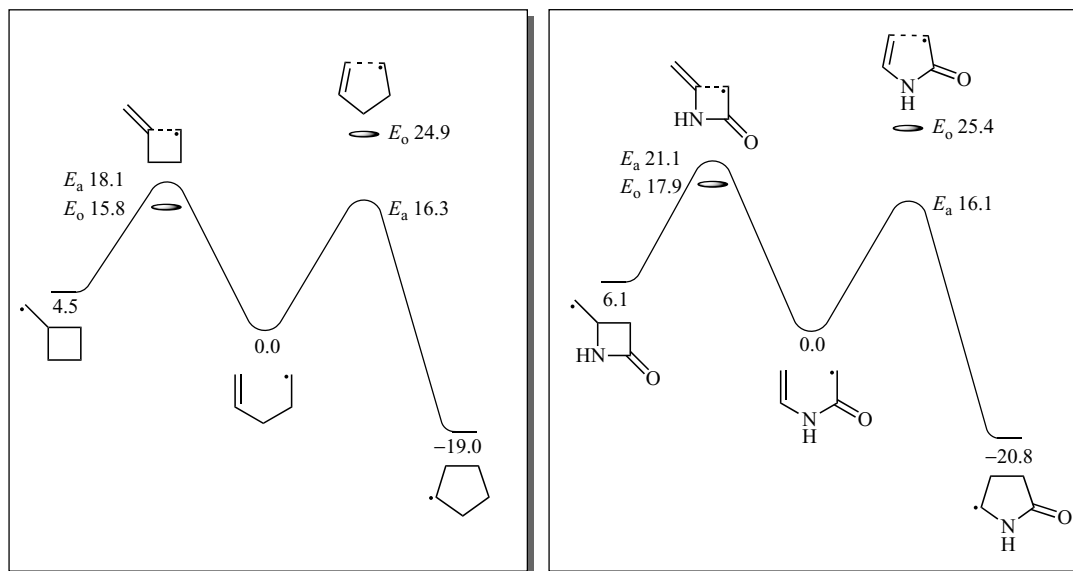
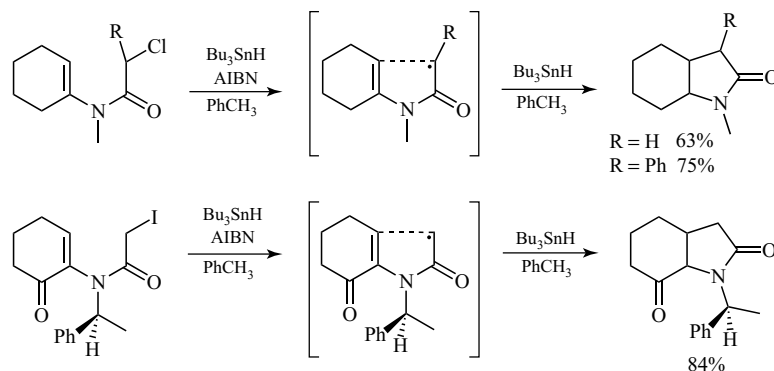


Figure 3 Calculated (UB3LYP/6-31G* level) exothermicities and activation barriers (in kcal mol⁻¹) for the parent and carbamoylmethyl radical depicting the kinetic and thermodynamic favorability of 5-*endo*-trig closure.¹⁶ Intrinsic barriers reveal the inherent preference for exocyclic closure (ovals).

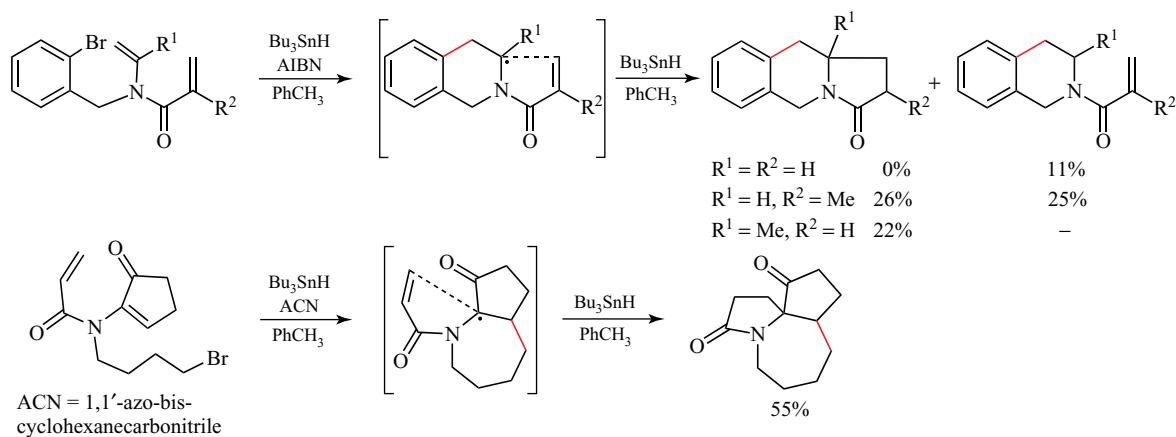


Scheme 15 γ -Lactam formation by 5-*endo*-trig closure of carbamoylmethyl radicals.

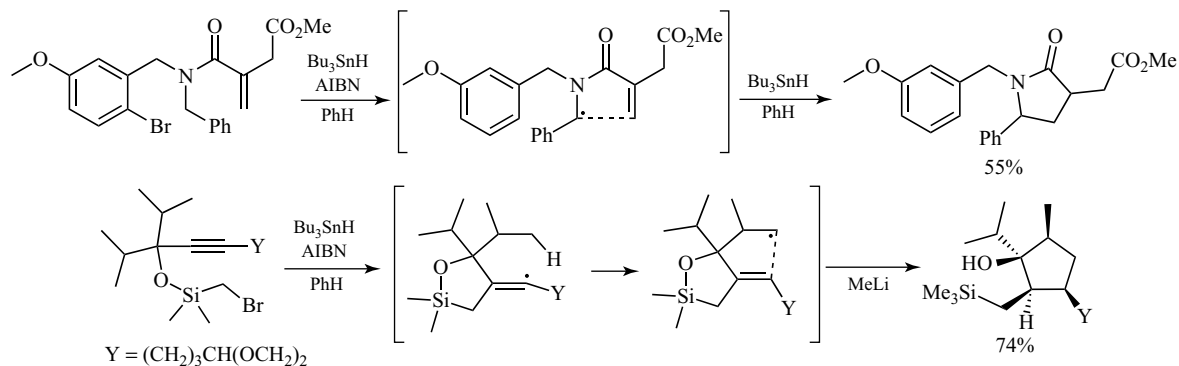
even more unusual examples where a 5-*endo*-trig cyclization is preceded by a 7-*endo*-trig closure onto a cyclic enamine (Scheme 16). The tertiary radical underwent 5-*endo*-trig onto the α, β -unsaturated system in 27–55% yield. This cascade gave slightly higher yields than the respective 6-*endo*/5-*endo* sequence. The authors have successfully utilized this method for the rapid construction of several natural products.^{91–94}

Cascades terminating with a 5-*endo*-trig closure can also be mediated by 1,5-*H* atom transfer (Scheme 17). For example, intramolecular hydrogen abstraction by an aryl radical resulted

in the anomerically stabilized benzylic radical, which Kamimura and coworkers successfully trapped via RCA in 56% yield.⁹⁵ A 1,5-hydrogen abstraction has been used as a key step for setting up a 5-*endo*-trig closure by Malacria and coworkers in their continuing studies on radical reactions of bromomethyltrimethylsilyl propargyl ethers.⁹⁶ Fensterbank, Malacria, *et al.* expanded this work and found that the presence of a sterically demanding quaternary propargylic position was critical to the success of the 5-*endo*-trig closure, which proceeded in up to 74% yield.⁹⁷



Scheme 16 Radical cascades that are terminated by 5-endo-trig RCA. Bonds formed prior to the 5-endo closure are shown in red.

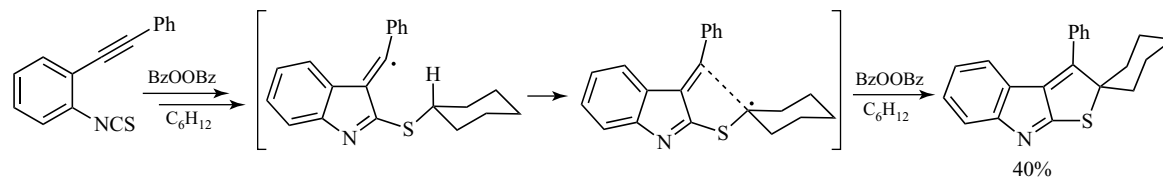


Scheme 17 5-Endo-trig closure set up by 1,5-*H* atom transfer.

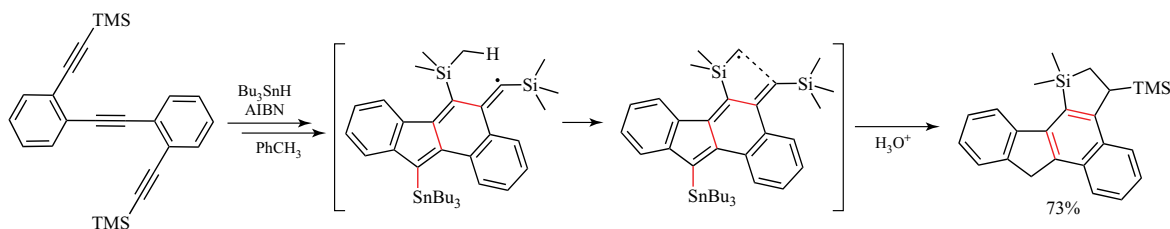
Recently, several other complex cascades have also been terminated in efficient 5-endo-trig cyclizations succeeding 1,5-translocation. In particular, Nanni, Zanardi *et al.* have shown that the addition of a cyclohexyl radical to an aryl isothiocarbamate initiates sequential 5-*exo*-dig closure and 1,5-*H* atom transfer, generating a tertiary anomeric radical (Scheme 18). This radical regioselectively closed in a 5-endo-trig fashion to give a highly

delocalized radical and the spirocyclic product ultimately in 40% yield.⁹⁸

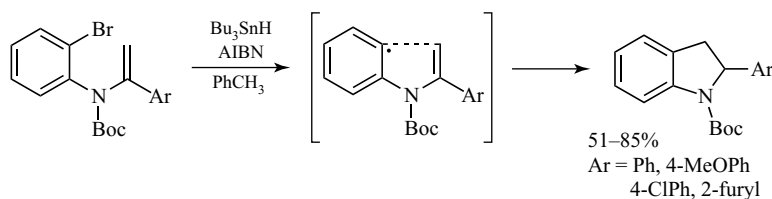
Alabugin and coworkers have set up an efficient 5-endo-trig cyclization via a radical transformation of aryl triynes capped with trimethylsilyl (TMS) groups. This cascade involved chemoselective addition of the Bu_3Sn radical to the central triple bond, two radical cyclizations (5-*exo*-dig and 6-*exo*-dig), and abstraction of a hydrogen atom from the TMS



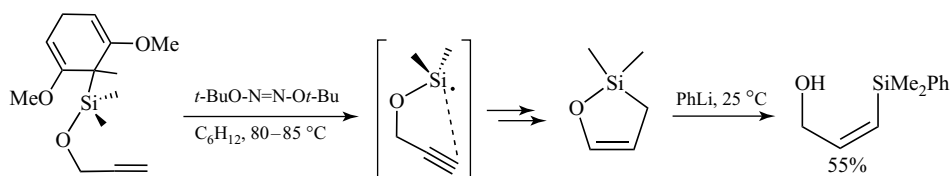
Scheme 18 5-Endo-trig closure of a tertiary carbon radical, set up by an addition, 5-*exo*-dig, and 1,5-*H* atom-transfer cascade.



Scheme 19 5-Endo cyclization of a silylmethyl radical forming a highly delocalized radical. Bonds formed prior to the final closure are shown in red.



Scheme 20 Regioselective closure of an aryl radical yielding the 5-endo radical product stabilized both anomerically and conjugatively.



Scheme 21 5-Endo-dig radical cyclization of Si-centered radical.

group (Scheme 19). While this abstraction was found to be mildly endothermic and had a significant activation barrier (5.3, 16.1 kcal mol^{−1}, respectively, at the UB3LYP/6-31G**//UB3LYP/3-21G* level of theory), the 5-endo-trig closure of the resulting primary radical was highly exothermic (−51.5 kcal mol^{−1}) owing to the aromatization of the polycyclic core.⁹⁹

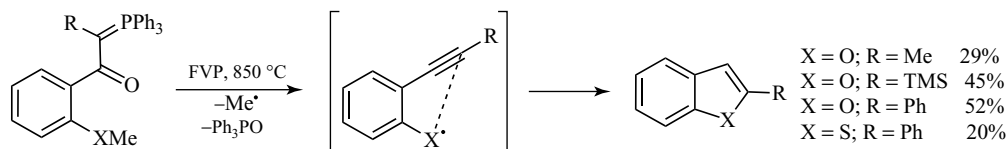
While the above 5-endo-trig cyclizations involve alkyl radicals, Fuwa and Sasaki have shown that aryl radicals efficiently close onto enamines bearing an aromatic group α to the nitrogen. The reaction works equally well using either Bu₃SnH/azobisisobutyronitrile (AIBN) or SmI₂/*t*-BuOH, providing the hydrogenated indoles in 51–85% (Scheme 20).¹⁰⁰

3.2 5-Endo-dig

While the respective trigonal closure is well established, as with the competing 4-exo cyclizations,

5-endo-dig radical cyclizations remained virtually unknown until recently. The 2002 report by Studer remained the only example of an efficient 5-endo-dig cyclization proceeding under kinetic control at relatively mild conditions (Scheme 21).⁶ The efficiency of this 5-endo cyclization is in excellent agreement with the relatively low cyclization barrier of ~ 6 kcal mol^{−1} calculated for this reaction by Alabugin and Manoharan⁷⁸ who have shown that, in addition to the stereoelectronic consequences caused by the presence of long C–Si bonds, this process is assisted by captodative SOMO–LUMO (singly occupied molecular orbital–lowest unoccupied molecular orbital) and HOMO–SOMO (highest occupied molecular orbital–singly occupied molecular orbital) interactions and the β -Si-effect.^{101–103}

An earlier report of the 5-endo-dig closure of O- and S-centered radicals, formed from 2-methoxyphenyl- and 2-methylthiophenyl-substituted phosphorus ylides, proceeded only under drastic



Scheme 22 5-Endo-dig radical cyclizations involved in FVP of substituted phosphorus ylides.

Table 1 Calculated activation barriers, reaction energies, and intrinsic barriers (kcal mol^{-1}) for the 5-endo-dig cyclization of *O*-X-substituted ($X = \text{N}, \text{O}, \text{and CR}_2$) ethynyl benzenes along with the incipient $\text{C} \cdots \text{X}$ distances ($\text{\AA}$) at the UB3LYP/6-31G** level.

	$r(R)$	$r(\text{TS})$	$\Delta E^\ddagger$	ΔE_τ	ΔE_o
$X = \text{NH}$	3.631	2.060	29.9	-13.0	36.1
$X = \text{O}$	3.640	1.922	31.7	-0.5	32.0
$X = \text{CH}_2$	3.706	2.316	31.1	-5.5	33.8
$X = \text{CHCN}$	3.668	2.216	31.9	6.0	28.2
$X = \text{CHNMe}_2$	3.951	2.325	21.3	5.0	18.7

conditions (flash vacuum pyrolysis (FVP) at 850°C , Scheme 22).^{104–106}

The activation barriers for these closures were calculated by Alabugin and Manoharan (Table 1).⁷⁸ As evidenced by the experimental conditions, the cyclizations are only expected to proceed under high temperatures. The trends in calculated reaction energies are controlled by the interplay of *gain* of aromatic stabilization and *loss* of conjugative radical stabilization as the starting materials are transformed into the products. The differences in reaction exothermicities are partially translated into the activation barriers. Interestingly, the cyclizations of CN- and NMe_2 -substituted radicals have almost identical reaction energies but the barrier is more than 10 kcal mol^{-1} lower in the case of the donor substituent. The data strongly suggest that both the activation energy ($\Delta E^\ddagger$) and the intrinsic reaction barrier (ΔE_o) decrease dramatically when electron density increases at the radical center.^{107–116}

Alabugin and coworkers investigated the apparent discrepancy between the Baldwin rules and scarcity of efficient radical 5-endo-dig cyclizations in an initial computational⁷⁸ and a subsequent experimental study.⁷ Analysis of the general factors controlling the efficiency of this process using coupled cluster and DFT methods revealed that the barriers for the parent 5-endo-dig and 4-exo-dig cyclizations are essentially identical, despite the

much higher exothermicity for the 5-endo-dig closure (Figure 4). According to these data, both cyclizations are expected to be sufficiently slow ($\Delta E^\ddagger(5\text{-endo}) = \Delta E^\ddagger(4\text{-exo}) = 17.6 \text{ kcal mol}^{-1}$ at UB3LYP/6-31G** level), potentially allowing side reactions to become competitive.

According to the DFT computations, the analogous cyclizations of vinyl radicals should be significantly faster ($\Delta E^\ddagger \sim 13\text{--}15 \text{ kcal mol}^{-1}$). Notably, the position of the double bond in the reactant is predicted to have a noticeable effect on the cyclization energy and selectivity. An interesting prediction (not confirmed yet experimentally) is that when the vinyl moiety is inside the new five-membered ring (the π -endo closure), 5-endo-dig cyclization should be kinetically favored over the 4-exo closure. In contrast, when the vinyl group is outside of the new ring (the π -exo closure), 4-exo-dig cyclization has a $0.8 \text{ kcal mol}^{-1}$ lower barrier despite being less exothermic than the 5-endo-dig process (Figure 4). Cyclizations of stabilized allyl radical are unfavorable because of the significant penalty caused by the 90° rotation of the radical orbital out of conjugation before it can reach the in-plane π -bond of the target alkyne.

The first efficient experimental 5-endo-dig radical closure of a carbon-centered radical, reported by Alabugin *et al.*,⁷ was discovered when radical cyclizations of 1,5-diynes were triggered with tosyl radicals. The 5-endo-dig product was formed

Motif	(a)	(b)	(c)	(d)
E_a (4- <i>exo</i>):	17.6	14.1	14.2	40.2
E_a (5- <i>endo</i>):	17.6	14.9	13.1	40.2
ΔE_r (4- <i>exo</i>):	-0.8	-12.0	-11.7	26.4
ΔE_r (5- <i>endo</i>):	-18.2	-32.1	-33.8	3.6

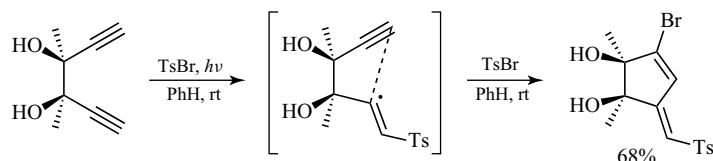
Figure 4 Activation (E_a) and reaction (E_r) energies (kcal mol⁻¹, UB3LYP/6-31G** level) for the 5-*endo*-dig and 4-*exo*-dig cyclizations of (a) nonconjugated sp³ radical, (b) sp² radical (π -*exo*), (c) sp² radical (π -*endo*), and (d) conjugated radical.

in 51–72% yield upon photolytic generation of Ts radicals from TsBr at the room temperature (Scheme 23). Yields were noticeably lower (2–23%) upon thermal activation (refluxing C₆H₆, AIBN). The cyclizations were also stereoselective, since the sulfonyl moiety is capable of selectively lowering the activation barrier for 5-*endo*-dig closure through a favorable hydrogen-bonding interaction with the relatively acidic sp-hybridized C–H bond (Table 2). A favorable stereoelectronic alignment of the vicinal

diols (the gauche effect¹¹⁷) preorganized the two π -systems for the cyclization without concomitant strain introduction.

Both the increased efficiency of the 5-*endo*-dig cyclization of Ts-substituted radicals and the observed stereoselectivity were fully supported by calculated activation barriers for the cyclizations. The introduction of a sulfonyl group next to the radical center leads to a 2.3 kcal mol⁻¹ decrease in the 5-*endo*-dig activation barrier and switch in regioselectivity toward the formation of the five-membered ring (Table 2).

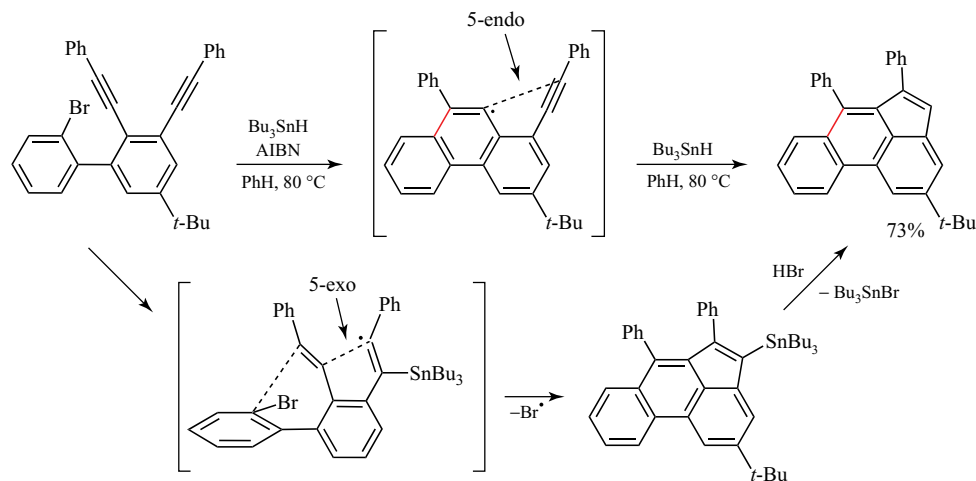
Several other possible examples of 5-*endo*-dig cyclizations can be found in the literature. Anthony and coworkers¹¹⁸ considered the involvement of a 5-*endo*-dig cyclization as a part of an unprecedented 6-*endo*-dig/5-*endo*-dig cascade leading to a relatively efficient (73% yield, Scheme 24) transformation of a constrained enediyne system into phenanthrene derivatives. Subsequent computational analysis, however, suggested that this transformation is likely to proceed via an alternative mechanism that includes intermolecular attack of Sn-radical at the triple bond, 5-*exo*-dig closure, attack at the aromatic ring and protodestannylation.⁷⁸



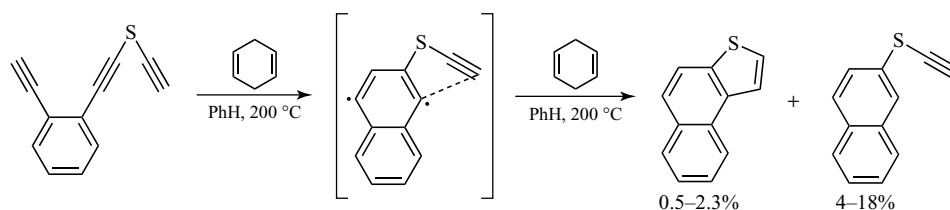
Scheme 23 The first efficient 5-*endo*-dig cyclization of a carbon-centered radical.

Table 2 Activation and reaction energies (kcal mol⁻¹) for 5-*endo*-dig and 4-*exo*-dig cyclizations (UBLYP/6-311 + G**//UBLYP/6-31G** level). Barriers for the Ts-substituted radicals are in bold.

	5- <i>endo</i>		4- <i>exo</i>			5- <i>endo</i>		4- <i>exo</i>	
	E_a	ΔE_r	E_a	ΔE_r		E_a	ΔE_r	E_a	ΔE_r
X = H	14.1	-24.8	13.8	-6.0	X = H	14.1	-24.8	13.8	-6.0
X = Br	13.7	-24.4	13.9	-6.4	X = Br	14.2	-21.4	14.1	-2.4
X = Ts	11.8	-25.7	13.4	-6.0	X = Ts	14.2	-22.1	14.4	-2.7



Scheme 24 Proposed 6-endo-dig/5-endo-dig radical cyclization cascade in brominated biphenyl diacetylenes (a) and an alternative 5-exo-dig mechanism (b).



Scheme 25 The 5-(π -endo)-endo-dig cyclization of the diradical intermediate formed upon Bergman cyclization.

In addition, Matzger and coworkers^{119,120} reported that a radical cascade initiated by Bergman cycloaromatization can be terminated via a 5-endo-dig closure, albeit in low yields (<2.3%, Scheme 25). Although the dominant process was still the formation of bicyclic reduced product, this important result showed that 5-endo-dig cyclizations are capable of competing (though not very efficiently) with H-abstraction even in the presence of a good H-atom donor (1,4-cyclohexadiene).

The experimental observations agree well with the computed activation barrier for this reaction by Alabugin and Manoharan.⁷⁸ The barrier is decreased (by 4.9 kcal mol^{-1}) to the extent that the cyclization should be able to compete with H-atom abstraction from C–H donors. Most of the decrease comes from the thermodynamic component. Since the radical orbital in the reactant is kept out of conjugation by intramolecular restraints, the system does not need to lose this stabilizing interaction in order to reach the transition state, unlike the above-mentioned systems illustrated in Figure 4d. The transformation

is further aided by the formation of an aromatic benzothiophene moiety, which provides an additional $12\text{--}16\text{ kcal mol}^{-1}$ stabilization to the product. Thus, this example provides the first demonstration of aromatic stabilization being a driving force for 5-endo-dig radical cyclizations. Longer C–S bonds also help in alleviating the geometric requirements in achieving the required attack angle.

4 UNUSUAL PATHWAYS FOR THE FORMATION OF FIVE- AND SIX-MEMBERED RINGS

In this section of the article, we briefly discuss the formation of five- and six-membered rings via an unusual type of radical transformation, which is dramatically different from the traditional radical cyclizations discussed above. A typical radical cyclization conserves the number of radical centers in the bond-forming step. In other words, a radical center is present in *both*

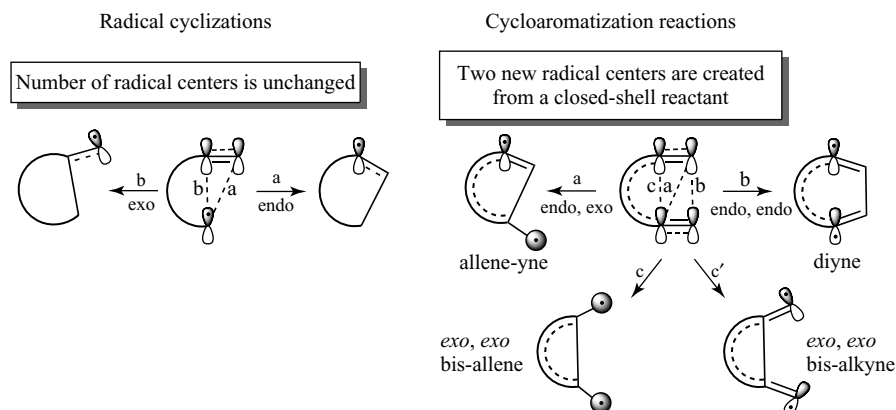


Figure 5 Comparison of radical cyclizations and cycloaromatization reactions. Possible cyclization topologies are shown below together with the suitable starting material needed to give the σ - or π -diradical products.

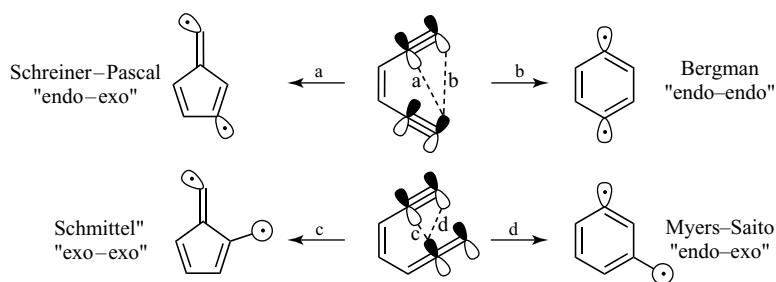


Figure 6 Four cycloaromatization patterns of enediynes and allene enyne.

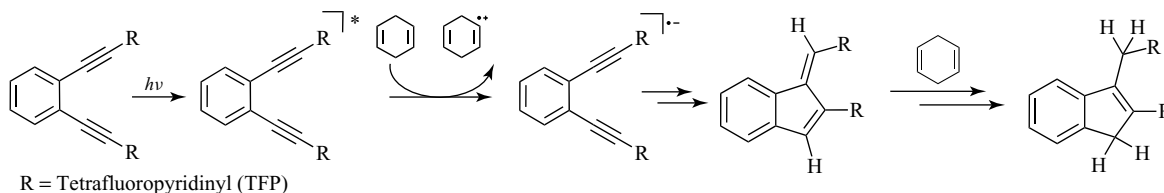
the reactant and the product. However, there is a rapidly growing list of unusual cyclizations that transform a closed-shell, nonradical reactant into a *diradical* product (Figure 5). These atypical transformations are referred to as *cycloaromatization reactions*.

These unusual cyclizations occur without the need for external radical initiators because simultaneous *formation* of two radical centers is *coupled* to the bond-forming step. Diradicals are formed in this processes as *two* π -bonds are traded for only *one* σ -bond. This net loss of one chemical bond makes these processes thermodynamically feasible only when an aromatic system is also formed *simultaneously* with the ring closure. Since σ -bond formation and aromatization of the π -system involves two orthogonal π -arrays, cycloaromatization reactions require reactants that contain two alkynes, two cumulenes, or a combination thereof.

Note that σ -radicals are formed through the endo path, whereas exoclosures may produce either a σ -radical, when a triple bond is involved, or

a conjugated π -radical when the new bond is formed at the central carbon of an allene. The most well-known cycloaromatization process is the transformation of (*Z*)-3-ene-1,5-diyne into a *p*-benzynes diradical (the Bergman cyclization¹²¹), which drew significant attention as the key step in the mechanism of biological activity of natural enediyne antibiotics.¹²²

Figure 6 summarizes the cyclizations of the two prototype molecules, (*Z*) hex-3-ene-1,5-diyne and (*Z*) hept-3,5,6-triene-1-yne. In all of these processes, bonds are formed from in-plane π -orbitals in the presence of an orthogonal π -system. However, it is clear that the properties of the newly formed cyclic conjugated systems can be quite different. A new aromatic system is formed only in the Bergman and Myers-Saito cyclizations and thus, in a sense, only these two processes in Figure 8 are bona fide cycloaromatization reactions. However, with proper design, the other two parent cycloaromatization reactions are also possible. Many examples of the “exo-exo” closure (the Schmittel cyclization)



Scheme 26 PET radical anionic C₁–C₅ closure of 1,2-(bistetrafluoropyridine)enediyne.

are known.^{123–126} The “endo–exo” closure is more difficult to accomplish because the parent transformation has been predicted to be $\sim 40 \text{ kcal mol}^{-1}$ endothermic at a high (BCCD(T)/cc-pVDZ) level of theory.¹²⁷ However, recent experimental findings suggest that even this intrinsically unfavorable process is possible.¹²⁸

A number of reviews are available on various aspects of the chemistry and biochemical application of cycloaromatization reactions. Rawat and Zaleski^{129,130} analyzed geometric and electronic properties of metallocenediynes in thermal Bergman cyclizations, while Basak and coworkers¹³¹ concentrated even more closely on the use of enediynyl ligands in chelation-controlled Bergman cyclizations. The Schreiner group¹³² reviewed the application of computational methods toward a variety of cycloaromatization reactions and König and coworkers¹³³ provided a compendium of experimental results related to the electronic effects on the Bergman cyclization. Intricate details of the biological activity of natural enediynes were most recently reviewed by Shen and coworkers,¹³⁴ whereas the medicinal utility of designed enediynes was expertly discussed by Jones and Fouad.¹³⁵ Alabugin and Breiner dissected orbital and electronic effects involved at the different stages of these processes.¹³⁶ Kar and Basak¹³⁷ compared different approaches to selective activation of enediyne prodrugs including photo- and pH-activation, whereas Popik *et al.*¹³⁸ and Alabugin *et al.*¹³⁹ reviewed light-activated cycloaromatization reactions. Research on new structural^{44,140} and electronic^{141–143} effects useful for the control of such processes continues to develop.

The scope of available cycloaromatization reactions increases dramatically when electron-transfer processes are involved. For example, the formation of five-membered radical-anion products benefits from the aromaticity of the cyclopentadienyl anion (Scheme 26).^{144–147} The results of

such reactions are interesting from a practical perspective (*vide infra*). Photoinduced electron transfer (PET)-mediated reductive C₁–C₅ cyclization of a 1,2-(bistetrafluoropyridine) enediyne led to the formation of indenenes with the concomitant formal abstraction of four H-atoms from the environment.¹⁴⁸

Radical anionic cycloaromatization reactions can be controlled via orbital crossings, involving states corresponding to the population of the *in-plane* and *out-of-plane* orbitals. An interesting consequence of such crossings is that the antiaromatic benzene radical-anion core in the reactant regains aromaticity in the product simultaneously with the formation of a new five-membered aromatic moiety, in a process termed *cyclorearomatization*.¹⁴⁹ Because the reductive C₁–C₅ cyclization results in the abstraction of four hydrogen abstractions from the environment as opposed to two in Bergman cyclizations, this new type of cycloaromatization process has been suggested to increase the efficiency of double-strand (ds) DNA damage.^{150–153} Combined with the ability of these molecules to undergo two-photon excitation¹⁵⁴ and target intracellular DNA,¹⁵⁵ the future medical applications of this *cyclorearomatization* process are promising.

5 UNUSUAL CYCLIZATIONS FORMING MEDIUM AND LARGE RINGS

There are no significant strain, stereoelectronic, or thermodynamic obstacles hindering the formation of six-membered rings by standard radical cyclizations. However, as one increases the ring size, a new set of problems arise from entropic factors. The formation of medium-sized rings (8- to 11-membered) is often the most difficult to accomplish,^{21,156} because only a small subset of the reactant conformational space is preorganized for the cyclization. Regarding nucleophilic *exo-tet* cyclizations, Illuminati and

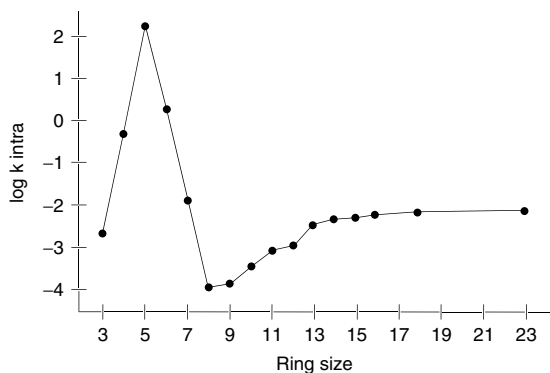


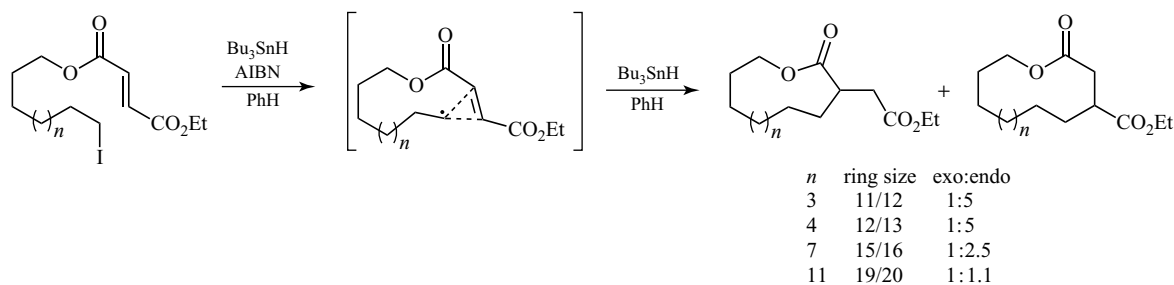
Figure 7 Rate of nucleophilic S_N2 -ring closures with respect to the formed ring size.¹⁵⁶

Mandolini nicely portray the facility of ring formation as a function of size. Of particular interest is the 10^5 increase in rate in going from three- to five-membered ring formation and the million-fold decrease in going from five to eight (Figure 7).¹⁵⁶ Despite this, a variety of methods, including radical closures, have been developed for the synthesis of medium-sized rings. There have been several comprehensive reviews covering the formation of medium- and large-sized rings via radical intermediates.^{157,158}

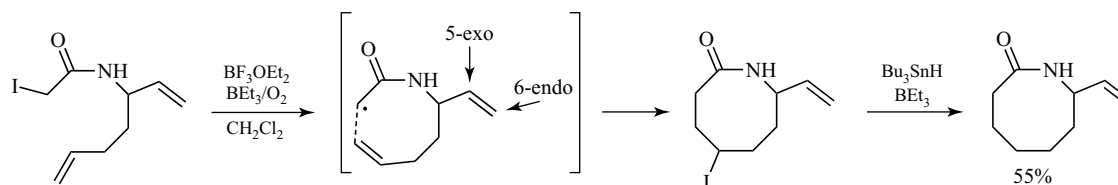
Porter and coworkers have shown that, in trigonal systems, endoclosure is preferred, particularly

for the smaller cycles (12-*endo*/11-*exo*-trig and 13-*endo*/12-*exo*-trig).¹⁵⁹ The effects of chain length, substituents, and solvent on the rate of endocyclic RCA of ω -(acryloyloxy)polyoxaalkyl radicals¹⁶⁰ has been examined thoroughly in the formation of medium/large macroheterocycles by Beckwith, Maillard, and coworkers (Scheme 27).²¹ While nine-membered ring formation was too slow to compete with reduction, the authors found a large rate enhancement for larger ring formation with respect to the all-carbon acrylate derivative (12-*endo*-trig: 1.5×10^5 vs 4.8×10^3 s⁻¹, respectively).

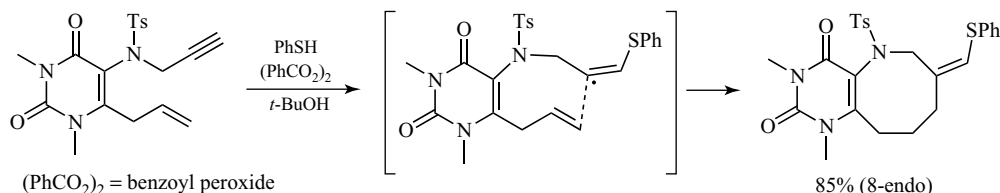
Eight-membered rings can also be efficiently synthesized by radical closure. Li and coworkers, in their investigations of the effects of Lewis acids (LAs) on the efficiency and stereoselectivity of 8-*endo*-trig closure of carbamoyl radicals, have observed the exclusive formation of an eight-membered ring in a system where 5-*exo*/6-*endo* closure is possible.¹⁶¹ DFT analysis (UB3LYP/6-31G* level) revealed that the competing 7-*exo*-trig cyclization suffered from amide bond distortion in the transition state, accounting for a 4 kcal mol⁻¹ higher barrier than the observed 8-*endo*-trig closure. The chemoselectivity observed (8-*endo* vs 5-*exo*) was determined to stem from the amide bond orientation (Scheme 28). While the calculated barriers are similar (8-*endo*, 10.9 kcal mol⁻¹; 5-*exo*, 10.6 kcal mol⁻¹), the *Z*-rotamer is less stable than the *E*-rotamer and radical cyclizations



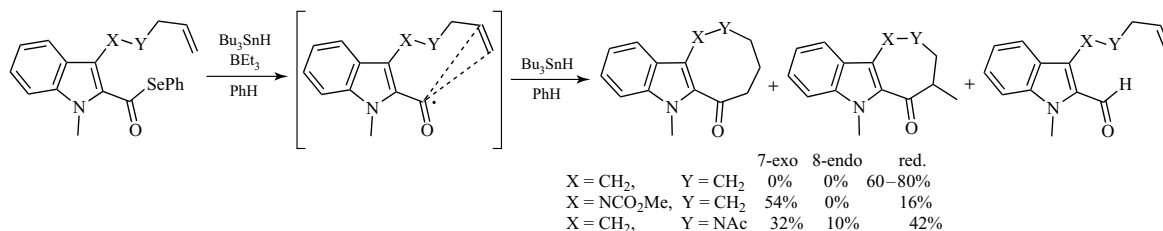
Scheme 27 Decrease in regiospecificity as the size of the ring formed increases.



Scheme 28 Regio- and chemoselectivity controlled by amide bond distortion.



Scheme 29 Formation of partially saturated pyrimidine-fused azocine by 8-*endo*-trig closure.



Scheme 30 Necessity of an electrophilic nitrogen in the acyl radical cyclization/ring-expansion pathway.

have been shown to be faster than the amide bond rotation.^{161–163}

Majumdar and coworkers took advantage of the preferential endo-regioselectivity in their synthesis of pyrimidine-fused azocine derivatives. The vinyl radical closed efficiently onto the monosubstituted olefin to give the 8-*endo*-trig product in 70–85% yield, although the authors did not rule out the ring-expansion pathway following 7-*exo*-trig closure (Scheme 29).^{164,165}

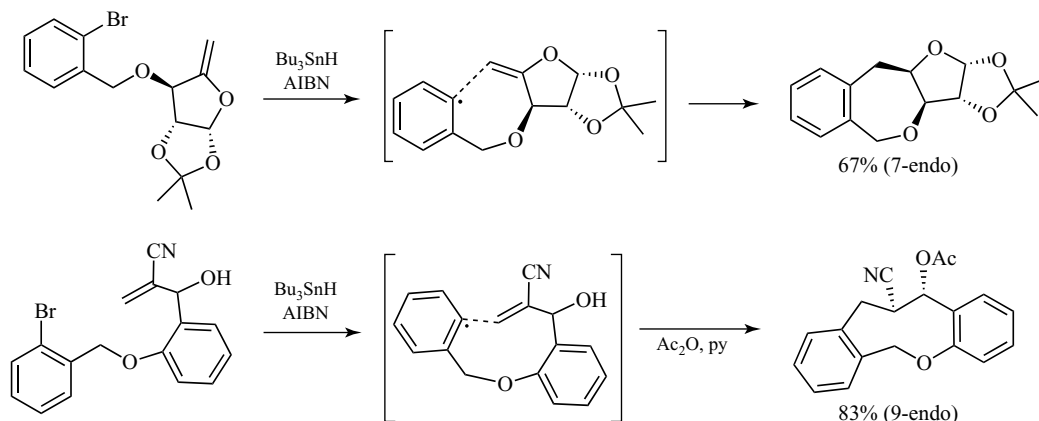
Ring expansion has also been observed in the 7-*exo*/8-*endo*-trig closures of acyl radicals (Scheme 30). Bennasar *et al.* discerned that the presence and position of an electron-deficient nitrogen group was critical to the success of radical closure in the formation of indole-fused eight-membered rings.¹⁶⁶ While only the reduced aldehyde was obtained in the absence of the heteroatom, the cyclizations proceeded with complete endo-regioselectivity for the formation of the tricycle. When the nitrogen was in the β -position relative to the indole ring, a 3 : 1 mixture of endo : exo products was obtained. However, this ratio was shifted to yield more of the eight-membered product when the concentration of hydrogen donor was decreased, indicating a rearrangement/ring expansion was occurring.

Chattopadhyay and coworkers have studied the synthesis of oxocines via the 7-, 8- and 9-*endo*-trig closures of aryl radicals. Unactivated alkenes underwent regioselective endo-closures to form fused

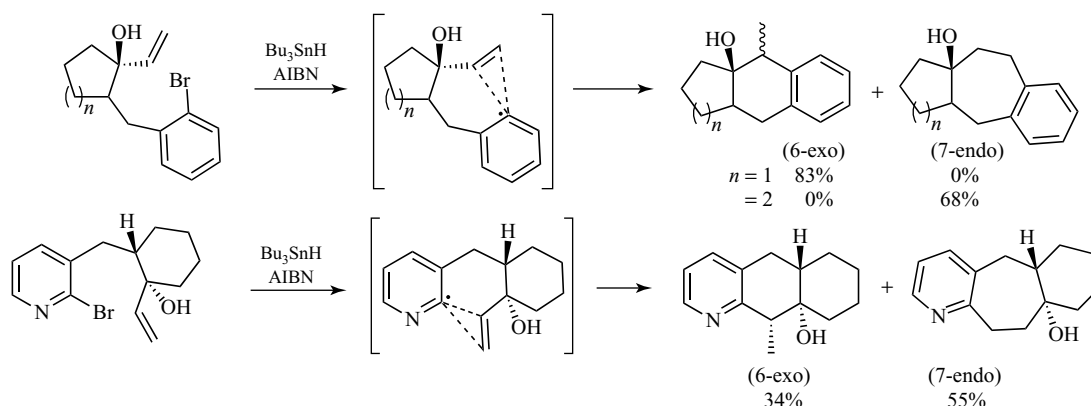
tri- and tetracyclic structures with a similar efficiency (60–70%) for 8,5¹⁶⁷ and 8,6¹⁶⁸ fused ring systems. Electron-poor olefins bearing cyano or ester groups on the interior position of the olefin also underwent regioselective endo-closure, generating nine-membered rings in up to 83% (Scheme 31).^{169,170}

In contrast, the cyclizations of aryl radicals onto vinylcyclohexanols and vinylcyclopentanol are sometimes less selective. Ghosh and Ghatak have observed that closure onto the cyclohexyl derivative proceeds regioselectively in a 7-*endo*-trig fashion, giving the tricyclic structure in 68% yield. However, the cyclopentyl starting material provided only the 6-*exo*-trig product in 83% yield (Scheme 32). 8-Endo and 9-*endo*-trig closures occurred regioselectively for both the cyclohexyl and cyclopentyl derivatives.¹⁷¹ *O*-pyridyl radicals were not found to be as selective for the cyclizations of cyclohexanol derivatives, yielding a mixture of 6-*exo* and 7-*endo*-trig products (Scheme 32). However, for the larger systems, as was observed for the aryl radicals, the cyclizations were regioselective for 8- and 9-*endo*-trig closure.¹⁷²

Contrary to the above-mentioned examples featuring a general endo-selectivity, several exocyclic closures have recently been reported. In their synthetic efforts toward ciguatoxin and 51-hydroxy CTX3C, Inoue, Hiram, and coworkers examined the chemoselectivity of radical cyclizations, with competing attacks at an unactivated alkene



Scheme 31 Regioselective endocyclic closure of aryl radicals.



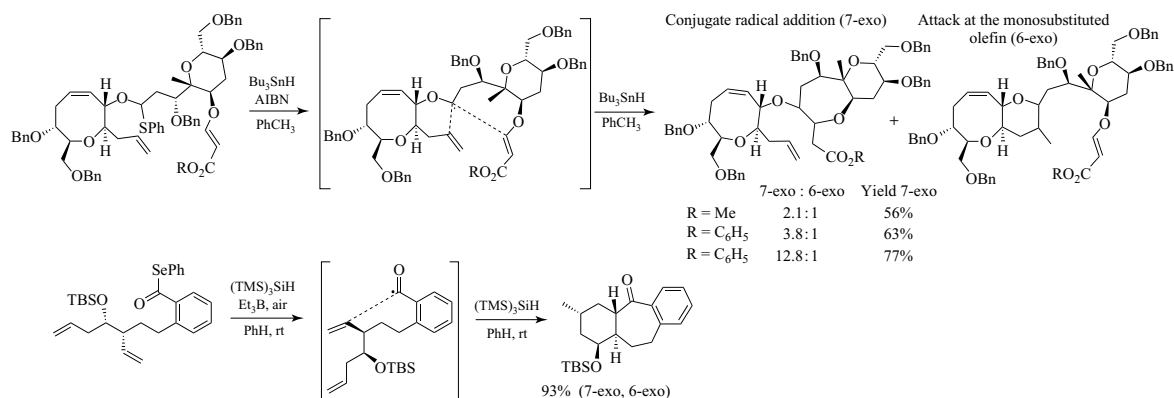
Scheme 32 Regioselectivity of aryl radicals dictated by the size of the cyclic alcohol. Note that *O*-pyridyl radicals lack regioselectivity in this system.

(6-*exo*/7-*endo*) and one which is electron deficient (7-*exo*/8-*endo*). A significant increase in the chemoselectivity, as well as the yield, for 7-*exo*-trig closure was observed when the strength of the electron-withdrawing ester was increased.¹⁷³ Castle *et al.* have shown that 7-*exo*-trig closures onto unactivated monosubstituted olefins are possible, trapping the exocyclic radical in either a 5-*exo* or 6-*exo*-trig closure to give the cascade product in up to 93% yield (Scheme 33).¹⁷⁴

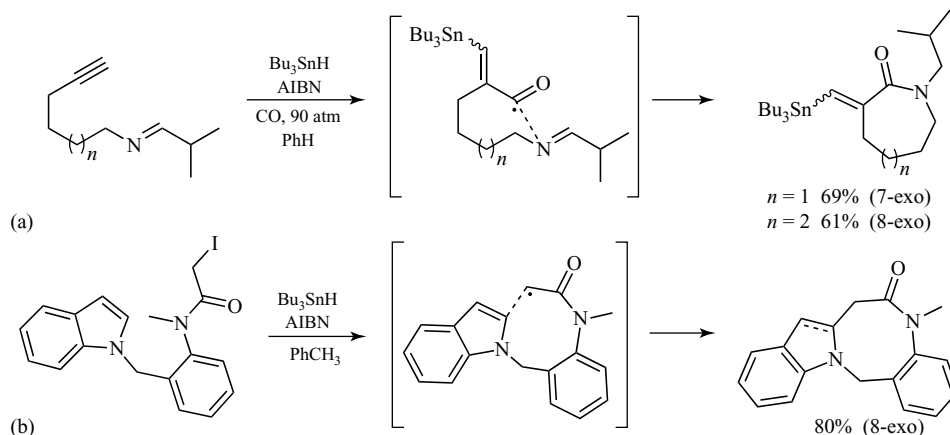
As discussed in the subsequent section, acyl radicals have been utilized in the synthesis of lactams by *N*-philic closure onto imines. Ryu and coworkers have exploited this chemo- and regioselective closure in the synthesis of seven- and eight-membered

lactams by *exo*-trig closure in 69% and 61% yields, respectively (Scheme 34).^{175,176} Bremner and Sengracha have also successfully obtained cyclic amides as a result of 8-*exo*-trig cyclization. The latter regioselectivity was dictated by the formation of a benzylic radical that was trapped either by hydrogen abstraction or aromatization by loss of an adjacent hydrogen atom (Scheme 34).¹⁷⁷

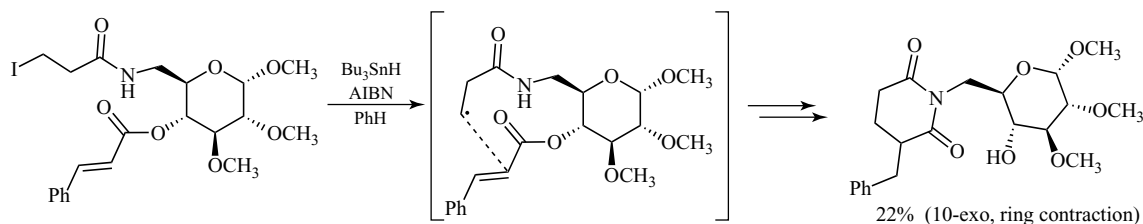
Alves *et al.* observed that benzylic stabilization was sufficient to obtain 10-*exo*-trig closure, as opposed to endocyclic RCA (Scheme 35). The exocyclic benzyl radical was then trapped through hydrogen abstraction and, following a ring-contraction event, the observed imide is obtained in 22%.¹⁷⁸



Scheme 33 7-Exo-trig closure facilitated by either an electron-deficient ester or trapping in a subsequent cyclization.



Scheme 34 Exocyclic closure dictated by the electronics of the transition state (a) and the stability of the cyclic radical (b).



Scheme 35 10-Exo-trig closure forming a benzylic radical.

Additional examples of medium-size ring formation via a CuCl atom-transfer reactions^{179,180} (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**) and titanocene reduction of epoxides¹⁸¹ (see **Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**) are known.

6 CYCLIZATIONS PROCEEDING VIA AN UNUSUAL BOND FORMATION

In the previous sections, we discussed cyclizations rendered unusual by the size of a forming ring. However, independent of the size of the ring formed, certain factors disfavor even the well-represented cyclization topologies and are involved in several

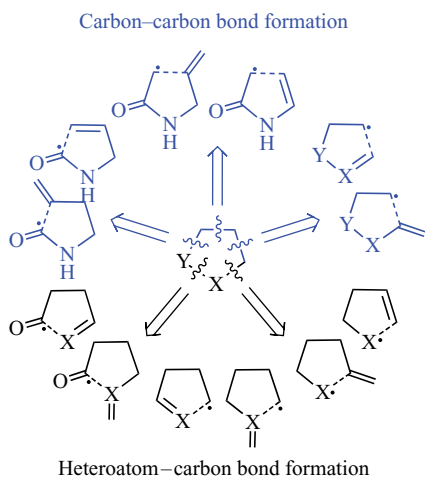


Figure 8 Carbon-carbon and carbon-heteroatom bond disconnections for a representative five-membered heterocycle formation by radical cyclization where $Y = \text{CR}_2$, CO, and $X = \text{O}, \text{N}$.

underrepresented bond-forming reactions. In particular, most cycle closures involve carbon-carbon bond formation via carbon radical addition to an alkene or alkyne, whereas radical ring closure via the formation of a carbon-heteroatom bond is relatively scarce. In the following section, we discuss two common approaches to such C-X bond formation: radical closures at the X-end of a $\text{C}=\text{X}$ bond, or cyclizations of heteroatom- (oxygen- or nitrogen-) centered radicals at a $\text{C}=\text{C}$ bond. Both of these methods often enable efficient construction of useful heterocycles (Figure 8).

6.1 Oxygen- and Nitrogen-Centered Radical Closures

In our discussion of cyclizations mediated via the carbon-heteroatom bond formation, we limit ourselves to the formation of C-O and C-N bonds. We first discuss trigonal and digonal cyclizations of heteroatomic radicals in comparison with the more common carbon derivatives, followed by closures of carbon radicals onto the heteroatom of a $\text{C}=\text{X}$ bond, referred to as X-philic closures (Figure 9, $X = \text{O}, \text{N}$).

6.1.1 Nitrogen-Centered Radicals

The rate of 5-*exo*-trig cyclization of *N*-methylpent-4-enylaminyl radical has been found to lie in the

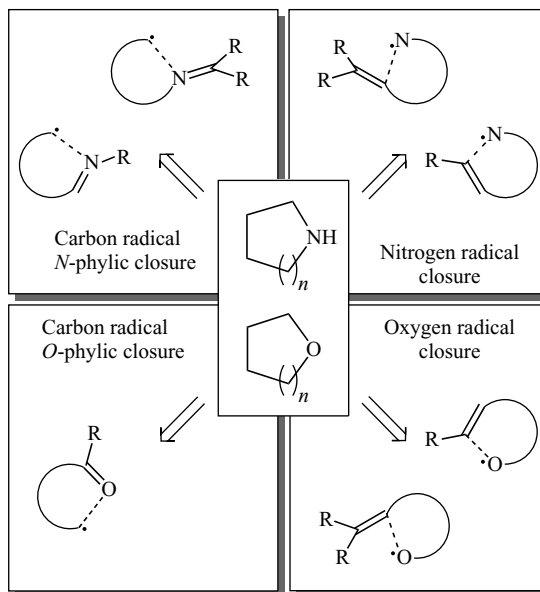


Figure 9 Unusual cyclizations proceeding through the formation of a carbon-nitrogen or carbon-oxygen bond.

range of 3×10^3 to $4 \times 10^4 \text{ s}^{-1}$,^{182–187} 1–2 orders of magnitude slower than that of the 5-hexenyl radical ($2 \times 10^5 \text{ s}^{-1}$).¹⁸⁸ The rate can be accelerated by the addition of a catalytic amount of an LA. However, high LA concentrations have a detrimental effect, possibly owing to disruption of the chain propagation step or to activation of the cyclic radical for nucleophilic attack and degradation.¹⁸⁹ This coordination has no effect, however, on the *exo* regioselectivity of closure. As the electrophilicity of nitrogen radicals increases, for example, amidyl radicals, the rate of 5-*exo*-trig closure becomes 3–4 orders of magnitude *faster* than the carbon species (5×10^8 to $2 \times 10^9 \text{ s}^{-1}$).²⁰

The activation barriers (UB3LYP/6-311++G**//UB3LYP/6-31G* level) for 5-*exo* closure of a primary aminyl radical in the parent trigonal systems are slightly lower ($10.2 \text{ kcal mol}^{-1}$) than endocyclic closure ($12.1 \text{ kcal mol}^{-1}$).¹⁸² The regioselectivity can be tuned, as with carbon-centered radicals (*vide supra*), by stabilizing groups on the interior position of the alkene. The observed selectivity, and calculated activation energies, begin to favor 6-*endo*-trig closure with increasing steric bulk in the δ -position. Through introduction of a strongly stabilizing group, such as chloro or phenyl, the barrier of closure is 2.3 and $3.8 \text{ kcal mol}^{-1}$,

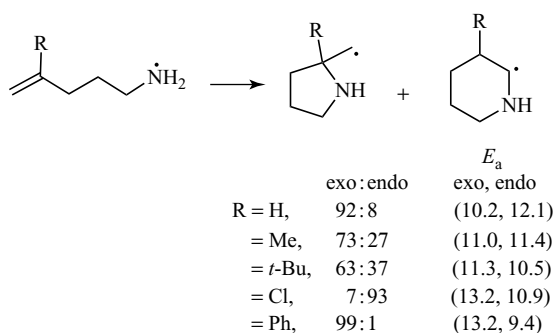


Figure 10 Observed regioselectivities and calculated activation barriers (in parentheses) for the cyclizations of primary nitrogen radicals (kcal mol⁻¹, UB3LYP/6-311++G**/UB3LYP/6-31G* level, Ref. 182).

respectively, lower for endocyclic closure with observed regioselectivities greater than 93% (Figure 10).¹⁸² The respective digonal system has yet to be investigated.

The rates and regioselectivities for the competition of 5-*exo*-trig and 6-*endo*-trig of aminyl radicals are well documented. This competition exhibits an inherent preference for 5-*exo*-cyclic closure.^{182, 190–194} Although there are numerous examples of nitrogen-centered radical cyclization reactions with olefins,^{195–198} to the best of our knowledge, there are very few isolated examples of a nitrogen radical closure onto an sp carbon. A nitrogen-centered 5-*endo*-dig cyclization has been proposed by Montevecchi and Navacchia for the formation of indole products from the reaction of *O*-(1-pentynyl)aniline with phenylthiol and AIBN. In the absence of a good hydrogen donor (heat, PhSSPh), the indole product was obtained in 90% yield (45% conversion, Scheme 36).¹⁹⁹

In their studies of the intramolecular reductions of *N*-stannyl aminyl radicals, Kim and coworkers observed an unexpected cyclic by-product. This minor product (27%) resulted from a competitive 6-*exo*-dig cyclization of the aminyl radical onto the carbon of the nitrile.²⁰⁰ This work was later expanded by Leardini, Spagnolo, and coworkers

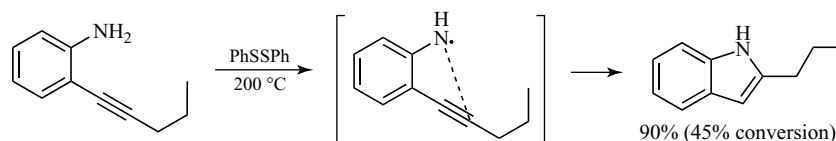
who examined the cyclizations of both aliphatic and benzylic azides, obtaining up to 66% yield for the 5-*exo*-dig product (Scheme 37). In an attempt to elucidate the radical nature of the reaction, the authors attached a pendant alkene to trap the iminyl radical, successfully yielding the bicyclic product in up to 88% yield (6-*exo*-dig and 5-*exo*-trig).²⁰¹

6.1.2 Iminyl Radicals

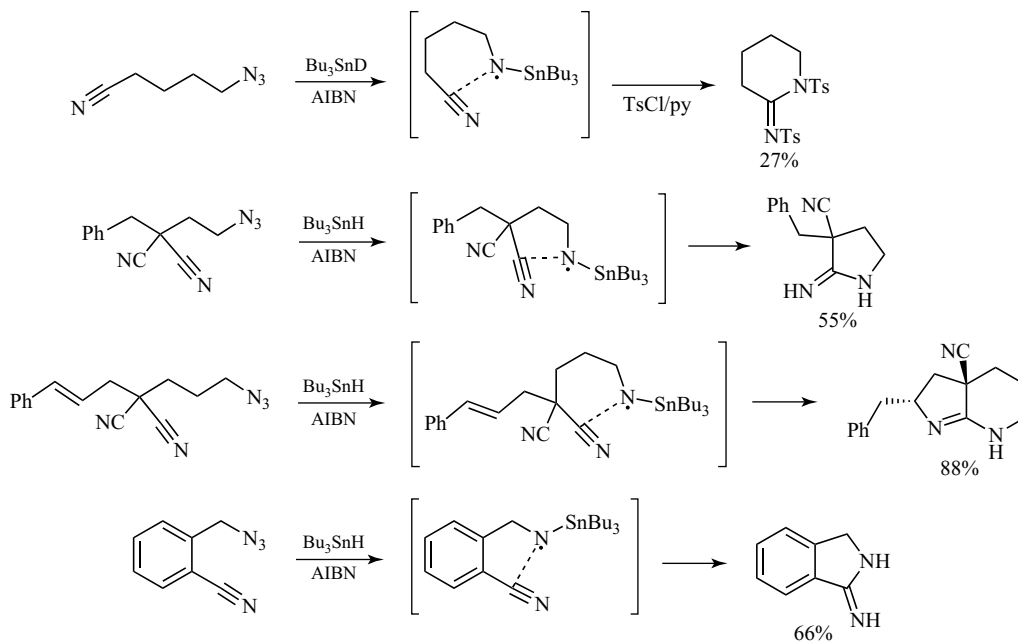
Zard has published several reviews covering the chemistry of iminyl radicals, most recently in 2008.^{202,203} While the rate of 5-*exo*-trig closure of 2-methyl-6,6-diphenyl-5-hexeniminyl radical has been found to be 10-fold faster than the respective secondary aminyl radical (2×10^6 vs 3×10^5 s⁻¹, respectively, Scheme 38), the secondary carbon derivative still proceeds at a faster rate (2×10^7 s⁻¹).¹⁹ These radical species are often generated from the heterolytic cleavage of such species as sulfenimides,^{204,205} oximes,^{206–209} and *N*-thiocarbonylhydrazones,²¹⁰ and can even result from hydrogen-atom abstraction alpha to an azide followed by loss of N₂.²¹¹ They are also found within cascades, resulting from radical addition to nitrile groups.^{212,213}

6.1.3 Oxygen-Centered Radicals

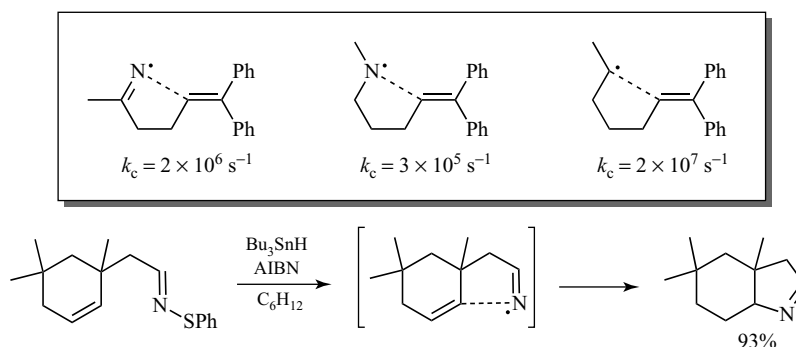
Small rings can be formed via trigonal closure of oxygen radicals (Scheme 39). Amaudrut and Wiest have shown that epoxides can not only be formed by 3-*exo*-trig closure, but trapped successfully by an arylthiyl radical when the olefin is substituted with a phenyl group.²¹⁴ Computational analysis revealed that the closed oxiranylbenzyl radical is preferred to the open cinnamyloxy radical by 5.1 kcal mol⁻¹ (B3LYP/6-31G* level). These results not only support the notion^{215,216} that the ring-opening of the oxiranyl methyl radical is thermodynamically



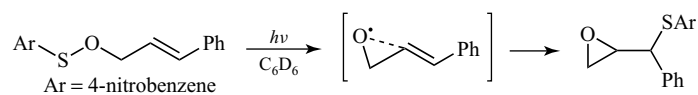
Scheme 36 5-*Endo*-dig closure of an N-centered radical.



Scheme 37 Cyclizations of aminyl radicals onto sp-hybridized carbons.



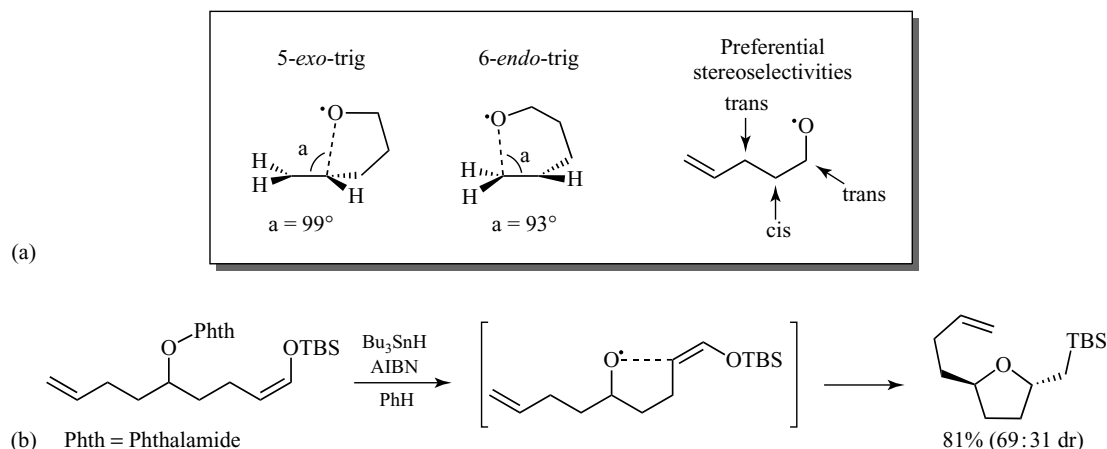
Scheme 38 5-Exo-trig closure of an iminyl radical.



Scheme 39 3-Exo-trig closure of an alkoxy radical trapped by atom transfer.

governed but also allowed for the estimation of the lower limit of the rate constant for 3-*exo*-trig of an oxygen-centered radical ($k_c = 3.2 \times 10^{10} \text{ s}^{-1}$).²¹⁴ In the absence of the phenyl group, the oxiranyl carbinyl radical can be trapped by *t*-butyl nitrite and detected by electron spin resonance (ESR) spectroscopy.²¹⁷

Hartung has thoroughly analyzed the trigonal cyclizations of oxygen radicals, particularly the competition between 5-*exo* and 6-*endo*-trig closures.²¹⁸ Interestingly, while the angles of attack for 5-*exo* and 6-*endo* for the parent 4-pentenyl-1-oxy radical are quite similar (99° and 93° , respectively, UB3LYP/6-31+G* level,



Scheme 40 (a) Calculated angles of attack and observed trends regarding substituents effect on stereoselectivity for alkoxy radicals. (b) Chemoselective closure onto the *Z*-vinylsilyl ether.

Scheme 40),²¹⁹ the alkoxy radical closes regioselectively on the parent system to give a 98 : 2 ratio of 5-*exo*: 6-*endo* products.²²⁰ The rate constant for 5-*exo*-trig closure has been calculated to be $5.2 \times 10^8 \text{ s}^{-1}$ (80 °C).¹⁸ The regioselectivity begins to deteriorate as steric bulk increases at the δ -position. Upon introduction of a phenyl group, the regioselectivity is completely reversed, giving a 7:93 ratio of *exo*:*endo* products.²¹⁹ Hartung and coworkers have derived general guidelines regarding the stereoselectivity of these closures, where 1- and 3-alkyl-substituted pent-en-yl-1-oxy radicals yield *trans*-tetrahydrofurans preferentially and substitution at position 2 gives *cis* products.^{220,221} The cyclizations of oxygen-centered radicals can also be chemoselective, as shown by the work of Sammis, who observed selective 5-*exo*-trig closure onto the *Z*-vinylsilyl ether as opposed to the monosubstituted olefin (Scheme 40).²²²

6.2 O- and N-Philic Radical Closures

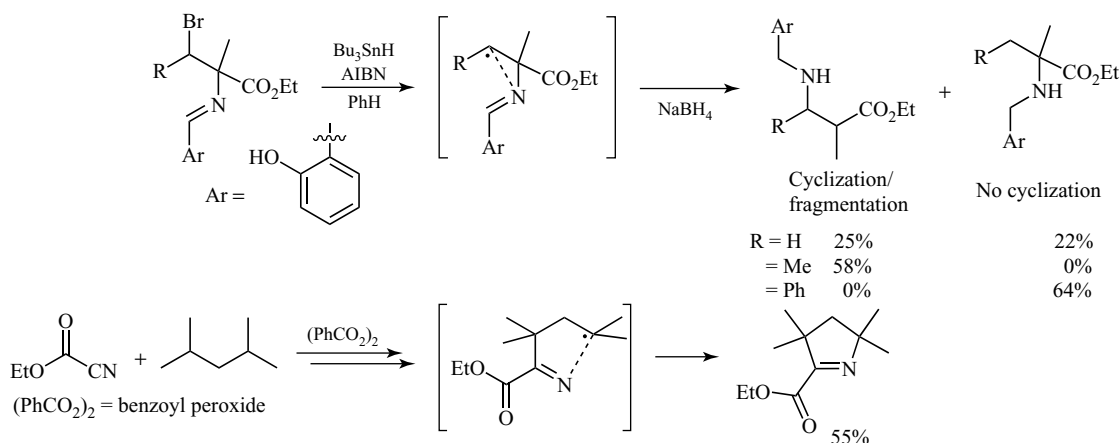
6.2.1 N-Philic Closure

The chemoselective addition of carbon-centered radicals to the carbon of imines,^{223,224} proceeds at the position with the larger LUMO coefficient.²²⁵ The regioselectivity appears to be kinetically favored,

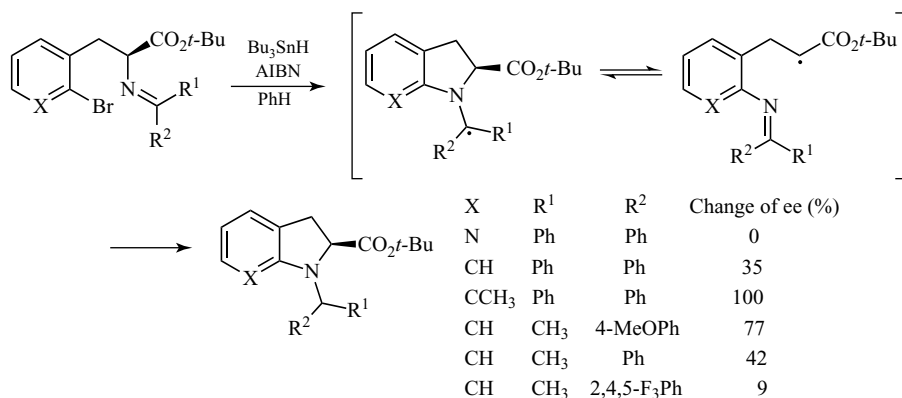
as shown by the *ab initio* calculations of Ryu and Komatsu (*vide infra*).^{224,226} However, regioselective closure onto the nitrogen, called *N*-philic closure, can be achieved by manipulation of the electronics of both the radical species as well as the carbon–nitrogen π -bond. These closures can result in both *exo*- and *endocyclic* closure depending on whether the nitrogen is in the interior or exterior position of the C=N bond.

Handa and Rose²²⁷ expanded the work of Han and Frey,²²⁸ also observing complete regioselectivity for 3-*exo*-trig closure onto the nitrogen of aldimines (Scheme 41). Bowman and coworkers thoroughly examined the cyclizations of primary carbon radicals onto aldimines for the 4-*exo*/5-*endo*, 5-*exo*/6-*endo*, and 6-*exo*/7-*endo* pairs.^{229,230} While the authors were unable to isolate any cyclic products for either imine variant for small ring formation (4-*exo*/5-*endo*), a strong stereoelectronic preference for exocyclic closure was observed for the 5/6 competition, regardless of the position of the nitrogen or the stabilizing effects of the substituent. The study of 6/7 was marred by competing 1,5-*H* abstraction. While primary carbon radicals were not found to undergo 4-*exo*-trig or 5-*endo*-trig closure, Tanner and Rahimi have reported a rare example of a 5-*endo*-trig cyclization where a 3° radical regioselectively closes onto the nitrogen of a ketimine (Scheme 41).²³¹

The 5-*exo*-trig closure of an sp^3 carbon radical onto the nitrogen of an ketimine is reversible,



Scheme 41 3-Exo-trig and 5-endo-trig *N*-philic closure of carbon-centered radicals.



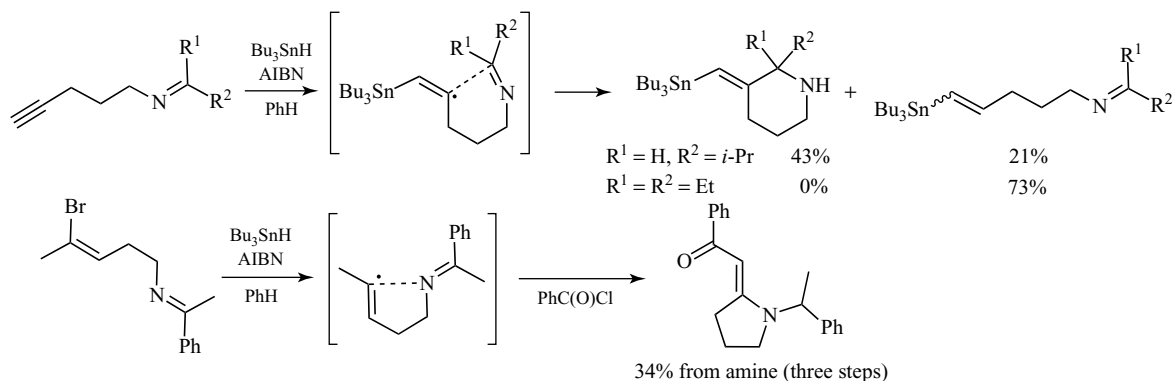
Scheme 42 Steric and electronic control of cyclic isomerization.

and the degree of isomerization can be controlled by both sterics and electronics (Scheme 42). Johnston *et al.*²³² observed a loss in enantiomeric excess with increasing steric strain *ortho* to the formed ring. The isomerization equilibrium can also be shifted by electronic effects on the ketimine—the cyclic α -aminyl radical is stabilized by electron-withdrawing groups and destabilized by electron-donating substituents. A higher degree of racemization is observed in the latter case.

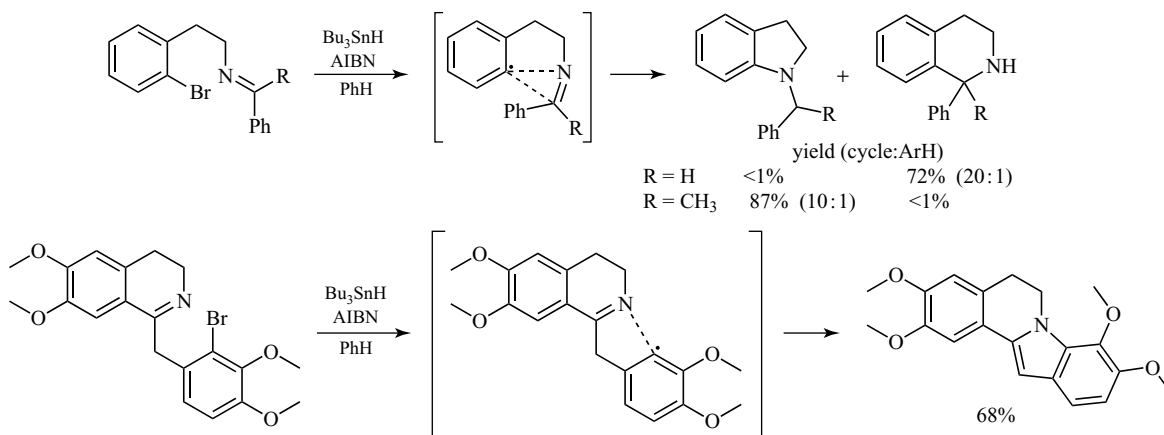
The regiochemical preference for both vinyl^{233–235} and acyl^{236,237} radical closure onto olefins is that of exocyclic closure. However, the paths of the two radical species diverge when the olefin is exchanged for an imine. Ryu, Komatsu, and coworkers examined the cyclizations of vinyl radicals onto aldimines, observing regioselective

6-*endo*-trig closure onto the carbon of the C=N bond.²²⁶ Ketimines, however, resulted only in hydrostannylation (Scheme 43). The thermodynamic stability of the cyclic radicals was found to be similar (−32.7 and −33.1 kcal mol^{−1} for 5-*exo* and 6-*endo*, respectively, at UHF/3-21G level of theory). The regioselectivity is believed to arise from the kinetic preference caused by the 3.4 kcal mol^{−1} lower TS for endocyclic closure.²²⁶ This regioselectivity can be reversed if sufficient stabilization is provided for the 5-*exo* cyclic radical, as shown by the imine derived from acetophenone.²³⁸

Reactions of aryl radicals with aldimines proceed differently from the reactions with ketimines. Similarly to vinyl radicals, aryl radicals preferentially close at the carbon of aldimines.^{239–243} However,



Scheme 43 Closure of π -*exo* and π -*endo* vinyl radicals onto aldimines and ketimines.

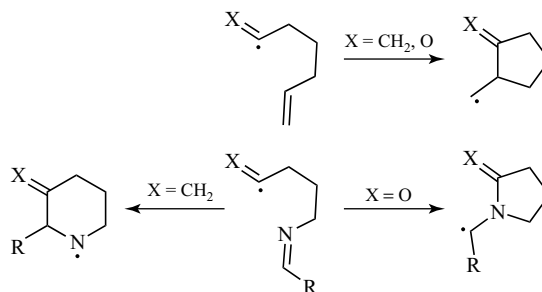


Scheme 44 Change in regioselectivity of aryl radicals between aldimines and ketimines.

the ketimine derivative has been shown to have the opposite regioselectivity, closing in a 5-*exo*-trig fashion onto the nitrogen to give the stable tertiary, benzylic radical (Scheme 44). The nature of the radical-stabilizing aryl group (electron-donating, electron-withdrawing) was found to have little effect on the regioselectivity.²⁴⁴ Orito *et al.* have shown that more unusual ring-closure pathways (5-*endo*-trig) can be successfully achieved with aryl radicals and ketimines (Scheme 44).²⁴⁵

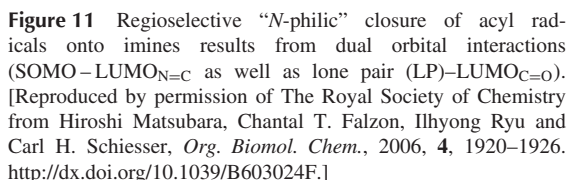
As discussed above, the cyclizations of aryl and vinyl radicals preferentially cyclize onto the carbon of an imine system. However, when the sp^2 carbon is part of a C=O double bond, a complete reversal in the regioselectivity is observed (Scheme 45).²⁴⁶

This holds true for the formation of monocyclic, bicyclic, and benzo-lactams,²⁴⁷ the only exception being closure onto hydrazones.²⁴⁸ Ryu *et al.* have



Scheme 45 C- versus N-philic regioselectivity for radical 5-*exo*-/6-*endo*-trig cyclizations of vinyl and acyl radicals.

shown that the exocyclic closure of acyl radicals onto imines can be used to successfully to form four-, five-, six-, seven-, and eight-membered lactams (Scheme 46).^{175,176} The regioselectivity of

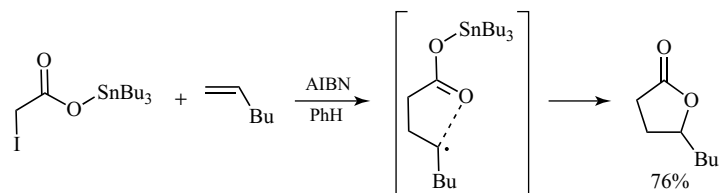


6.2.2 O-Philic Closures

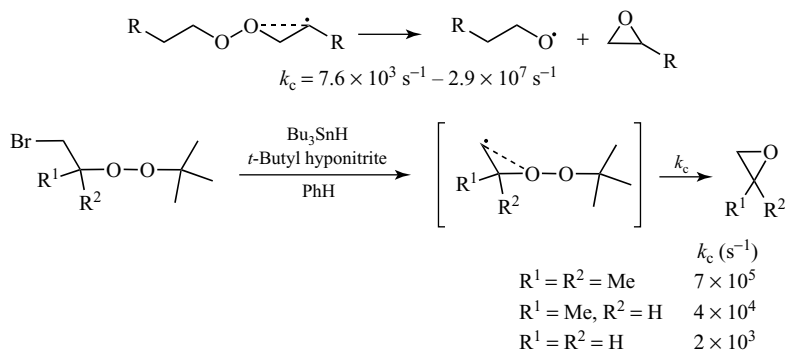
The closure onto the oxygen of a carbonyl moiety is far less represented in the literature than the nitrogen examples discussed in the previous section. Lactones can be synthesized via an *O*-philic radical cyclization/elimination reaction. Kraus and Landgrebe studied the reactions of iodostannyl esters with a series of alkenes in the presence of a catalytic amount of AIBN and observed up to 78% yield for the corresponding lactone (Scheme 47). There are, however, two possible reaction pathways that proceed to the product following the initial addition, cyclization onto the carbonyl followed by fragmentation to form the lactone and tin radical, or an S_H1 closure onto the sp^3 oxygen.²⁵⁵ The formation of lactones from 1°-carbon radical cyclization onto methyl esters (with loss of methyl radical) have also observed, however in low yields.^{256,257} Aryl radicals, however, do not undergo *O*-philic 5-*endo*-trig closure onto *ortho*-acetate groups.^{258,259}

Carbon radicals have also been found to attack the oxygen of a peroxide bond, yielding epoxides and alkoxy radicals, with rates of 3-*exo*-tet closure ranging from $7.6 \times 10^3 \text{ s}^{-1}$ for stabilized benzylic radicals to $2.9 \times 10^7 \text{ s}^{-1}$ for a cyclooctyl radical.¹³ Davies and coworkers have studied these closures using ESR spectroscopy, and found that the rate of 3-*exo*-tet closure was greatly accelerated when *gem*-dimethyl groups were present (Scheme 48).²⁶⁰

As early as 1964, Menapace and Kuivila found that 2-phenyltetrahydrofuran was formed upon reaction of γ -chlorobutyrophenone with $\text{Bu}_3\text{SnH/AIBN}$ in 52% yield, along with 13% of butyrophenone.²⁶¹ Mendenhall, Luszyk, and workers examined the cyclizations of 2-formylbenzoyl radical and observed complete regioselectivity for closure onto the oxygen atom of the formyl group, with no evidence of the 4-exo alkoxyl radical by ESR, laser flash photolysis (LFP), or trapping



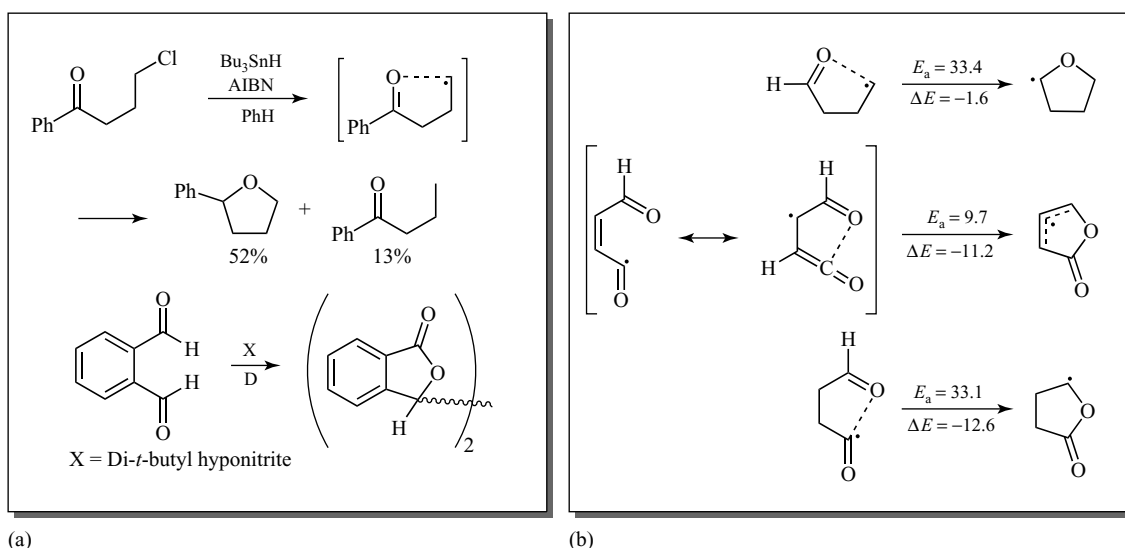
Scheme 47 Irreversible *O*-philic closure by 5-endo-trig cyclization/fragmentation closure.



Scheme 48 Rates of 3-*exo*-tet *O*-philic closures as a function of substitution α to the acyclic radical.

studies. The rate of 5-endo closure was found to be much faster than expected ($2 \times 10^8 \text{ s}^{-1}$).¹⁷ The activation barrier for this closure was calculated to be $12.4 \text{ kcal mol}^{-1}$ by Eguchi *et al.* (UHF/6-31G* level). However, the authors proposed that the

closure of conjugated acyl radicals onto the oxygen of a carbonyl moiety proceeds through a nonradical mechanism, as the SOMO was calculated to be perpendicular to the molecular plane and does not change throughout the course of the reaction. The



Scheme 49 Experimental *O*-philic closure of carbon and acyl radicals (a) and computational analysis of related systems in kcal mol^{-1} (b).

proposed ring-closure pathway consists of the addition of the lone pair of the oxygen to the carbon of the stabilized ketene-substituted α -carbonyl radical ($E_a = 9.7 \text{ kcal mol}^{-1}$, $\Delta E = -11.2 \text{ kcal mol}^{-1}$). The authors also examined the 5-*endo*-trig closure of the saturated derivative as well as the primary carbon radical and while both cyclizations have large activation barriers (33.4, 44.1 kcal mol^{-1} , respectively), the acyl radical derivative is considerably more exothermic ($\Delta E = -12.6$ and $-1.6 \text{ kcal mol}^{-1}$, respectively, Scheme 49).²⁶² The large barriers and low exothermicity, particularly for the alkyl radical, may be one of the reasons why *O*-philic closures remain underrepresented.

7 CONCLUSION

Enthalpic and entropic factors conspire against unusual radical cyclizations. However, these obstacles can be overcome via judicious choice of reaction conditions, use of the Thorpe–Ingold effect, destabilization of reactants and stabilization of the cyclic products, coupling of thermodynamically unfavorable ring closures with highly exothermic follow-up steps, as well as control of the electronic interactions of the reacting centers. In addition, electron-transfer and photochemical processes can bypass energetic obstacles that make cyclizations of neutral molecules in their ground state difficult.

Modern computational methods start to play a more important role in the discovery of new radical cyclizations, providing a useful alternative to chemical intuition. Quantitative information on the potential energy surfaces involved in radical cyclizations point to possible ways to avoid the bottlenecks associated with the intrinsic stereoelectronic preferences and unfavorable thermodynamics of such processes. Once the limitations are understood and the energy landscape is carefully mapped, new and creative ways for traversing this rugged terrain can be charted.

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Radical Cascade Reactions

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1 INTRODUCTION

Cascade reactions, understood as transformations allowing the formation of multiple bonds under the same reaction conditions, represent one of the most challenging and fascinating aspects of radical chemistry. Employed in numerous syntheses of natural products,¹ they embody control over chemical reactivities. Furthermore, they contribute to progress toward green chemistry since they allow a large increase in molecular complexity in a minimum of steps, and hence waste generation.

Since the addition of a radical onto an unsaturation generates a new radical species that can further react, organic radicals are inherently prone to engage in cascade reactions. Besides, radical transformations generally occur under mild conditions, which avoid the requirement of protection/deprotection steps and allow access to high stereocontrol.^{2–4} Organic radicals are thus tools of choice for the development of efficient and selective cascade reactions as demonstrated by the huge number of applications reported in the literature.^{5–9}

Cascade radical reactions have been reviewed in depth by our group in 2006,¹⁰ so only the literature starting from this year will be covered in this account. Even if clear-cut classification is often difficult, we will separate the cascades occurring via a chain radical process from those involving

non-chain redox processes implying organometallic species.

2 CASCADE REACTIONS INVOLVING CHAIN RADICAL PROCESSES

2.1 Intramolecular Processes

The most widespread application of radical cascades is the construction of polycyclic compounds from polyunsaturated precursors via several intramolecular steps. These unimolecular processes consist mostly of reductive cyclizations but can also include less usual radical steps such as homolytic substitutions, fragmentations, and translocations. This review is subdivided according to the type of processes involved.

2.1.1 Cascade Reactions Involving Polycyclizations Only

As early as 1976, Baldwin's rules based on stereochemical requirements have given helpful guidance to predict the favored cyclization mode and design suitable precursors. Poly 5- or 6-exo cyclizations are the most straightforward strategies for the construction of polycyclic frameworks. In a synthetic study toward azadirachtin, Watanabe

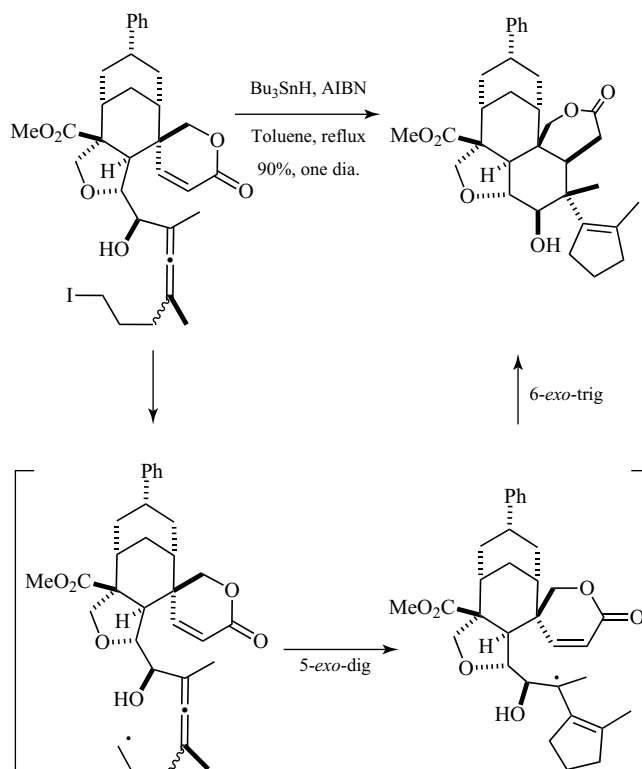


Figure 1 Stereoselective radical cascade as a key step in the construction of AB rings of azadirachtin.

employed a cascade involving 5-*exo*-dig/6-*exo*-trig radical cyclization using a tetrasubstituted allene and an α,β -unsaturated lactone as radical acceptors.¹¹ The rigidity of the spirolactone ring embedded in the precursor seemed to favor the cyclization and allowed the synthesis of the two key carbocycles of the target molecule in a diastereoselective manner and with an excellent 90% yield (Figure 1). An efficient synthesis of angularly fused carbocycles by a combination of 5-*exo*-dig and 5-*exo*-trig cyclizations was described by Mohanakrishnan.¹²

The presence of heteroatoms in the linkage is generally well tolerated and allows the smooth synthesis of heterocycles.^{13,14} Another elegant strategy to access these frameworks is the use of heteroatom-containing acceptors. *O*-benzyl oxime seems to be a particularly suitable partner since the 5-*exo* cyclization rate of an alkyl radical on this moiety ($k_{5\text{-exo}} = 4.2 \times 10^7 \text{ s}^{-1}$ at 80 °C)¹⁵ is two orders of magnitude higher than the cyclization on an alkene and one order higher than the cyclization on an imine ($k_{5\text{-exo}} = 6.0 \times 10^6 \text{ s}^{-1}$ at 80 °C).¹⁶ A

synthesis of tricyclic pyrrolidines via a radical cascade employing *O*-benzyloximes was described by Jaramillo-Gómez (Figure 2).¹⁷ Treatment of precursor **1** with Bu₃SnH and 2,2-azo-bis-isobutyronitrile (AIBN) generates aryl radical **2**, which adds to the electrophilic carbon of the oxime ether. The alkyl-oxyaminyl radical **3** formed cyclizes onto an electron-poor olefin to give the tricyclic compound **4** after reduction.

Heterocyclic frameworks can also be built by radical cascades starting with heteroatom-centered radicals, as illustrated by Zard. Employing hydroxamic benzoates as amidyl radical precursors, he developed a new access toward indolizidine and pyrrolizidine skeletons via radical cascades.^{18,19} Interestingly, the mode of cyclization, for example, 5-*exo*-trig/5-*exo*-trig or 5-*exo*-trig/6-*endo*-trig, is completely directed by the absence or presence of a chlorine substituent on the second double bond (Figure 3).

As demonstrated by the latter example, 6-*endo* can become the favored mode of cyclization with

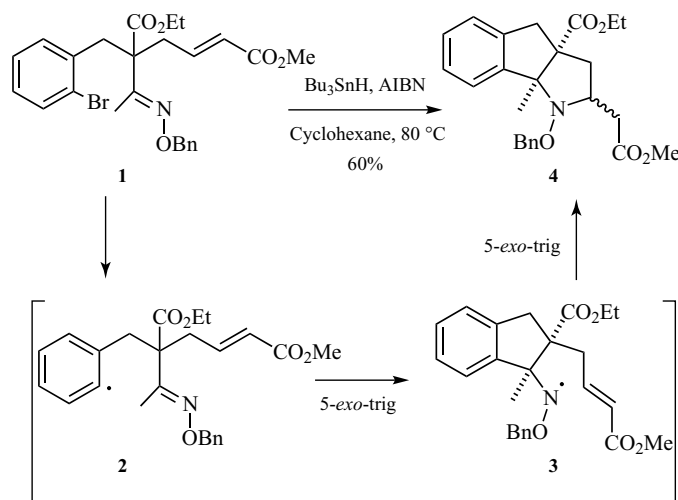


Figure 2 Synthesis of tricyclic pyrrolidine employing oxime ethers as radical partners.

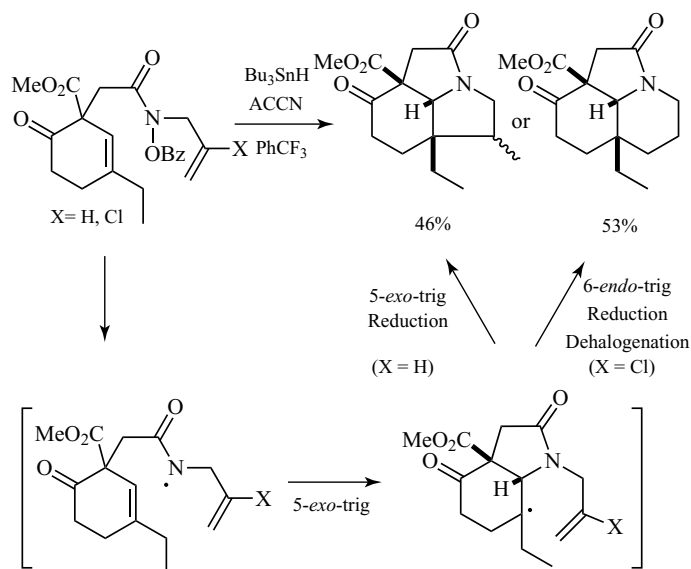


Figure 3 Access to indolizidine and pyrrolizidine skeletons by radical cascades triggered by amidyl radicals.

specifically designed substrates. Hishibashi has, for instance, shown that the 6-*endo*-trig selectivity of radical cyclization onto the double bond of enamides could be determined by the position of the carbonyl group.^{20,21} He used this selective cyclization in combination with a 5-*endo*-trig cyclization to afford a concise synthesis of cyclindricine skeleton (Figure 4).

Using a similar substrate-directed strategy, Hishibashi developed several radical cascades

involving first a 7-*endo*-trig cyclization onto the double bond of an enamide followed by 5-*endo*-trig cyclization of the α -amidoyl radical generated.^{22–24} Selective 7-*endo*-trig cyclization in a radical cascade was also achieved by Kahne for the synthesis of norbornyl-based tetracyclic amine, presumably owing to the inherent preorganization of the precursor and the stability of the radical intermediate formed.²⁵

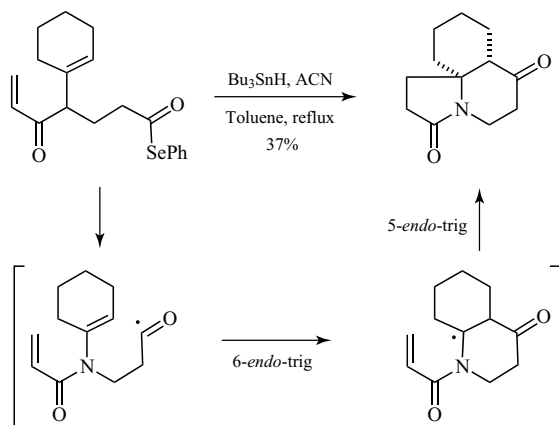


Figure 4 Synthesis of cyclindricine skeleton via two consecutive endo-selective cyclizations.

Castle cleverly exploited the slower reduction rate of acyl radicals²⁶ to develop a radical cascade featuring a 7-*exo*-trig cyclization followed by a 6-*exo*-trig cyclization.²⁷ Thus, treatment of selenoester **5** with tris(trimethylsilyl)silane in the presence of Et₃B and air allows the generation of acyl radical **6** that cyclizes under a 7-*exo*-trig mode to give alkyl radical **7**. 6-*exo*-trig Cyclization and final reduction afford the bicyclo[5.4.0]undecane ring **8**, a structural motif present in the framework of anticancer alkaloid Lyconadin A (Figure 5). It is noteworthy that the use of a faster hydrogen donor

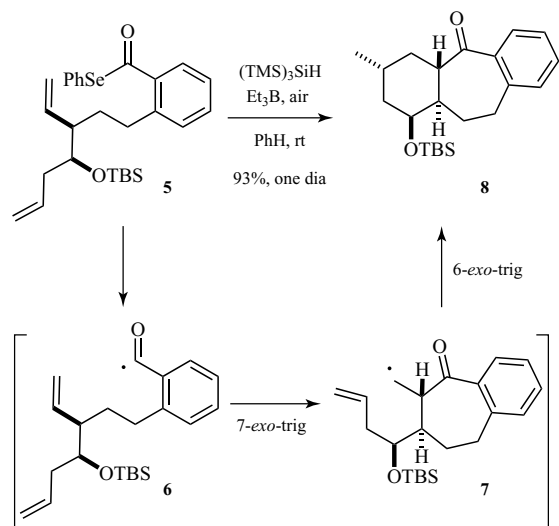


Figure 5 7-*exo*/6-*exo* Cyclization triggered by an acyl radical.

such as Bu₃SnH instead of (TMS)₃SiH resulted in a complex mixture probably because of abortive reductions.

Radical transannulation reactions, leading to the construction of bonds between atoms on opposite sides of a ring, occur favorably in medium and large cycles. Sequential macrocyclization/transannulation reactions thus offer unique opportunities for the fast synthesis of ring-fused systems, such as those found in the structure of terpenoids, taxoids, and steroids.²⁸ Pattenden developed the use of ynones as radical acceptors for the macrocyclization step (Figure 6). This approach allowed him to access efficiently the 6,8,6-ring fused taxane system via a 12-*endo*-dig/6-*exo*-trig radical cascade.²⁹ More recently, he examined new applications toward the elaboration of the oestrane ring.^{30–32} Upon treatment of precursor **9** with Bu₃SnH and AIBN, he did not obtain the expected macrocyclization/radical Diels–Alder cascade reaction but an original cascade process leading to tetracyclic dihydrofuran **12**. Initial 13-*endo*-dig macrocyclization generates vinyl radical **10**, which adds to the furan ring. Allylic migration of the radical **11** formed leads to a stabilized benzylic radical, which is finally reduced.

2.1.2 Cascade Reactions Involving Fragmentation/Cyclization Steps

Ring-opening fragmentations with concomitant release of strain are particularly attractive steps in radical cascades since they generally lead to the formation of a double bond that can act as a new acceptor. Cyclopropyl methyl radical fragmentation is extremely fast ($k = 1.2 \times 10^8 \text{ s}^{-1}$ at 37 °C³³) and has consequently found the most significant number of applications in radical cascade reactions.³⁴ Pattenden recently disclosed a new synthetic approach toward C-nor-D-homosteroid ring system via consecutive macrocyclization, cyclopropane ring-opening, and transannular reactions.³⁵ Starting from seleno ester precursor **13**, the corresponding acyl radical **14** is generated and cyclizes in a 13-*endo*-trig manner onto the vinylcyclopropane. Ring opening delivers the benzylic radical **15**. Sequential 5-*exo*-trig and 6-*exo*-trig transannular cyclizations lead to a 1:1 mixture of C10 methyl epimers of the desired tetracyclic core **16** (Figure 7). This work was the first report

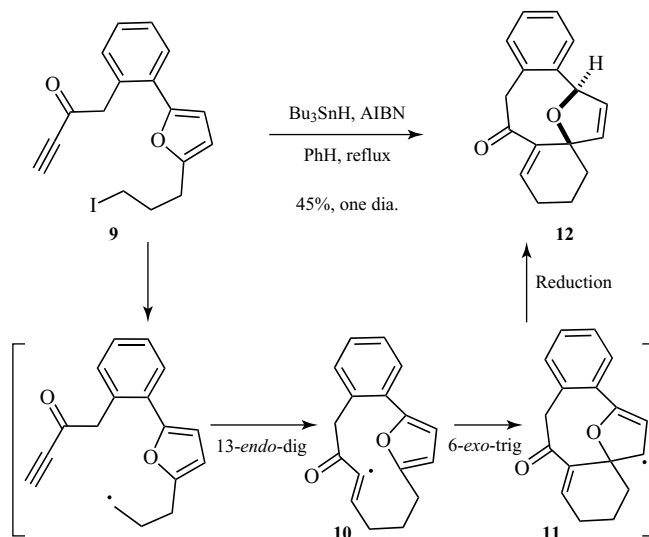


Figure 6 Use of an ynone acceptor in a macrocyclization/transannulation sequence.

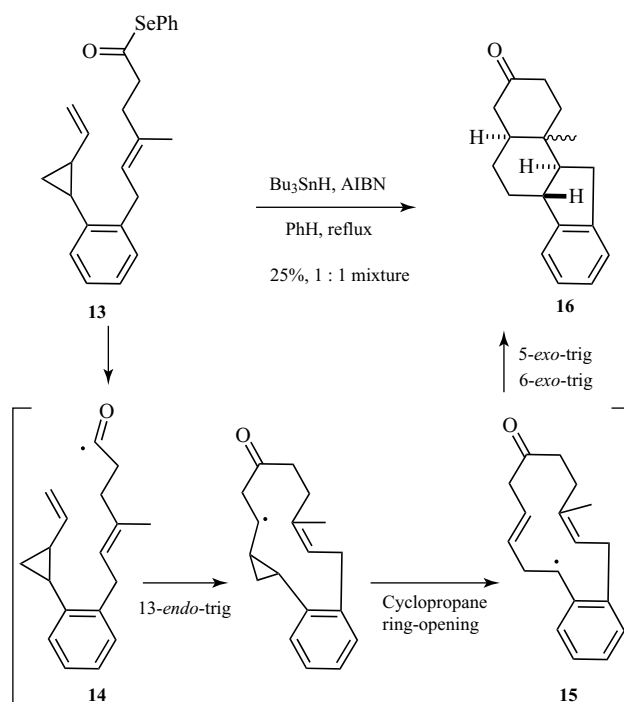


Figure 7 Cascade reaction involving macrocyclization, cyclopropane ring opening, and transannulation triggered by an acyl radical.

of a macrocyclization/transannulation sequence triggered by an acyl radical.

The regioselectivity of the cyclopropyl-homoallyl radical rearrangement in azabicyclic systems has

been thoroughly studied by Hodgson. He found that the stabilization of radicals in the α position of nitrogen drove the selectivity of the skeletal rearrangements efficiently.³⁶ He applied this

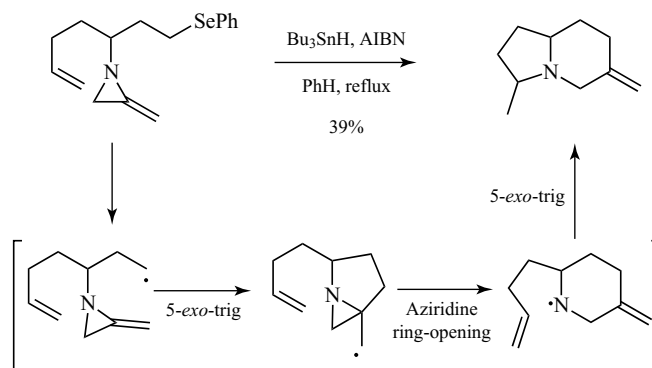


Figure 8 Radical cascade using methyleneaziridine.

strategy to the synthesis of various azabicyclic frameworks via radical decarboxylation–homoallylic rearrangement–reduction sequences.^{37,38}

Rings other than cyclopropanes can be fragmented when stereoelectronic factors favor the ring-opening reaction.³⁹ Thus, Shipman demonstrated that the strain energy associated with the methyleneaziridine ring (12–13 kcal mol^{−1} more ring strain than simple aziridine⁴⁰) allowed the

development of new radical rearrangements.⁴¹ For instance, he disclosed a sequence involving 5-*exo*-trig cyclization, C–N bond fission of aziridinylcarbiny radical, and second 5-*exo*-trig cyclization leading to the indolizidine framework (Figure 8).⁴²

Since alkoxy radicals fragment easily,⁴³ ring opening of cycloalkoxy radicals is an efficient way to obtain skeletal rearrangements.

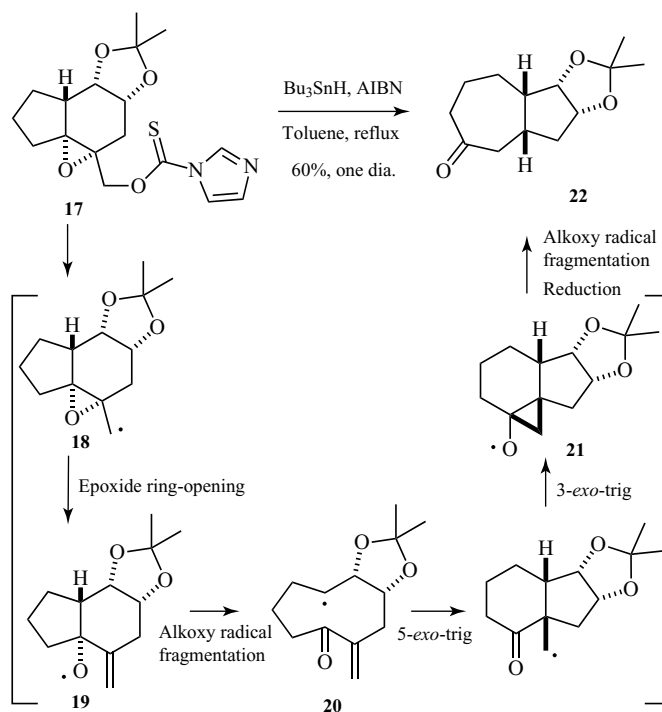


Figure 9 Cascade synthesis of hydroazulenone via alkoxy radical fragmentations.

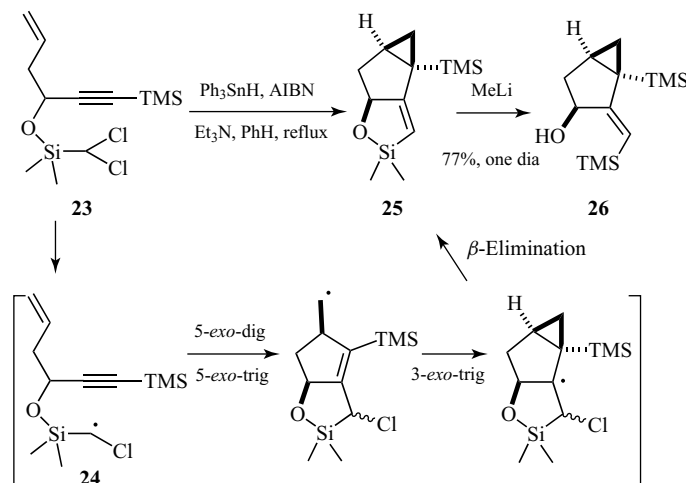


Figure 10 Approach to fused polycyclic cyclopropane via radical cascade reaction involving cyclizations– β -elimination of chloride.

Kawahara reported an elegant cascade synthesis of hydroazulenone **22** from epoxy-hydroindan **17** via alkoxy radical fragmentation.⁴⁴ A plausible mechanism is depicted in Figure 9. Treatment of precursor **17** with Bu_3SnH and AIBN forms methyl radical **18**, which rearranges to alkoxy radical **19** through epoxide ring opening. Fragmentation affords the nine-membered ring intermediate **20**. 5-*exo*-trig Transannular cyclization and subsequent 3-*exo*-trig on the carbonyl moiety generates a second alkoxy radical **21** that fragments to give the hydroazulene core in 60% yield. Since the reports of Kawahara⁴⁴ and Renaud,^{45,46} applications of alkoxy radical fragmentation in purely radical cascades have been scarce, but beautiful examples using single-electron transfer reagents have been published (see Section 3).

β -Elimination steps can elegantly terminate radical cascades and prevent undesired rearrangements, when the kinetics involved is suitably matched. Our group thus reported the synthesis of fused polycyclic vinylcyclopropanes via a radical cascade terminated by β -elimination of chloride.⁴⁷ The approach employs (dichloromethyl)dimethylsilyl ether as the point of both initiation and termination of the radical cascade reaction. Treatment of homoallylic propargyl ether **23** with Ph_3SnH , AIBN, and triethylamine as HCl scavenger generates α -silyl radical **24**. The latter undergoes successive 5-*exo*-dig, 5-*exo*-trig, and 3-*exo*-trig cyclizations. The fast β -elimination of chloride avoids the retro-fragmentation of cyclopropane and affords tricyclic product **25**, which is

immediately quenched with MeLi to provide the silylated alcohol **26** in overall excellent yield and diastereoselectivity (Figure 10). Parker reported the enantioselective synthesis of (–)dihydroisocodeine using a cascade radical cyclization terminated by the β -elimination of a thiophenyl radical as a key step.⁴⁸

2.1.3 Cascade Reactions Involving Translocation/Cyclization Steps

Intramolecular hydrogen transfer reactions are often considered as undesired side reactions; however when introduced in a controlled manner in radical cascades, they open the way to exciting new possibilities. Indeed, they allow the functionalization of remote unreactive positions by extremely selective C–H activations.

The most commonly employed process is the rearrangement of highly reactive vinyl radical to a more stable alkyl radical via 1,5-H transfer. The resulting translocated radical is then perfectly placed to perform rapid 5-*exo*-trig cyclization. Such cascade translocation/cyclization of vinyl radicals has been elegantly employed in the preparation of various five-membered rings and has been recently reviewed in depth by Renaud.⁴⁹ Our group reported a synthesis of cyclopentanol derivatives via cascade 5-*exo*-dig cyclization of α -silyl radical, diastereoselective 1,5(π -*exo*)-H-transfer on the vinyl radical formed, and 5-*endo*-trig cyclization.⁵⁰

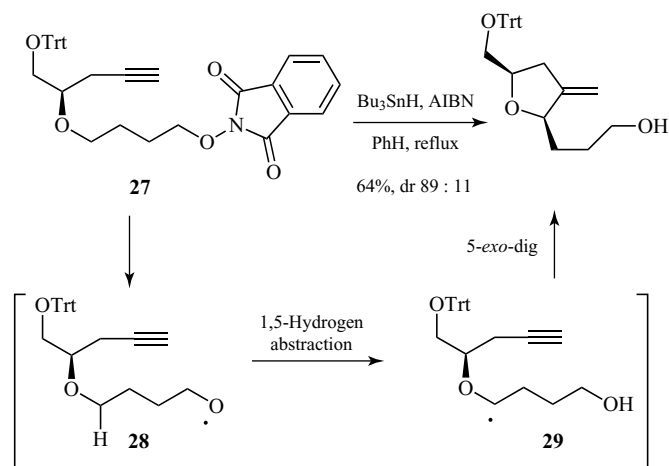


Figure 11 Construction of tetrahydrofuran core of (-)-amphidinolide K via radical relay cyclization.

Another way to exploit 1,5-H transfer in cascades is radical relay cyclizations initiated by oxygen-centered radicals. Sammis recently reported a beautiful methodology applied to the synthesis of the tetrahydrofuran core of (-)-amphidinolide K.⁵¹ *N*-Alkoxyphthalimide **27** is used as a precursor for alkoxyradical **28**, which undergoes 1,5-hydrogen abstraction (Figure 11). The resulting alkyl radical **29** is perfectly placed to cyclize onto the terminal alkyne. Conveniently, this strategy is effective for

the synthesis of five- and six-membered carbocycles or heterocycles starting from the suitable linear precursor.

1,6-Hydrogen transfer requires a disfavored seven-membered ring transition state. It is thus a far less common translocation. However, it can become a major pathway when conformational bias and stabilizing effects are adequately positioned. Reisert has reported a cascade 1,6-hydrogen transfer and 5-*exo*-trig cyclization of the allylic radical

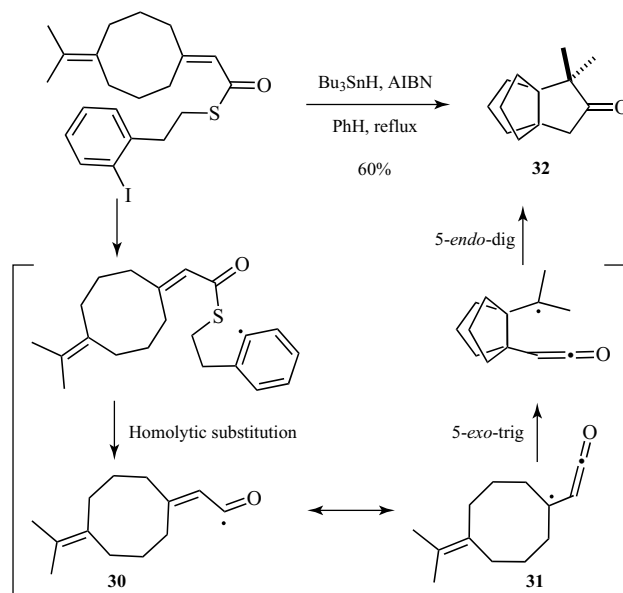


Figure 12 Cascade synthesis of 3,3,3 propellane ring system triggered by homolytic substitution at sulfur.

generated for the synthesis of 2,3-disubstituted dihydrobenzofurans.⁵²

2.1.4 Cascade Reactions Involving Homolytic Substitution/Cyclization Steps

Intramolecular homolytic substitution at the sulfur atom can provide an efficient trigger for radical cascades, as reported by Crich (see **Intramolecular Homolytic Substitutions in Synthesis**).⁵³ This strategy is especially useful for the generation of radicals that are difficult to form with standard approaches. Thus, in a sophisticated cascade synthesis of the propellane ring system, Patten den used a iodoaryl-thioester as a precursor for the desired α,β -unsaturated acyl radical.^{54,55} Once generated by homolytic substitution at sulfur, the α,β -unsaturated acyl radical **30** undergoes cascade 5-*exo*-trig and 5-*endo*-dig cyclizations via its corresponding α -ketenyl alkyl radical resonance form **31** to afford the desired tricyclic ketone **32** (Figure 12).

Aromatic homolytic substitution refers to the addition of a radical to an aromatic ring with subsequent rearomatization through the loss of a leaving group (see **Radical Arylations**). The involvement of this type of step in radical cascades offers interesting possibilities for the synthesis of polycyclic products containing fused aromatic rings.⁵⁶

In most of the cases, the leaving group is hydrogen, and the mechanistic details of rearomatization

are still unclear. Several mechanistic studies have been performed, leading to the conclusion that various pathways could be involved according to the conditions, and that the initiator or the dioxygen present in the reaction mixture could be responsible for the required hydrogen abstraction.⁵⁷ A short synthesis of tetracyclic alkaloid lennoxamine was achieved by Ishibashi through aryl radical-induced 7-*endo*-trig cyclization on enamide and subsequent homolytic aromatic substitution on a dimethoxyphenyl group.⁵⁸

Bowman developed the cyclization of vinyl radicals onto suitably placed nitrile groups followed by aromatic homolytic substitutions by the iminyl radicals generated. He proposed that in his case, the final H-abstraction step was performed by either the *tert*-butoxyl radical or the methyl radical generated from hexamethylditin. Using this strategy, he reported the efficient cascade synthesis of biologically active mappicine and luotonin A.⁵⁹ Another cascade synthesis of luotonin A under tin-free conditions was developed in our group using *N*-acylcyanamide moiety as the original radical partner (Figure 13).⁶⁰ Irradiation generates quinolinyl radical **33**, which cyclizes onto the cyanamide to form an amide-iminyl radical **34**. Density functional theory (DFT) calculations and experimental data suggest that the aromatic homolytic substitution occurs via a 6-*endo* addition rather than via an *ipso* substitution followed by a neophyl rearrangement. Final rearomatization is presumably induced by dioxygen.

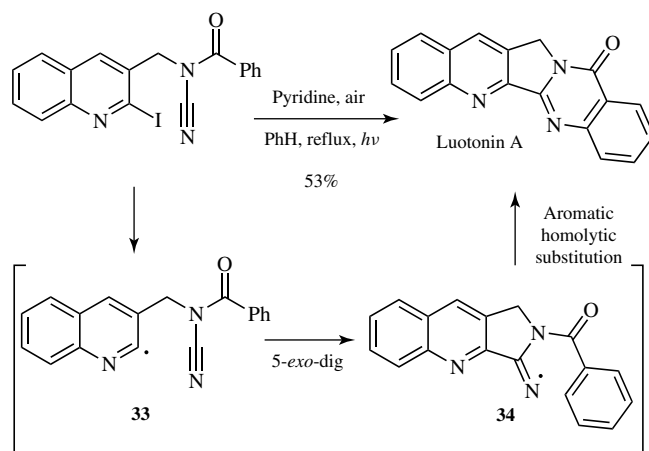


Figure 13 Synthesis of luotonin A via consecutive cyclization/aromatic homolytic substitution reactions.

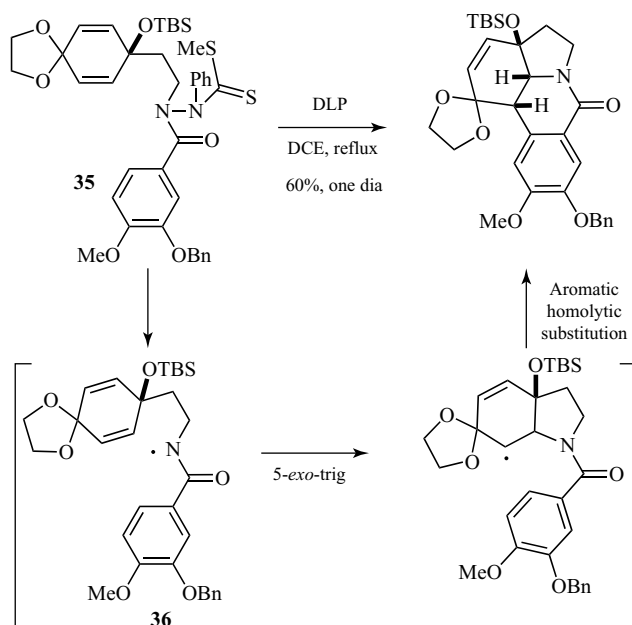


Figure 14 Synthesis of the pentacycle core of fortucine via a cascade cyclization/aromatic homolytic substitution reaction triggered by an amidyl radical.

The initiation of radical cascades by nitrogen-centered radicals is always challenging since these species are often less reactive than their carbon counterparts. However, they provide beautiful entries toward polycyclic alkaloids, as illustrated by Zard with the synthesis of ($\pm$)-fortucine.^{61,62} Treatment of precursor **35** with dilauroyl peroxide (DLP) delivers amidyl radical **36**, which undergoes a 5-*exo*-trig cyclization followed by aromatic homolytic substitution. The cascade is regio- (14:1 para/ortho ratio with respect to the benzyloxy group) and stereoselective (Figure 14). Aminyl radicals generated from the corresponding azides were employed by our group in radical cascades involving consecutive 5-, 6- or 7-*exo*-dig cyclizations on *N*-acyl cyanamides and aromatic homolytic substitutions, providing the first radical synthesis of guanidines.⁶³

In less widespread cases, the aromatic homolytic substitution occurs on a carbon bearing a substituent, leading to the extrusion of a carbon- or heteroatom-centered radical. Cascades beginning with the addition of an aryl radical to *N*-acylcyanamide and ending with the displacement of methyl, methoxy, and fluorine radicals from an aromatic carbon were reported by our

group.⁶⁴ DFT calculations were performed to gain insights into the mechanism of these extrusions. A possible transition state for the departure of the methyl radical was proposed (14.6 kcal mol⁻¹), in which the cost of breaking the C–C bond is minimal compared to normal values. Interestingly, when the initial radical was switched from aryl to vinyl, it was possible to trap the extruded substituents via addition onto the suitably placed double bond (Figure 15).⁶⁵ Hydrogen and carbon substituents, such as methyl, isopropyl, and trifluoromethyl, were found to undergo this unprecedented complex migration whose mechanism was studied thanks to deuteration experiments. Hydrogen migration was found to probably occur via a bimolecular exchange.

Another possibility is that the leaving group is linked to the chain connecting the radical and the arene undergoing addition. The homolytic substitution can then be followed by other intramolecular radical steps, as exemplified by Robertson.⁶⁶ He proposes that when vinyl radical **37** cyclizes onto the aryl ring via an ipso mechanism, rearomatization occurs with extrusion of a carbamoyl radical **38**. The latter is thought to undergo a second aromatic homolytic substitution to yield phthalimide **39** (Figure 16).

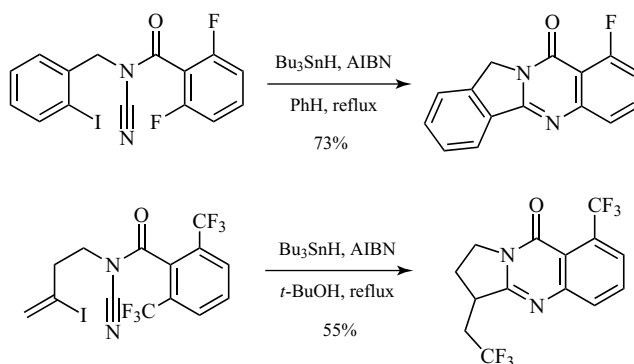


Figure 15 New cascades involving homolytic substitution at ortho-substituted benzoyl ring in the cases of aryl and vinyl radical precursors.

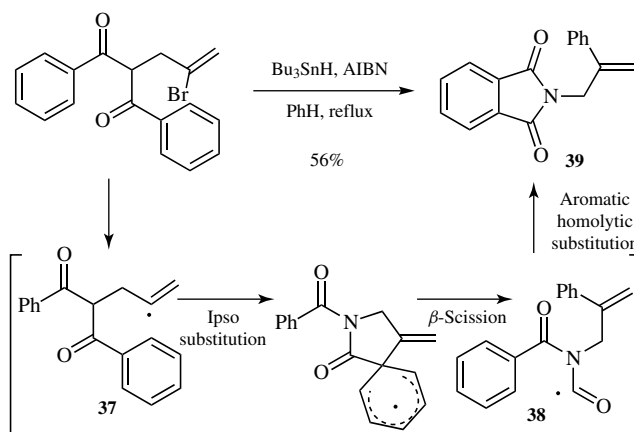


Figure 16 Radical cascades for the synthesis of substituted phthalimides through cascade homolytic substitutions/fragmentation reactions.

2.2 Cascade Reactions Involving Both Intra- and Intermolecular Steps

This reactivity has also been recently highlighted in detail in the related sections of reviews by Rowlands^{8,9} and Majumdar.⁶⁷

2.2.1 Sequences Involving Formation of Five-Membered Rings

Renaud and coworkers found that benzenesulfonyl azide is a suitable reagent to conduct an azido-sulfonylation reaction when the process is coupled with a fast cyclization (see **Unusual Radical Acceptors**).⁶⁸ They reported an efficient cascade

in which 1,6-dienes or enynes undergo a rapid 5-*exo*-trig cyclization of an alkyl (or a vinyl) radical upon phenyl sulfonyl radical addition, the whole process being terminated by the azidation step. The desired products are obtained with excellent yields (**40** and **41** respectively, Figure 17), although with low diastereoselectivity.

The group of Landais investigated distinct pathways for the cyclization of silylheptadienes **41** (Figure 18).⁶⁹ In particular, a sulfonyl radical triggers regioselective addition and subsequent 5-*exo*-trig cyclization of these dienes (at low temperatures up to 9 to 1 regioselectivity at the allylsilane terminus is achieved in **42**) while a thiyl-mediated reaction features a different outcome, as it is terminated by homolytic substitution at sulfur to yield a thiabicyclic product **43**.

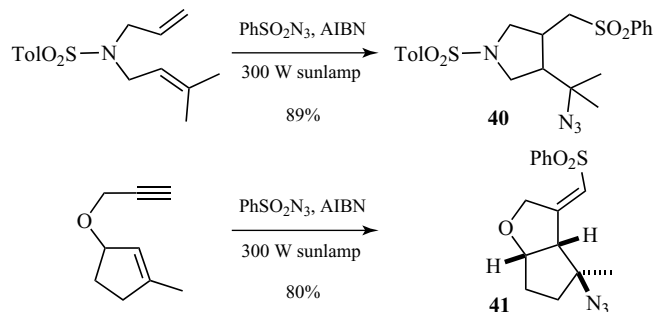


Figure 17 Azidosulfonylation of dienes and enynes coupled with 5-*exo*-trig cyclization.

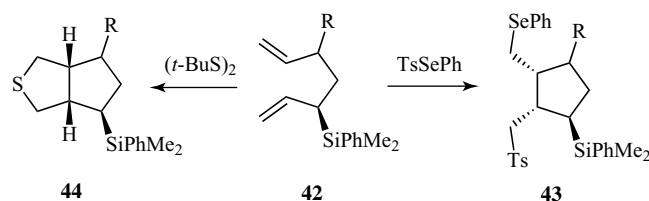


Figure 18 Different radical-mediated cyclizations of silylheptadienes.

A brief example of the relevance of thiophenol as a mediator in radical cascades is presented hereafter, while its role is presented more in detail in the section of this encyclopedia dedicated to sulfur-centered radicals (see **Main-Group Elements in Radical Chemistry**). The group of Renaud investigated various cascade reactions mediated by thiophenol. This reactivity has been applied for instance to *N*-homopropargylic piperidinones (45, Figure 19), which cyclize smoothly after

addition of a thiyl radical, leading to compound 46 through a sequential 1,5-hydrogen transfer, 5-*exo*-trig cyclization, and final reduction. Products are obtained in good yields and diastereoselectivities, and could be easily transformed to the corresponding *exo*-methylene derivatives 47 by oxidation to the related sulfoxides followed by thermal elimination.⁷⁰

Parsons reported an efficient approach to organophosphorus derivatives belonging to the

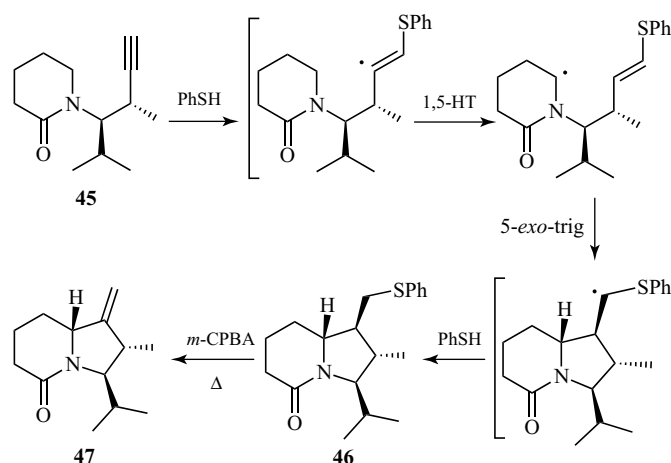


Figure 19 Thiophenol-mediated 1,5-hydrogen transfer followed by cyclization.

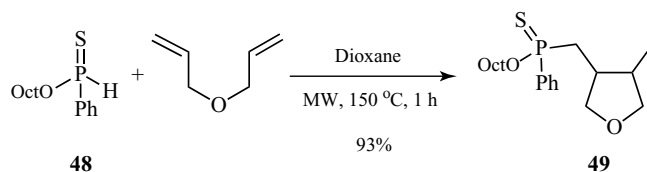


Figure 20 Sequential addition/cyclization of a P-centered radical on diallylether.

class of phosphonothioates, phosphinothioates, and phosphane sulfides.⁷¹ He showed that a phosphinothioate, such as **48**, which features a relatively weak P–H bond, can easily react with diallylether to deliver tetrahydrofurans **49** in excellent yields via a 5-*exo*-trig cyclization (Figure 20).

Formation of a P(V)-centered radical from an alkyne thiophosphonates could be exploited in several bond-forming processes. For instance, *S*-pentynyl thiophosphine oxides or dithiophosphonates (**50**, Figure 21) smoothly underwent cycloisomerization using thiophenol as a radical promoter to yields products **51** in good yield. Interestingly, the reactivity of the P-centered radical could be steered to an intermolecular fashion in the presence of an excess of olefin, leading to the adduct **52**.⁷²

The group of Landais reported the synthesis of fused piperidinones through a radical cascade and subsequent intramolecular lactamization.^{73,74} The reaction of an allylsilane bearing an oxime function (**53**, Figure 22) with a suitable α -halo ester affords the desired bicyclic products in good yield and with high diastereoselectivity. The radical from an α -iodoacetate adds to the less substituted

position of the alkene function of **53**, to generate a nucleophilic radical **54** which cyclizes through a 5-*exo*-trig process, providing a nitrogen-centered radical. At this stage, depending on the substitution of the oxime, two distinct pathways can occur. Employing carbon unsubstituted oximes, **55** can react with triethylborane to yield the amine–borane complex **56** which undergo a final lactamization via a polar crossover process, giving rise to the acyclic product **57**.

Grainger successfully employed the generation of a carbamoyl(aminoacyl) radical from the corresponding dithiocarbamate precursor (**58**, Figure 23) as a key step in the formal synthesis of (–)-aphanorphine to construct the azabicyclic core **61**.⁷⁵ Photomediated cleavage of the carbon–sulfur bond in **58** generates the carbamoyl radical **59**, which stereoselectively cyclizes through a 5-*exo*-trig process to give the carbon-centered radical **60**, which is eventually trapped by the dithiocarbamate **58** via a group transfer reaction.

Miyabe and Takemoto recently reported their progress in the field of enantioselective radical cyclizations through a Lewis acid tether approach (see **Stereoselective Radical Reactions**).^{76,77}

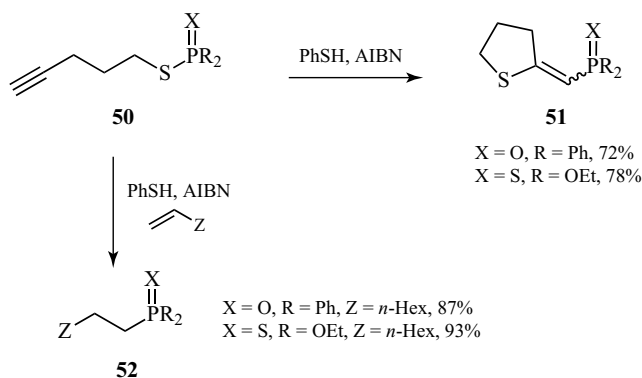


Figure 21 Selective reaction of conjugated acyclic trienes to polycyclic systems.

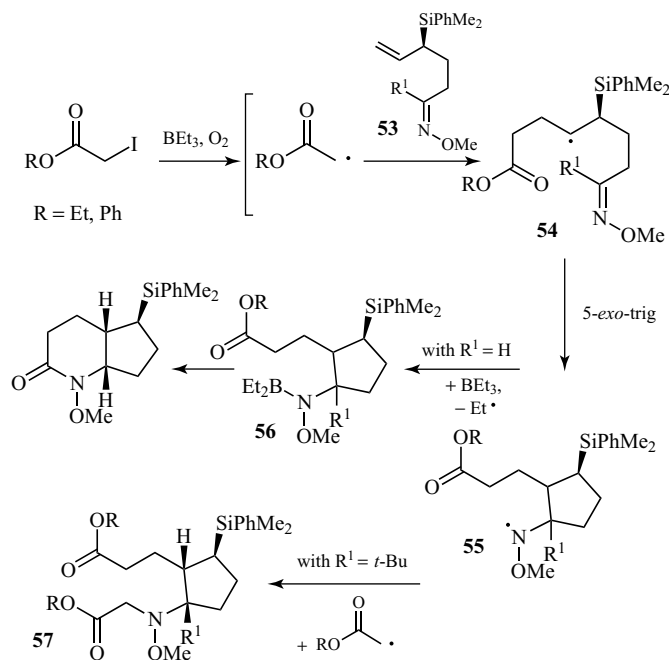


Figure 22 Different outcomes of the radical cascades between an haloester and an allylsilyloxime.

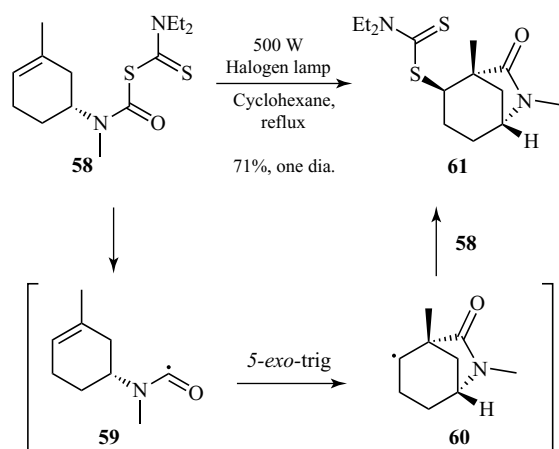


Figure 23 Photomediated radical reaction of a dithiocarbamate featuring sequential cyclization/group transfer.

Stereocontrol in this radical cascade was achieved through crucial coordination of a zinc chiral complex during the key cyclization step (intermediate **62**). This cascade features an initial radical addition onto the double bond of an oxime ether and the subsequent stereoselective ring closure directed by the chiral bis-oxazoline ligand on the zinc

metal center. The resulting radical could then be quenched by a halide to propagate the sequence. This approach was applied to the synthesis of various lactams such as **63** (Figure 24).

2.2.2 Sequences Involving Formation of Six-Membered Rings

The group of Zard reported the formal synthesis of mersicarpine through an intermolecular radical addition/cyclization cascade.⁷⁸ Activation of an indole xanthate (such as **64**, Figure 25) by lauroyl peroxide allows the addition of the resulting carbon-centered radical on a terminal olefin, delivering the intermediate **65**, which then undergoes 6-*exo*-trig cyclization to the indole ring **66**. This radical led to the product **67**, along with **68**, obtained either through disproportionation or by hydrogen transfer to the peroxide. The authors reported that the presence of an electron-withdrawing carboxylate substituent at the 3-position of the heterocycle is crucial for the process, suggesting that the reversibility of the radical addition onto the indole could be overcome by proper stabilization of the intermediate **66**.

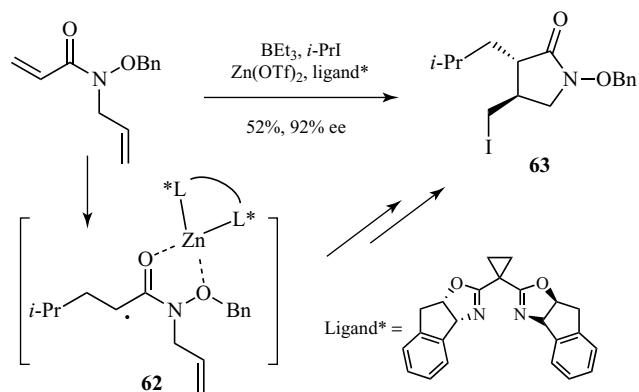


Figure 24 Enantioselective radical cyclizations triggered by chiral zinc complexes.

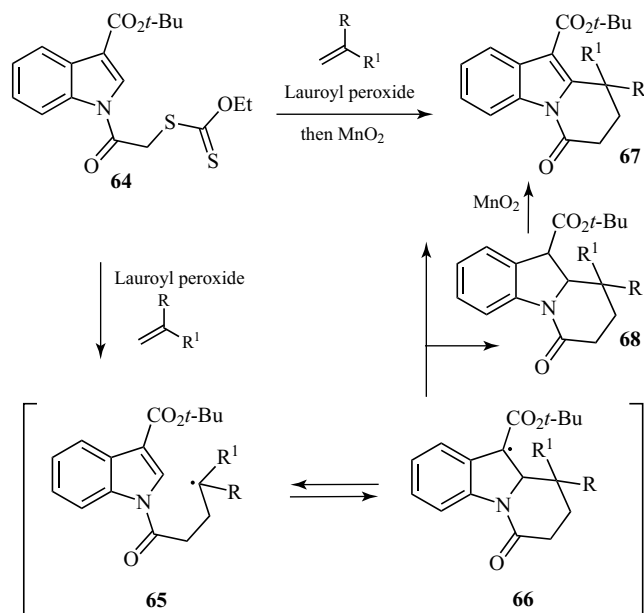


Figure 25 Access to polycyclic indoles by radical addition/cyclization.

Alabugin and coworkers reported an elegant radical cascade that involves three consecutive ring closures.⁷⁹ Initial addition of a tributyltin radical on the central triple bond of a terminally substituted tris(*o*-aryleneethynylene) (**69**, Figure 26) allows to obtain the desired products **70** and **71** in good yield after acidic destannylation. However, as the success of the process depends on the regioselectivity of the initial radical addition, the scope of the sequence is limited to substrates bearing terminal phenyl, *p*-tolyl (**70**) or trimethylsilyl (**71**) groups. A complex mechanism is at work in this cascade that involves,

besides cyclizations, hydrogen atom abstraction from a terminal TMS group in the latter case.

The group of Bennasar proposed a radical route to the quinine-based natural product calothrixin B.⁸⁰ As a part of their studies on the generation of 2-indolylacyl radicals from the corresponding phenyl selenoesters, the authors synthesized the radical precursor **72** (Figure 27). They propose that the initial abstraction of the selenoester group by a silyl radical delivers the acyl radical **73**, which undergoes a regioselective cyclization on the quinoline ring to afford radical **74**. Oxidation of **74**

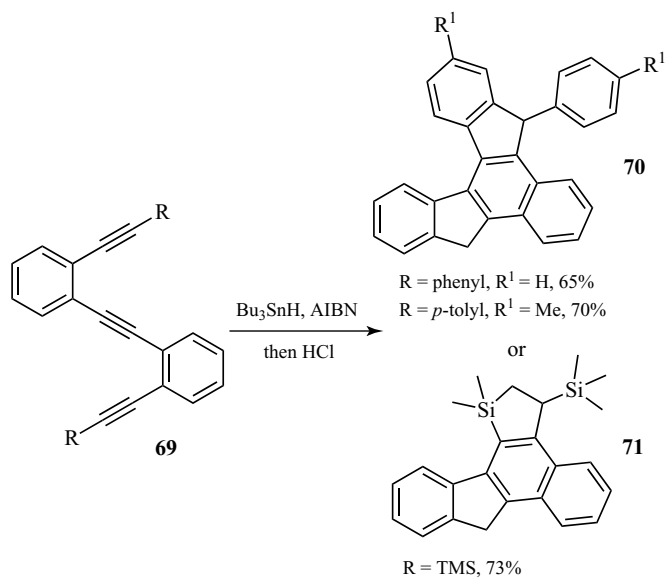


Figure 26 Selective reaction of conjugated acyclic triynes to polycyclic systems.

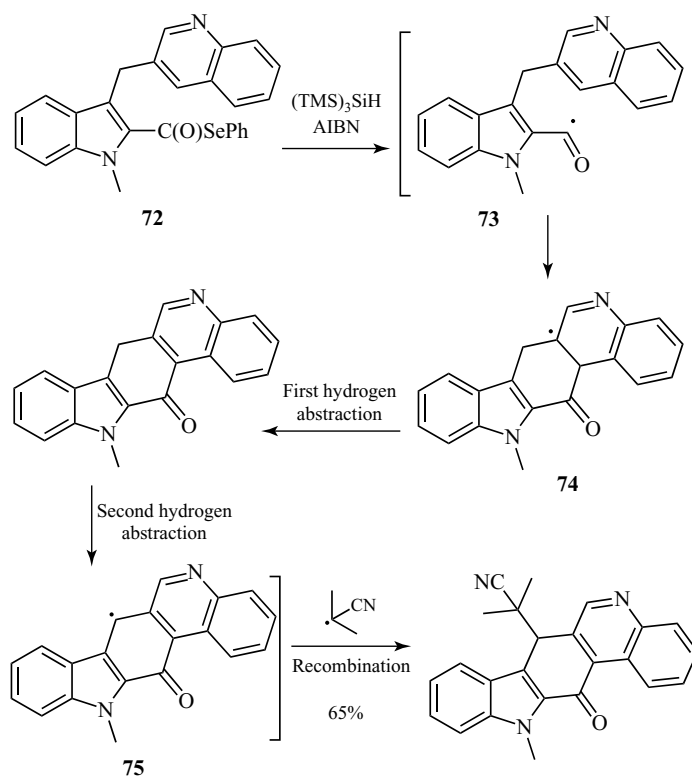


Figure 27 A radical cascade as key step in the formal total synthesis of calothrixin B.

by AIBN-induced hydrogen abstraction, followed by H-abstraction at the C-ring benzylic position generates radical **75**, which quenches the radical derived from AIBN decomposition. However, it is rather surprising that a radical/radical recombination step should be so selective. Other mechanisms are probably operative.

2.2.3 Miscellaneous

The group of Ryu has been active in the field of radical cascades including radical carbonylation steps. They reported the synthesis of methylene-2-piperidinones by an efficient carbonylation of an alkynyl imine in the presence of tributyltin hydride and AIBN (Figure 28; product **76** is shown before acid destannylation).⁸¹ When the substituent on the nitrogen is a suitable leaving

group, such as an α -styryl one, 2-methylenelactams could be selectively obtained through the same approach.⁸² The authors expanded the synthetic applications of this method to α,β -unsaturated compounds bearing a terminal triple bond and using an alkyl thiol as mediator. When employing substituted acrylates, a 5-*exo* cyclization occurred and led to the formation of compound **77**.⁸³ When the ester group of the reagent is replaced by a nitrile function, the same reactivity can be observed with trimethylsilylhydride as mediator instead of the thiol. Further developments were accompanied by theoretical studies on the reaction mechanism^{84,85} and allowed the group to achieve the tin-radical-mediated synthesis of 3-substituted cyclohexanones **78**. Interestingly, in the presence of allyltributyltin a four-component cascade delivers product **79**, which features a quaternary carbon at the 3 position of the cyclic ketone.⁸⁶ The

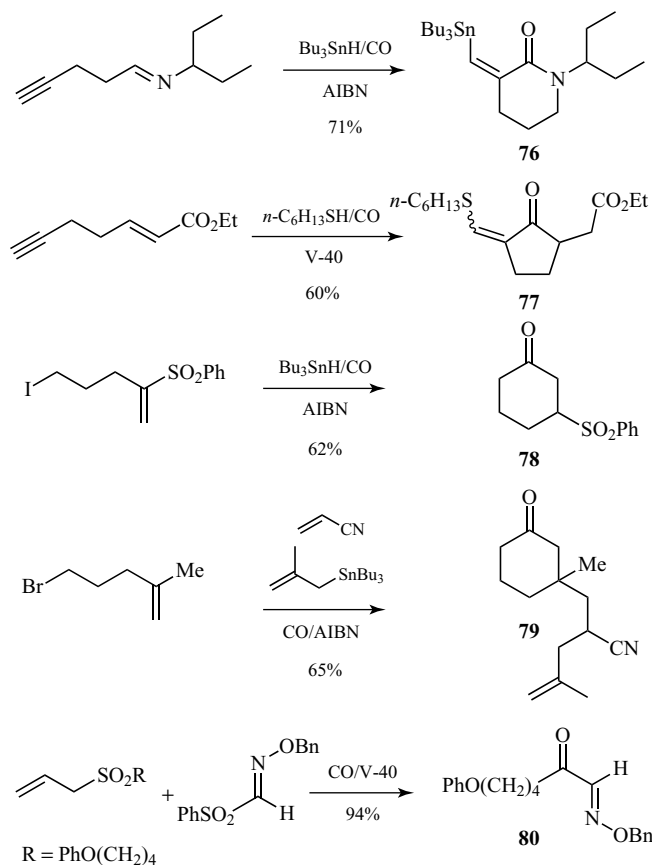


Figure 28 Radical cascades involving carbonylation of a carbon-centered radical.

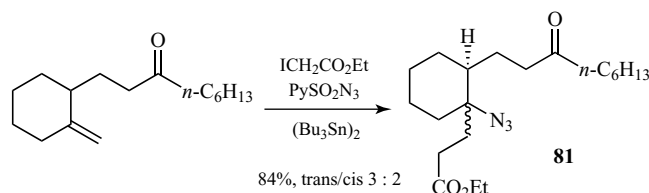


Figure 29 Radical carboazidation in the total synthesis of lepadiformine.

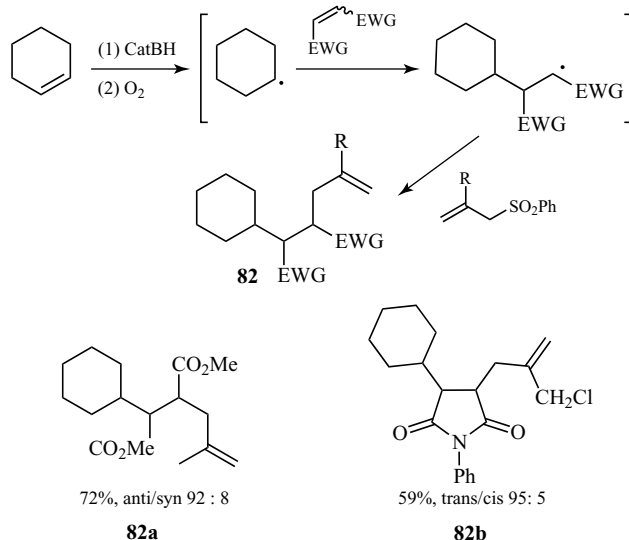


Figure 30 Three-component intermolecular cascade involving B-cyclohexylcatecholborane.

three-component coupling of a substituted allyl sulfone, carbon monoxide, and a phenylsulfonyl oxime similarly delivers a substituted acylated oxime **80**, together with allyl phenyl sulfone as the coproduct.⁸⁷

2.3 Radical Cascades Involving Intermolecular Steps Only

Renaud proposed a total synthesis of lepadiformine in which one of the key step is a carboazidation of a substituted methylenecyclohexane as shown in Figure 29.^{88,89} Hexabutylditin was used to generate an α -carboethoxy radical, which adds at the *exo*-methylene position of the olefin. The resulting radical is quenched by azidation from pyridinesulfonylazide to give **81** in good yield.

The same group proposed an interesting three-component radical-mediated sequence using B-alkylcatecholboranes (Figure 30).⁹⁰ The B-alkylated

adduct derived from cyclohexene and placed in the presence of oxygen generates efficiently a nucleophilic carbon-centered cyclohexyl radical, which added smoothly to an electrophilic double bond. Termination was achieved by allylation from a substituted allylsulfone, yielding the desired product **82**.

3 CASCADE REACTIONS INVOLVING NON-CHAIN REDOX PROCESSES

3.1 Cascade Reactions Promoted by Titanium Complexes

Titanium(III) chloride and related complexes constitute remarkable single-electron reductive reagents, widely used in organic synthesis for promoting radical reactions (see **Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**). As

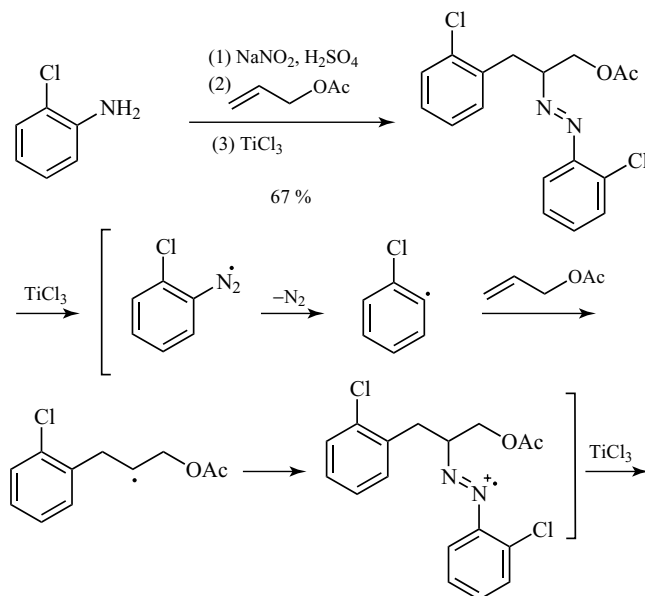


Figure 31 Carbodiazenylation of alkenes from aryldiazonium salts.

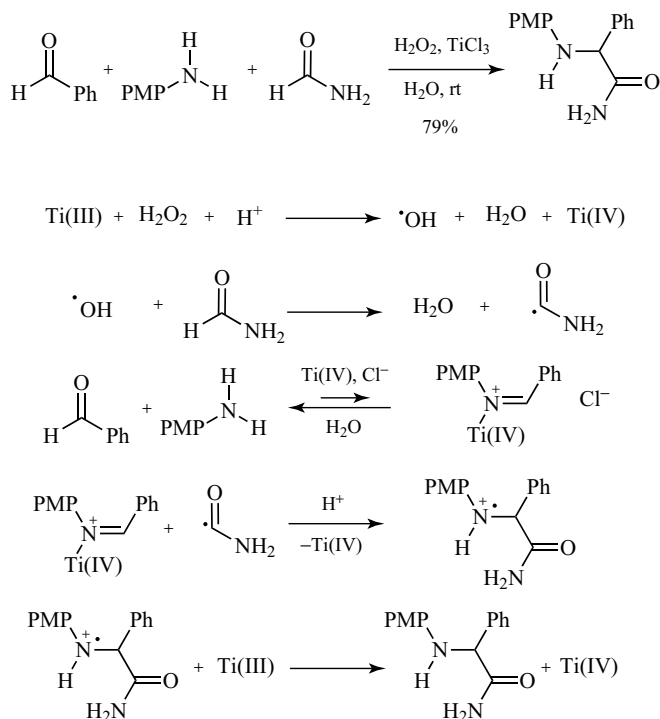


Figure 32 Radical version of the Strecker synthesis of α -aminoamides.

reported by Heinrich, carbodiazenylation of non-activated olefins can be accomplished with aryl-diazonium salts in the presence of TiCl_3 .⁹¹ The reduction of the diazonium salt by Ti(III) generates an aryl diazenyl radical. After nitrogen extrusion, the aryl radical liberated can add on to the olefin to form an intermediate alkyl radical, which then reacts with a second equivalent of diazonium salt. The resulting aminyl radical cation was finally reduced to the azo compound (Figure 31). This process allowed achieving the carbodiazenylation of nonactivated alkenes through an easy way. Neither dry solvents nor an inert atmosphere were needed to reach good yields. The carbodiazenylation was then extended to aliphatic derivatives through initial radical iodine atom transfer reactions of iodoacetonitrile and iodoacetate with the olefin.⁹²

A radical version of the Strecker synthesis of α -aminoamides in aqueous medium was proposed by Porta. This three-component reaction between formamide, an amine, and an aldehyde mediated by the $\text{TiCl}_3/\text{H}_2\text{O}_2$ system proceeded efficiently to

afford α -aminoamides (Figure 32).⁹³ The proposed mechanism first involves reduction of H_2O_2 by Ti(III) to the hydroxyl radical, followed by hydrogen atom abstraction from formamide. The resulting nucleophilic carbamoyl radical adds to the imine, generated *in situ* by condensation between the aldehyde and the amine with assistance of Ti(IV) salts, and liberates the aminium radical. Then, a final reduction of this intermediate by Ti(III) provides the α -aminoamide. A wide range of α -aminoamides was synthesized with moderate to good yields starting from cheap and commercially available substrates. This methodology was then extended to the aminomethylation of ethers⁹⁴ and the hydroxymethylation of imines⁹⁵ leading, respectively, to 1,2-amino ethers and 1,2-amino alcohols. As reported recently, addition to ketimines allowed the formation of quaternary α -aminoamides.⁹⁶

Titanocene(II) chloride (Cp_2TiCl) is a common and efficient reductive reagent for radical ring opening of epoxides, which can trigger radical polyene cyclization cascades.⁹⁷ Fernandez-Mateos disclosed

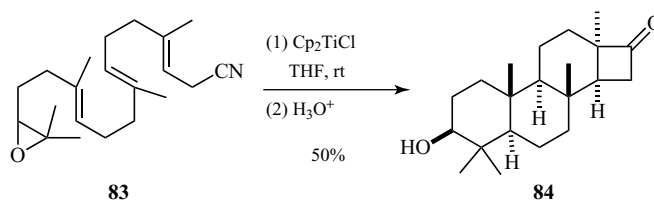


Figure 33 Quadruple radical cyclization terminated by a 4-*exo* process onto nitrile.

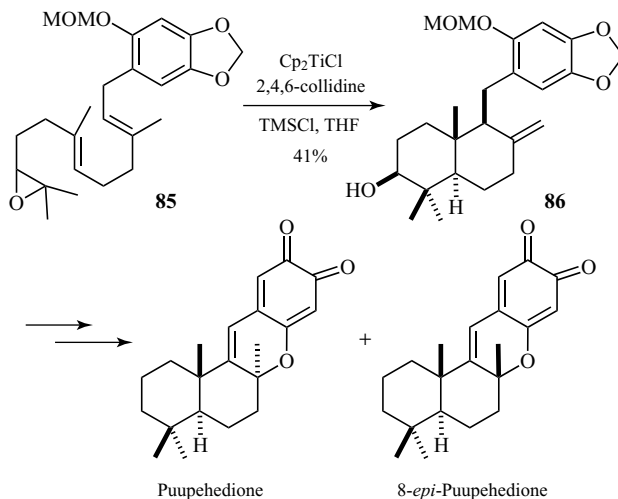


Figure 34 Titanocene-catalyzed epoxypolyene cyclization.

interesting examples of radical cascade cyclizations of unsaturated epoxynitriles with noticeable yields and diastereoselectivities.⁹⁸ Homolytic cleavage of epoxide **83** complexed with Cp_2TiCl gave the corresponding β -alkoxy radical, which underwent three successive 6-*endo*-trig cyclizations followed by a 4-*exo*-dig cyclization onto the nitrile group as the termination step. After hydrolysis, the tetracyclic ketone **84** was isolated in 50% yield as a unique diastereoisomer (Figure 33).

Gansäuer *et al.* applied their new catalytic system $\text{Cp}_2\text{TiCl}/2,4,6$ -collidine to the radical epoxypolyene cyclization of the epoxyfarnesyl derivative **85** for the formal synthesis of puerhedione and its 8-epimer. The key steps feature two 6-*endo*-trig cyclizations and subsequent β -hydride elimination of an intermediate Ti derivative to yield the bicyclic alcohol **86** as a common building block for marine natural products and other derivatives (Figure 34).⁹⁹

Barrero *et al.* reported some results on cascade cyclizations of epoxypolyenes catalyzed by Cp_2TiCl for the synthesis of 6-5, 6-6, and 6-7 bicyclic frameworks. The size of the second ring can be tuned by changing the substitution pattern and modulating the electronic nature of the double bond involved in the last cyclization step.¹⁰⁰ Finally, Kobayashi realized the synthesis of AB ring moiety of fomitelic acids via a titanium-mediated radical cyclization of epoxypolyene **87**.¹⁰¹ This reaction was completely stereocontrolled, leading to the tricycle **88** in moderate yields (Figure 35).

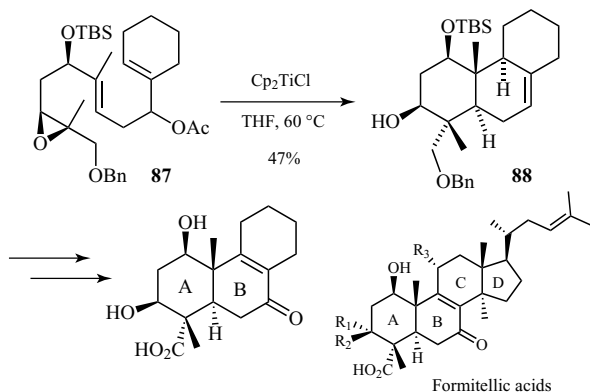


Figure 35 Synthesis of the AB ring moiety of fomitelic acids.

3.2 Cascade Reactions Promoted by Manganese Complexes

On the basis of Snider's chemistry, manganese(III) acetate proved a powerful oxidative reagent that can be used to perform radical cascade reactions (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**). In 2006, Chen disclosed an efficient synthesis of various polycyclic core skeletons of natural products such as ageliferin or massadine, involving Mn(III)-mediated oxidative heterobicyclizations leading to the formation of two C–C bonds and three stereogenic centers.¹⁰² The treatment of allylic β -imidazolinonyl- β -ketoesters with $\text{Mn}(\text{OAc})_3$ produced lactone tricyclic compounds by either a 5-*exo*-trig/6-*endo*-trig or a 5-*exo*-trig/5-*exo*-trig cascade radical cyclization. The regioselectivity depends of the substitution of the imidazolinonyl ring. For instance, the allylic β -imidazolinonyl- β -ketoester **89** is first oxidized by the Mn(III) salt to form a radical species, which then cyclizes cleanly into the tricycle **90**. The resulting radical was oxidized by another equivalent of Mn(III) and a proton was eliminated (Figure 36). Most of the transformations were performed with good yields, regioselectivities, and diastereoselectivities.

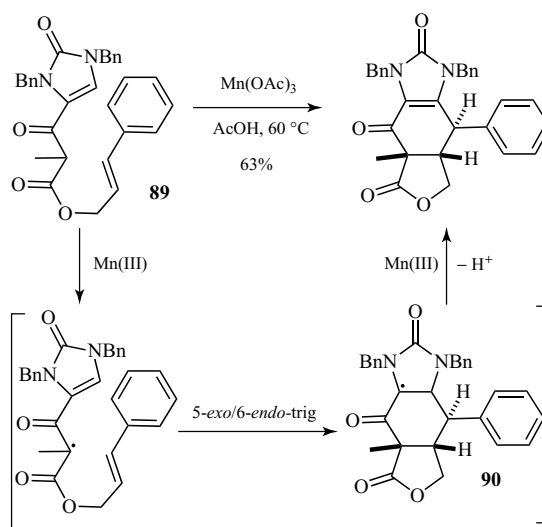


Figure 36 Mn(III)-promoted 5-*exo*/6-*endo* radical cyclization reactions.

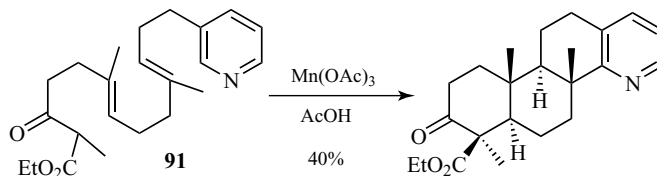


Figure 37 Radical cascade of polyene **91** terminating onto a pyridine ring.

González reported a new approach to the synthesis of spongidines based on the oxidative radical cyclization promoted by $\text{Mn}(\text{OAc})_3$ of an unsaturated β -ketoester containing a pyridine ring as radical trap. The reaction of polyene **91** gave

an isomeric structure of natural spongidines in moderate yield but with an excellent selectivity (Figure 37).¹⁰³

El Kaim studied the functionalization of Ugi adducts, resulting from a four or five component

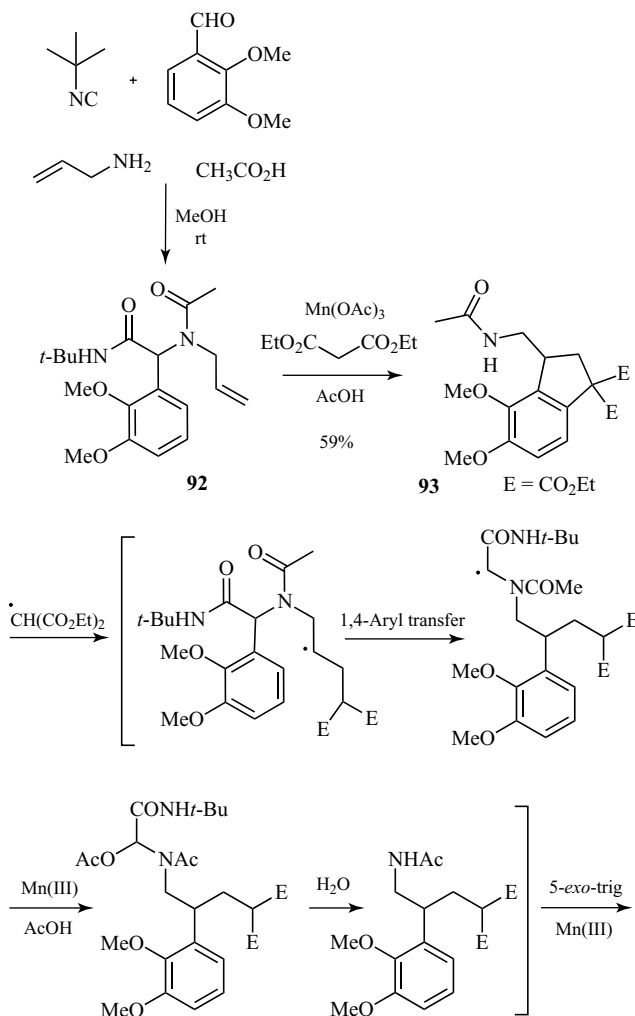


Figure 38 Radical cascade from an Ugi adduct and ethyl malonate induced by $\text{Mn}(\text{OAc})_3$.

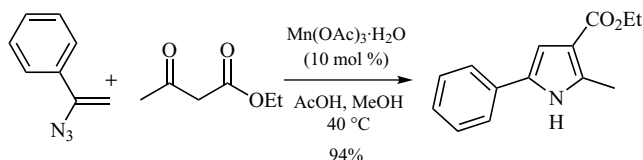


Figure 39 Mn(III)-catalyzed synthesis of pyrrole from ethyl acetoacetate and styrene azide.

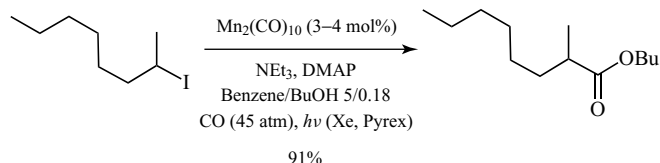


Figure 40 Atom transfer carbonylation of a secondary alkyl iodide.

reaction, through a Mn(III)-based radical cascade of malonates or β -ketoesters involving both inter- and intramolecular steps. In the following example, the malonyl radical generated by oxidation of diethyl malonate with $\text{Mn}(\text{OAc})_3$ adds onto olefin **92** and the resulting alkyl radical operates a 1,4-aryl transfer reaction. After oxidative cleavage and subsequent 5-*exo*-trig cyclization, indane **93** was isolated in 59% yield. It is noteworthy that when the second oxidative cyclization cannot occur, the corresponding δ -amidomalonate is obtained (Figure 38).¹⁰⁴

A new method for the synthesis of substituted pyrroles was proposed by Chiba and Narasaka and involved the Mn(III)-mediated cascade radical reaction of 1,3-dicarbonyl compounds and vinyl azides.¹⁰⁵ Several examples were performed by changing either the vinyl azide or the 1,3-dicarbonyl

compound, for example, β -ketoester or diketone (Figure 39). Details about this process are reported in **Main-Group Elements in Radical Chemistry**.

Manganese can also accelerate radical reactions such as the atom transfer carbonylation of alkyl iodides. Ryu showed that $\text{Mn}_2(\text{CO})_{10}$ is an effective catalyst for the transformation of primary, secondary, and tertiary alkyl iodides into carboxylic acid esters. Dimanganese decacarbonyl acts as a radical initiator and accelerates the carbonylation under irradiation (Figure 40).¹⁰⁶

Studer reported the formation of aryl radicals by the treatment of arylboronic acids with $\text{Mn}(\text{OAc})_3$ and their subsequent addition to alkenes. The resulting alkyl radical can either be trapped by oxygen under aerobic conditions or sequentially react with a second equivalent of alkene and then cyclize

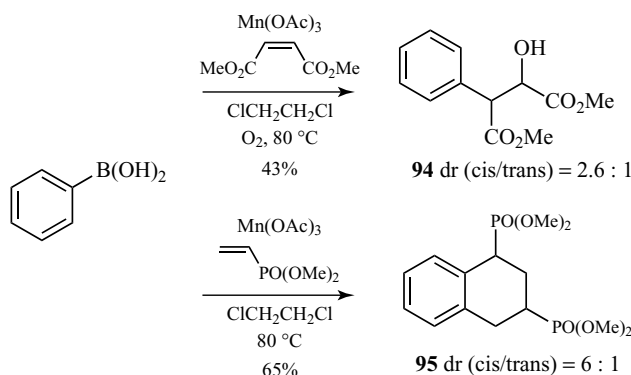


Figure 41 Radical cascade reactions with arylboronic acids and alkenes under oxidative conditions.

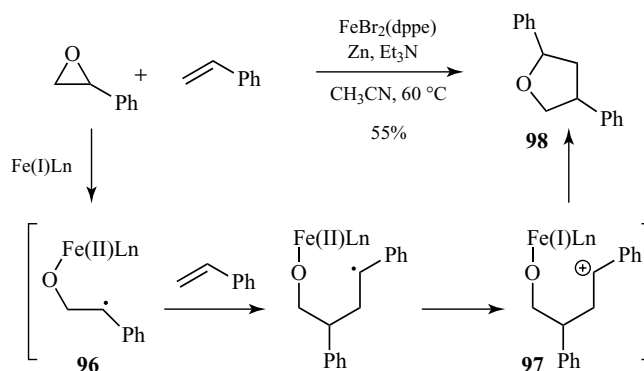


Figure 42 Fe(I)-catalyzed ring expansion of styrene oxide with styrene.

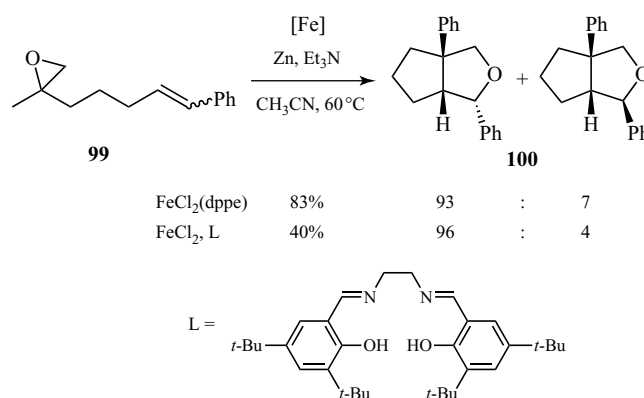


Figure 43 Intramolecular Fe(I)-catalyzed ring expansion.

through homolytic aromatic substitution to give arylhydroxylation products (**94**) and tetrahydronaphthalene derivatives (**95**), respectively (Figure 41).¹⁰⁷

3.3 Cascade Reactions Promoted by Iron Complexes

Hilt showed that low-valent iron(I) species, generated by reduction of iron(II) complexes with zinc powder, can catalyze inter- and intramolecular ring expansion reactions of epoxides in the presence of alkene moieties and furnished substituted tetrahydrofurans. Reduction of epoxystyrene by single-electron transfer from the iron(I) species provokes its ring opening and liberates the β -alkoxy iron(II) radical **96**, which can add to the alkene. A back electron transfer from the alkyl radical to the iron complex generates a stabilized

carbocation **97**, which subsequently cyclizes to form the tetrahydrofuran ring **98** (Figure 42).¹⁰⁸ Similarly, ring expansion of epoxylkene **99** gives rise to the corresponding bicyclic tetrahydrofuran **100** (Figure 43).¹⁰⁹ Noticeable improvements in diastereoselectivities from the original iron system were realized when using a salen-type ligand in the place of a diphosphine. An extension of this reaction to the synthesis of hexahydrocyclopenta[*c*]furans was also proposed.¹¹⁰

Another interesting aspect of iron chemistry is the reduction of diazonium salts reported by Heinrich and its participation in cascade reactions. Upon treatment with FeSO_4 , aryl diazonium salts generate aryl radicals which can add onto activated as well as nonactivated olefins. Then, the resulting alkyl radical can be trapped by a nitroxyl radical such as TEMPO (Figure 44).¹¹¹ The authors observed that the starting diazonium can be used itself as a radical scavenger when nonactivated alkenes are

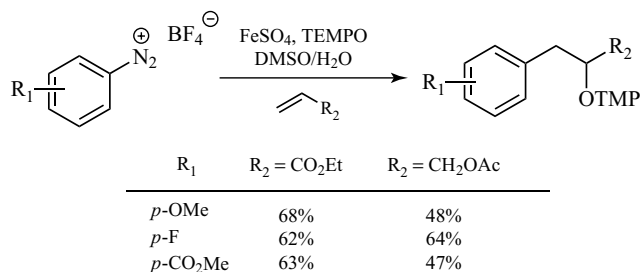


Figure 44 Intermolecular radical carboaminohydroxylation of olefins.

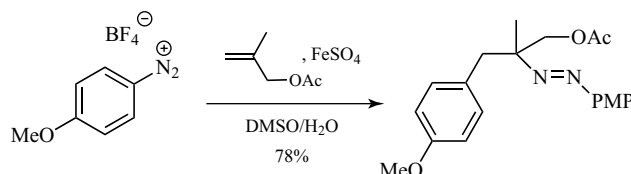


Figure 45 Intermolecular radical carbodiazenylation of olefins.

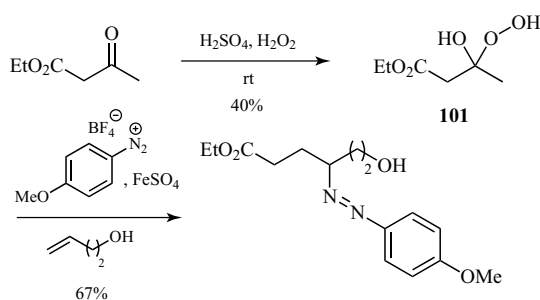


Figure 46 Iron(II)-mediated three-component carbodiazenylation reaction.

used. On the basis of this observation, an efficient radical carbodiazenylation process was developed (Figure 45).¹¹² In a recent work, Henrich envisaged combining the reduction of hydroperoxide **101** by

FeSO₄, which generates an ethyl acetate radical, with carbodiazenylation of nonactivated alkenes (Figure 46).¹¹³

Examples of cascade reactions involving iron(III)-mediated oxidation processes have also been reported. For instance, MacMillan achieved enantioselective cascade (4 + 2) cycloadditions between aldehydes with a pendant aromatic system and styrenes through asymmetric semi-occupied molecular orbital (SOMO) catalysis (Figure 47). Oxidation of the enamine, derived from the condensation of an aldehyde with a chiral imidazolidinone, delivers a radical cation which then participates in an olefin addition/radical oxidation/Friedel–Crafts sequence and provides enantioenriched substituted cyclohexyl rings. The good results obtained in terms of yields, diastereo- and enantioselectivities

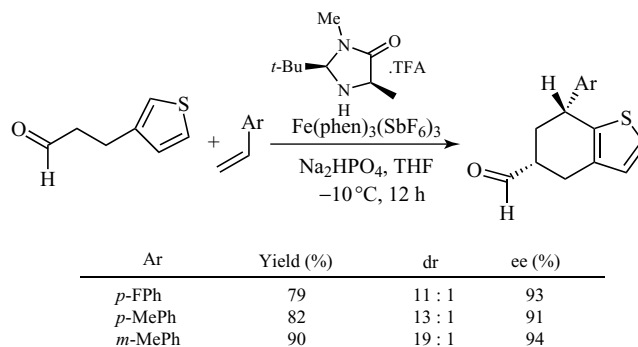


Figure 47 Cascade reactions of aldehydes and olefins using enantioselective SOMO-catalysis.

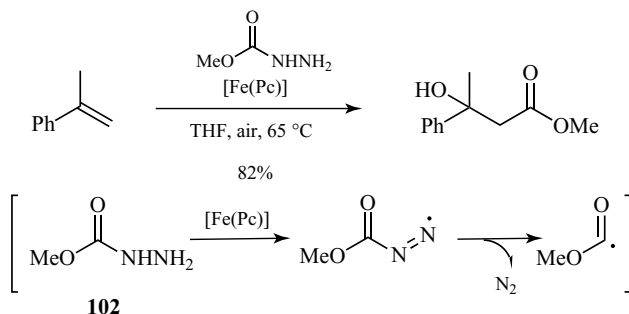


Figure 48 Radical reaction of methyl carbazate and α -methylstyrene in the presence of Fe(Pc).

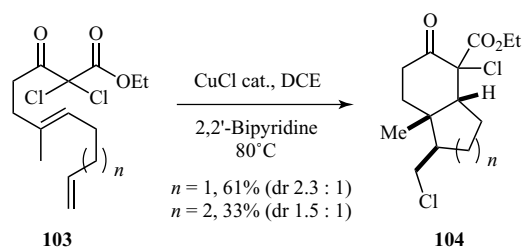


Figure 49 Atom transfer radical process by reduction of α -dichloro- β -ketoesters.

makes this process a powerful tool in organic synthesis.¹¹⁴

Taniguchi examined the intermolecular addition of alkoxy carbonyl radicals, generated by oxidation of the corresponding carbazates (**102**) by iron phthalocyanine, to alkenes in the presence of air. Thus, the reaction of various carbazates and terminal/gem-disubstituted alkenes afforded β -hydroxyesters in moderate to good yields (Figure 48).¹¹⁵

3.4 Cascade Reactions Promoted by Copper Complexes

Recently, Yang reported the single electron transfer reduction of α -dichloro- β -ketoesters (**103**)

catalyzed by copper(I) complexes (Figure 49).¹¹⁶ A chlorine atom transfer occurred in this radical cascade process involving polycyclizations. 6-*Endo*/5-*exo* and 6-*endo*/6-*exo* sequences have been done with moderate to good yields to afford bicyclic products (**104**). In order to reduce the Cu(II)/Cu(I) redox potential, ligands like bipyridine or bis(oxazoline) have to be used and the reduction of C–Cl bond allowed. The same procedure has also been applied to more simple systems to form cyclopentanone and cyclohexanone derivatives.

A copper-catalyzed cascade radical cyclization route has been proposed for the synthesis of benzospiro-indolizidinepyrrolidinones derivatives (Figure 50).¹¹⁷ Following an atom transfer radical process, the indole derivative **105** afforded the tetracyclic products **106** in moderate yields. The reduction of one C–Cl bond of the trichloroacetamide moiety generated a 1-(carbamoyl)dichloromethyl radical that initiated a 5-*exo*/6-*endo* cyclization sequence with a total diastereoselectivity.

MacMillan developed an enantioselective polyene cyclization mediated by copper(II) salts involving the organocatalysis concept also (Figure 51).¹¹⁸ An aldehyde function reacted with a chiral amine to generate the corresponding enamine derivative that was oxidized by copper(II) triflate according to

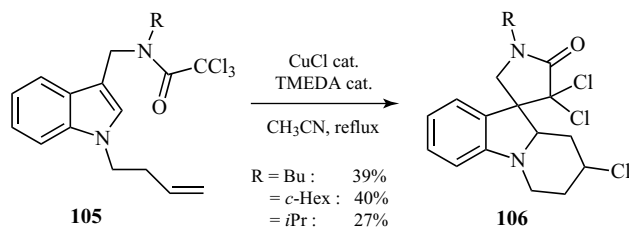


Figure 50 Copper-catalyzed cascade radical cyclization accessing spiro compounds.

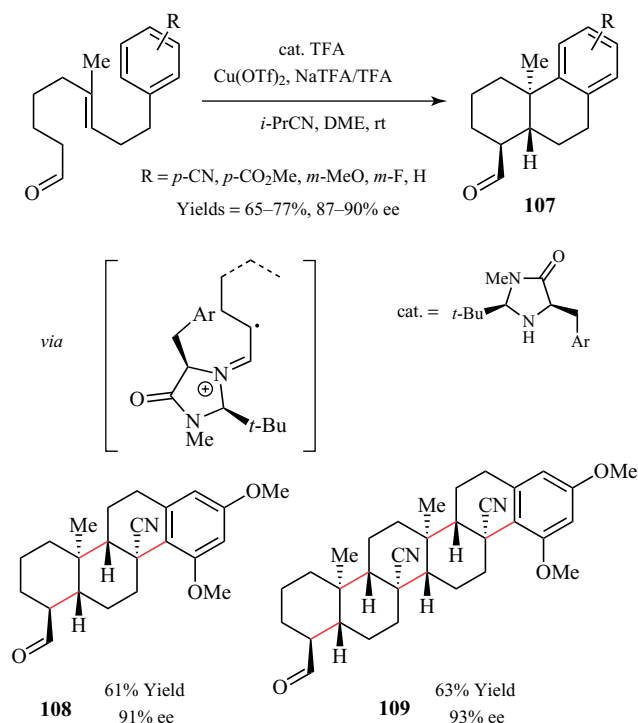


Figure 51 Enantioselective polyene cyclization involving organo-SOMO catalysis.

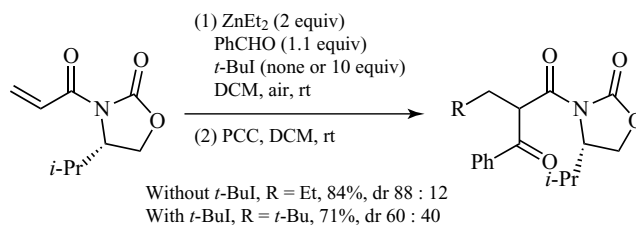


Figure 52 Three-component radical-polar crossover reaction.

a single electron transfer process. The resulting radical cation started the cascade reaction leading to the formation of polycyclic compounds (**107**) in good yields and enantioselectivities. Tri- to hexacyclic steroid analogs **108** and **109** have been obtained by this efficient transformation.

3.5 Cascade Reactions Promoted by Zinc Complexes

Bertrand reported the use of dialkylzinc in the presence of oxygen as chain-transfer reagent, which constitutes an alternative to borane reagents.

This reactivity was highlighted by the addition of C-centered radicals onto imines and enones.^{119,120} The same group published a one-pot, three-component, radical-polar crossover reaction (Figure 52).¹²¹ Under air atmosphere, the diethylzinc allowed the formation of an ethyl radical that can add onto Michael acceptor or generate the *tert*-butyl radical by iodine abstraction. Then, zinc enolate was immediately formed by homolytic substitution on the diethylzinc and reacted with benzaldehyde with moderate diastereoselectivities.

More recently, Chemla described a related radical-polar crossover cascade reaction with organozinc and mixed organocopper/organozinc

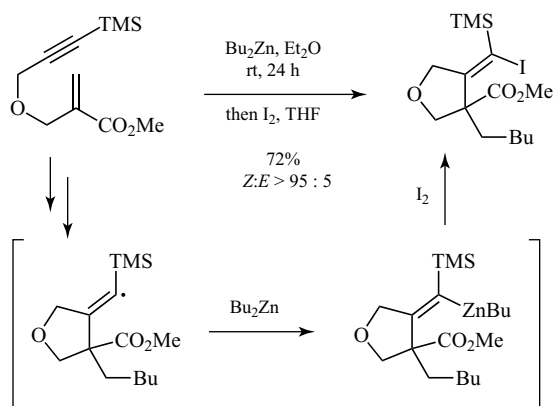


Figure 53 Radical-polar crossover cascade reaction initiated by organozinc reagents.

reagents. This sequence involved a radical Michael addition followed by a 5-*exo*-trig cyclization to afford pyrrolidine derivatives.¹²² This was extended by the same group to a stereoselective zinc atom radical transfer involving alkynes (Figure 53).¹²³ β -(Propargyloxy) enoates reacted with dialkylzinc reagents in the presence of oxygen. The so-formed alkyl radical added onto the acrylate moiety followed by a 5-*exo*-dig cyclization. The resulting vinyl radical underwent a homolytic substitution on alkylzinc to afford a vinyl zinc intermediate that reacted with the electrophilic iodine.

Dimethylzinc-mediated radical-anionic cascade have been proposed by Bertrand and Feray for the stereoselective synthesis of oxygenated five-membered ring heterocycles (Figure 54).¹²⁴ Depending on the additive, synthesis of lactone dihydrofuran, and lactol derivatives can be achieved in good to high yields. In the case of lactones, a diastereoselective acyl group transfer has been highlighted proceeding through a zinc enolate addition onto one ester function.

3.6 Cascade Reactions Promoted by Silver Complexes

In the context of single-electron transfer oxidation, Narasaka reported the generation of β -keto radicals from cyclopropanols by using silver(I) salts and ammonium persulfate as co-oxidant (Figure 55).¹²⁵ This transformation has been previously proposed by the same group with $\text{Mn}(\text{pic})_3$. The oxidant is supposed to be an $\text{Ag}(\text{II})$ complex that would be formed by the oxidation of $\text{Ag}(\text{I})$ with persulfate. Cyclopropanol derivatives were oxidized to the corresponding alkoxy radical that underwent a β -scission to afford the β -keto radical. This intermediate reacted with the electron-poor acrylonitrile followed by the addition of the resulting

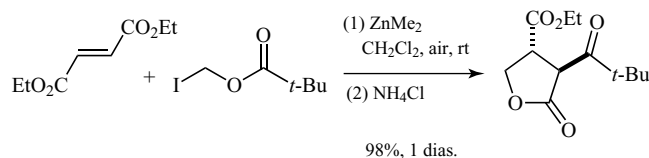


Figure 54 Dimethylzinc-mediated radical-anionic cascade reaction.

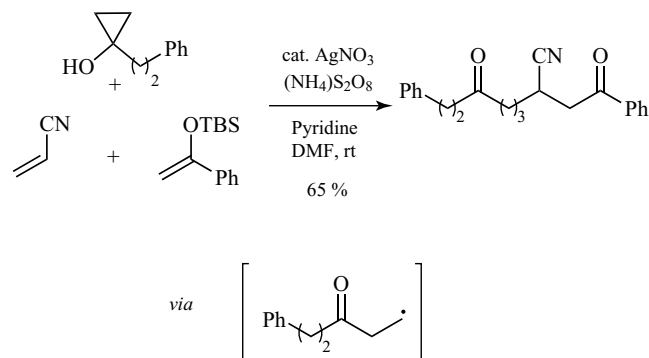


Figure 55 Multicomponent reaction initiated by the oxidation of cyclopropanol derivatives.

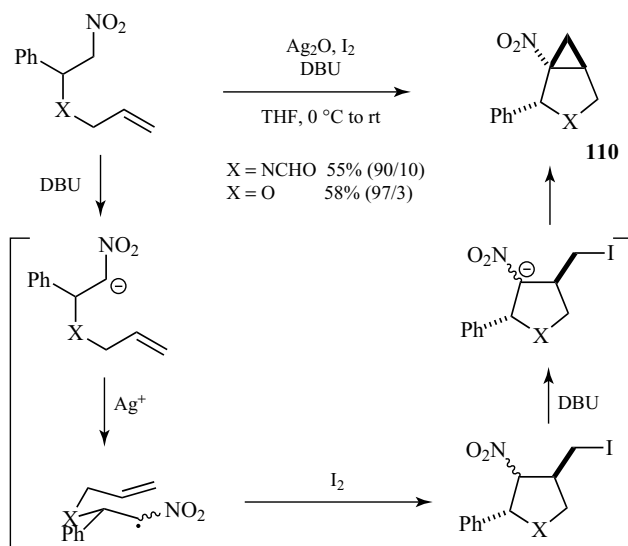


Figure 56 Oxidation of β -nitroamide or ether anions by silver salt.

electron-deficient radical onto the electron-rich enol ether. The same group applied this process in the total synthesis of (–)-sordarin.¹²⁶

Kamimura's group investigated the ability of Ag_2O to oxidize β -nitroamide or ether anions in a radical-anion cascade reaction and obtain bicyclic nitrocyclopropane derivatives (**110**) (Figure 56).¹²⁷ Deprotonation by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at the α position of the nitro group and the subsequent single electron transfer (SET) generated the α -nitro radical, which underwent 5-*exo*-trig cyclization. The resulting primary radical was able to react with I_2 to afford the corresponding primary iodide. Finally, the cyclopropyl ring was obtained by intramolecular nucleophilic substitution with good stereoselectivity. 6-*exo*-trig Cyclizations were also investigated to yield 6,3-bicyclic compounds (**110**).

3.7 Cascade Reactions Promoted by Cerium Complexes

Cerium ammonium nitrate (CAN) has been widely used as a single-electron oxidant in many cascade organic reactions (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**).¹²⁸ Its low toxicity, ease of experimental setup, and good solubility in several organic

solvents have shown its high utility in organic synthesis. A well-known activity of CAN is its ability to oxidize 1,3-dicarbonyl compounds into their radicals, which can react with substituted alkenes to form cyclic adducts. Different carbon skeletons can be formed with different alkenes. For example, Nair has reported the reaction between 1,3-dicarbonyl compounds and diphenylmethylenecyclopropane to form 5-oxaspiro[2.4]hept-6-ene derivatives (**111**) (Figure 57a).¹²⁹ whereas Meréndez has recently reported a CAN-promoted cyclization reaction between 1,3-cyclohexadiones and diaryl α,β -unsaturated ketones to furnish 2,3,6,7-tetrahydrobenzofuran compounds (**112**) (Figure 57b).¹³⁰ In both cases, the mechanism follows a radical addition to the alkene followed by cationic cyclization with one of the carbonyl groups of the dione.¹³¹

A similar pathway was also observed in the oxidation of styrene oxides allowing intramolecular cyclization with the styrene moiety in compound **113** (Figure 58a). The intermolecular trap of the formed benzyl cation with acetonitrile results in the formation of substituted piperidine **114** in good yields.¹³² On the other hand, *N*-vinyl amides can also be oxidized by CAN in the presence of diaryl imines to afford 1,2,3,4-tetrahydroquinolines **115** in high yields (Figure 58b).¹³³

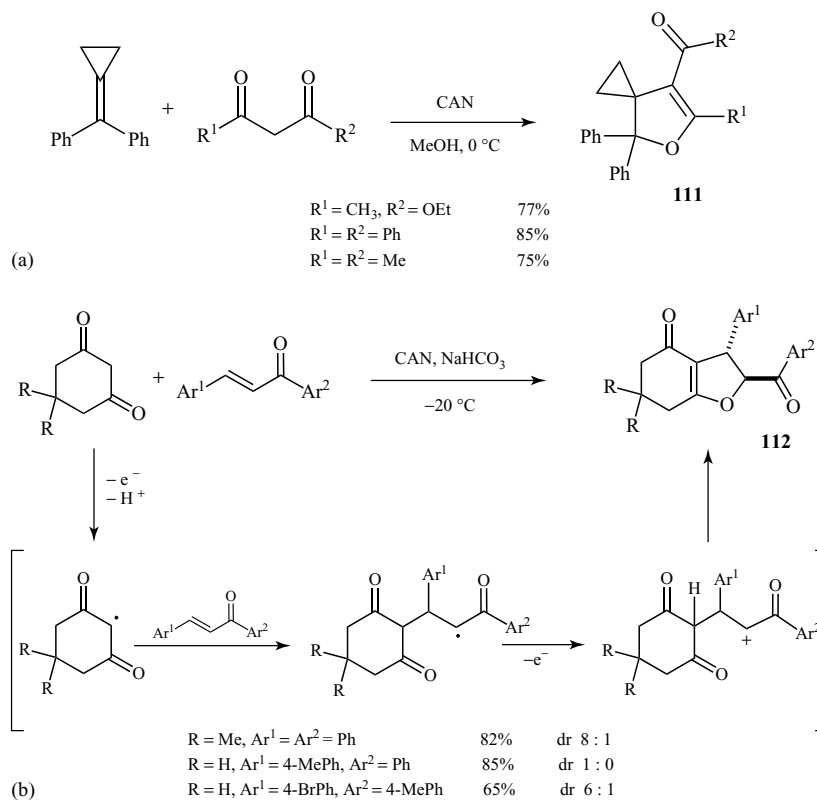


Figure 57 Cascade reactions of 1,3-dicarbonyls mediated by Ce(IV).

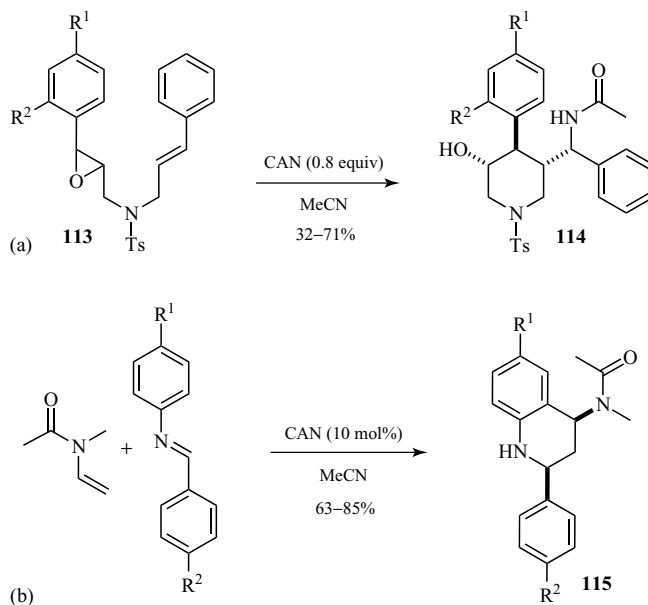


Figure 58 Oxidation of styrene oxides and *N*-vinyl amides by CAN.

3.8 Cascade Reactions Promoted by Samarium Complexes

Samarium diiodide became popular as a reducing agent in organic synthesis since its discovery by Kagan (see **Organic Synthesis Using Samarium Diiodide**). This one-electron-transfer reagent has been largely used thanks to the mild conditions it requires and its generally good chemoselectivity. Moreover, it is known to undergo either radical or ionic processes. Procter reported “radical then aldol” cyclization cascades from dialdehyde substrates (**116**), leading to tricyclic products (**117**) (Figure 59).¹³⁴ The reduction of one aldehyde function afforded the corresponding ketyl radical anion (**118**), which underwent an anti-selective 5-*exo*-trig radical cyclization onto the activated olefin with the formation of samarium enolates via an anti-selective pathway. By chelation to samarium(III), a diastereoselective aldol cyclization involving a six-membered transition structure **119** occurred and the final tricyclic compound **117** was obtained. Precoordination of samarium to the ester would favor the reduction of the nearer aldehyde selectively, thus explaining the difference in reactivity between the two aldehyde groups. This methodology has been applied by the same group to an original approach to pleuromutilin.¹³⁵

Polycyclic *N*-heterocycles can also be synthesized from cyanamides by intramolecular cascades

promoted by samarium diiodide (Figure 60).¹³⁶ The reduction of aryl iodide **120** led to the formation of aryl radical **121** which cyclized onto the nitrile group in a 6-*exo*-dig manner. The so-formed iminyl radical **122** underwent a 6-*endo*-trig cyclization followed by rearomatization and led to compound **123**. This transformation has been applied to the total synthesis of natural products or analogs.

Samarium diiodide proved to be very effective in cascade reactions. Thus, its applications in total synthesis are useful. In this field, Reissig reported a short formal total synthesis of strychnine by an SmI₂-induced cascade reaction (Figure 61).¹³⁷ In this key step, two cycles and three stereogenic centers were built with a high stereoselectivity and good yield. This forms the shortest route yet reported to racemic strychnine.

Procter reported the transformation of lactones bearing two alkenes or alkyne/alkene under reductive conditions.¹³⁸ An SmI₂/H₂O mixture allowed the formation of decorated azulenes in high yields and good diastereoselectivities (Figure 62). This reaction proceeds through unusual radical anion intermediates. The diastereoselectivities were rationalized by calculations. The same group reported a stereoselective cyclization cascade mediated by SmI₂/H₂O, which was applied in a study toward the synthesis of stolonidiol.¹³⁹

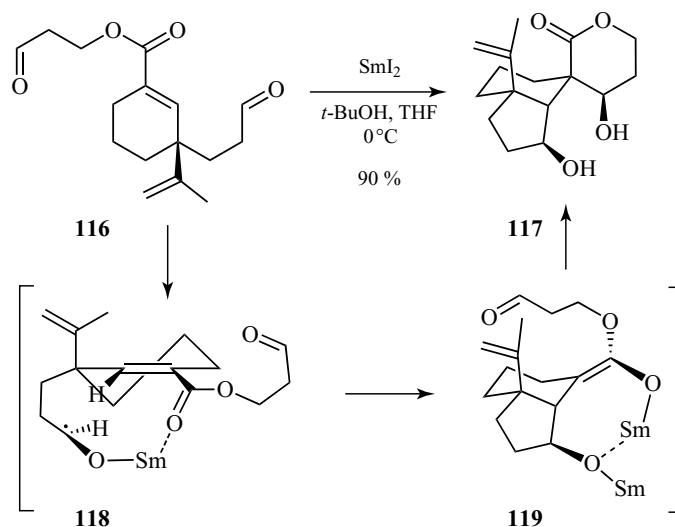


Figure 59 Radical/aldol sequence from dialdehyde compounds.

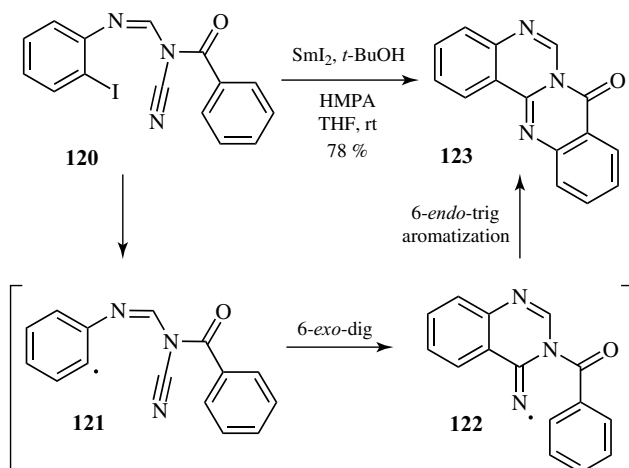


Figure 60 Radical cascade cyclizations involving *N*-acyl cyanamides mediated by SmI_2 .

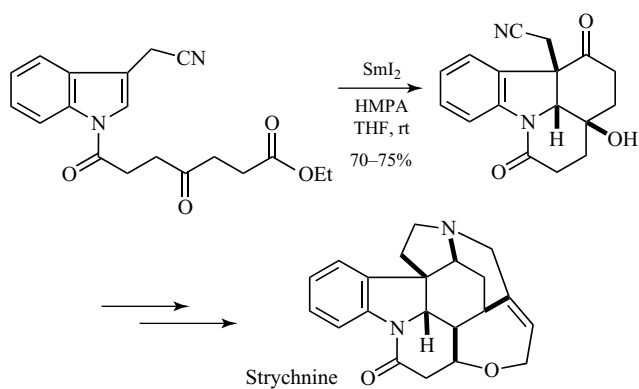


Figure 61 SmI_2 -induced cascade reaction through ketyl radical.

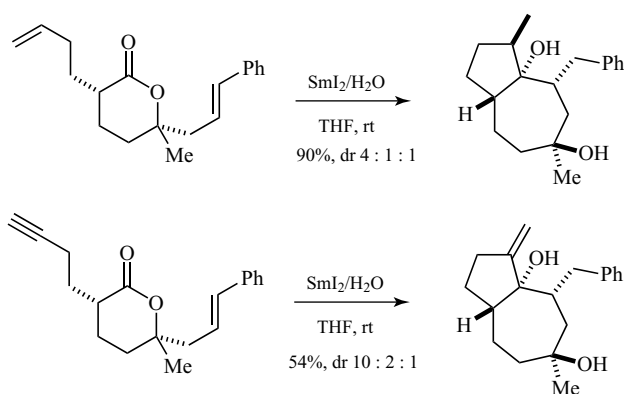


Figure 62 Formation of azulenes by reduction of the ester group with samarium diiodide.

3.9 Visible-Light Photocatalysis Promoted Cascade Reactions

Owing to its high efficiency and convenience, photocatalysis using visible light has become a promising, environmentally benign tool for organic synthesis (see **Synthetic Radical Photochemistry**). On the basis of the seminal work of Kellogg, a revival of this chemistry came about.¹⁴⁰ Recently, Stephenson has shown that carbon radicals formed by reductive cleavage of activated C–Br bonds in 2-bromomalonate esters can undergo efficient and diastereoselective 5-*exo*-trig/6-*exo*-trig (a)¹⁴¹ or 5-*exo*-trig/5-*exo*-dig (b)¹⁴² cascade radical cyclizations (Figure 63). This process is initiated by the oxidative quenching of the excited state of a metal complex such as tris(bipyridine)ruthenium(II) ($\text{Ru}(\text{bpy})_3^{2+}$), a commonly used photoredox catalyst, by SET from an electron donor (e.g., amine). Consequently, the metal catalyst becomes a strong reducing agent in its reduced form (e.g., $\text{Ru}(\text{bpy})_3^+$), which undergoes a second SET to

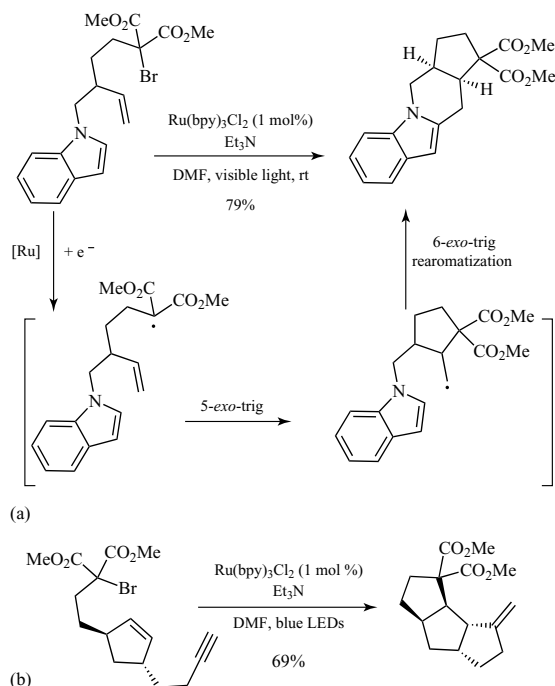


Figure 63 Radical polycyclizations initiated by reductive cleavage of activated C–Br bonds.

the organic substrate (bromide), and thus starts the catalytic cycle and regenerates the catalyst.

Yoon has also performed visible light photoredox catalysis in the [2 + 2] cycloadditions of enones.¹⁴³ It was shown that using a mixture of $\text{Ru}(\text{bpy})_3\text{Cl}_2$, *i*-Pr₂NEt and LiBF₄, aryl enones can be reduced to radical anions, which add to other enones and subsequently undergo 4-*exo*-trig cyclization to furnish cyclobutane adducts with excellent diastereoselectivity (Figure 64). Interestingly, the scope of this reaction was expanded to the toward the intramolecular cyclization of bis(enones). At least one aryl enone in a bis(enone) is required to facilitate the reduction (SET) process and, as a result, to undergo an intramolecular [2 + 2] cycloaddition to afford 4,5-membered fused bicyclic compounds (Figure 65a).^{144–146} An equivalent pathway was also observed when similar conditions were applied for the reduction of aryl cyclopropyl ketones.¹⁴⁷ In this case, 5,5-membered fused bicyclic compounds were formed in high stereoselectivity and good yields but needed the intervention of an additional Lewis acid (Figure 65b).

It is noteworthy that in all of the above examples, a sufficiently electron-poor substrate is required for a smooth reduction step. In contrast, Yoon have also performed the oxidative photocatalysis of electron-rich styrenes.¹⁴⁸ Hence, such reaction is initiated through the oxidative quenching of the

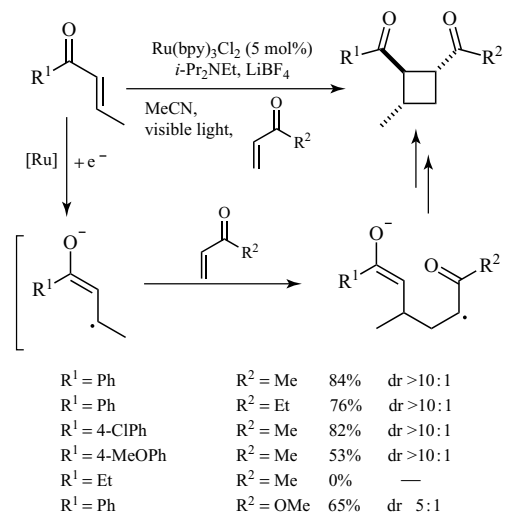


Figure 64 Intermolecular photoredox-catalyzed [2 + 2] cycloaddition.

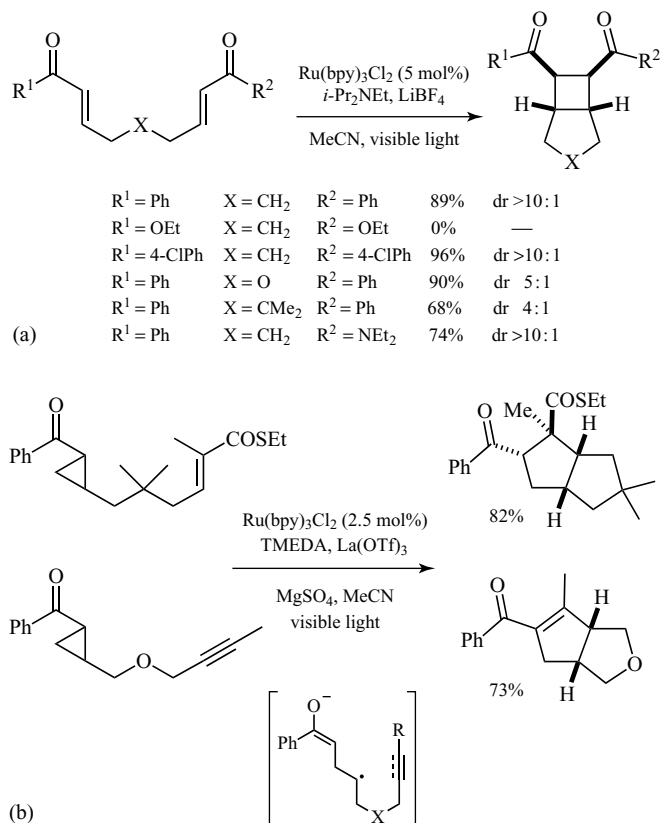


Figure 65 Intramolecular photoredox-catalyzed cycloadditions.

metal catalyst excited state $\text{Ru}(\text{bpy})_3^{2+*}$ by a good electron acceptor (e.g., methyl viologen MV^{2+}) to generate $\text{Ru}(\text{bpy})_3^{3+}$. Then, the electron-rich styryl moiety is oxidized into the radical cation, which can be involved in a cascade reaction. The formation

of 4,5-membered fused bicyclic compounds from the photocatalyzed [2 + 2] cycloaddition of aryl bis(styrenes) was demonstrated (Figure 66). This clearly shows how sensitive the reaction is to the nature and position of substituents on the styrene

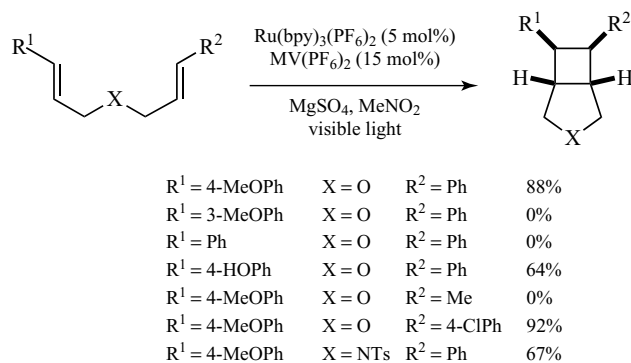


Figure 66 Intramolecular photoredox-catalyzed [2 + 2] cycloaddition.

ring and that the presence of an electron-donating group (e.g., MeO) is necessary for the oxidation/cycloaddition to occur.

4 CONCLUSIONS AND PERSPECTIVES

Radical cascades have demonstrated that they are particularly powerful tools to access complex scaffolds in one step starting from simple precursors. This efficiency has been illustrated by their involvement in numerous straightforward syntheses of natural compounds. The use of tin and silicon mediators has allowed the development of sequences featuring a high increase in molecular complexity and successfully involving a wide variety of radical partners. In order to avoid the toxicity and contamination issues inherent to the use of tin, the design of tin-free cascade reactions has been an area of intense research efforts over the last decade. The use of stoichiometric amounts of metal-based reagents such as titanium(III), samarium(II) species, and many others has proven its relevancy in this field. Excitingly, efficient cascades triggered by metal reagents used in catalytic amounts are now emerging, and open a new bunch of perspectives in term of sustainability, development of enantioselective processes, and diversity of mechanisms. One can certainly anticipate a lot of breakthroughs in this area over the coming years.

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Main-Group Elements in Radical Chemistry

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1 INTRODUCTION

In this article, we focus on aspects of free-radical chemistry that involve main-group elements. This can mean synthetic chemistry of heteroatom-centered radicals or reactions onto heteroatom-containing moieties. Main-group radical chemistry is a very large domain, which has been separated into several reviews of this encyclopedia. This article is dedicated to nitrogen-, oxygen-, phosphorus-, sulfur-, and selenium-based heterochemistry.

2 NITROGEN-CENTERED RADICALS

N-Centered radicals can be easily obtained by homolytic cleavage of relatively weak bonds, for example, N–N, N–S, N–O, and N–halogen bonds, and also strong N–H and N–C bonds starting from readily available nitrogen-based chemical functions, for instance, azides, or more elaborated precursors. Aminyl, iminyl, and amidyl radicals can be formed to take part in radical transformations generating heterocyclic structures found in natural products. This is covered through-

out this article, which is meant as an update to a book chapter and a tutorial review published in 2001 and 2008, respectively, by Stella¹ and Zard.²

2.1 N-Centered Radicals by Homolytic N–N Bond Cleavage

2.1.1 From Azide Compounds

Although organic azides are synthetically useful intermediates, their behavior toward radical species had been overlooked (see **Unusual Radical Acceptors**). Yet, radical reactions of azides have gained renewed interest recently. This chemistry has been thoroughly reviewed by Spagnolo.³ Carbon or heteroatom radicals can add at the α or γ position of the azido moiety to give 1,3- or 3,3-triazenyl radicals **1** and **2**. With both aliphatic and aromatic azides, the latter fragments by loss of N₂ to form an aminyl radical, whereas with sulfonyl azides the 1,3-triazenyl radical intermediate releases the corresponding alkyl azide and a sulfonyl radical by β -elimination (Figure 1). This aspect is addressed further in Section 5.

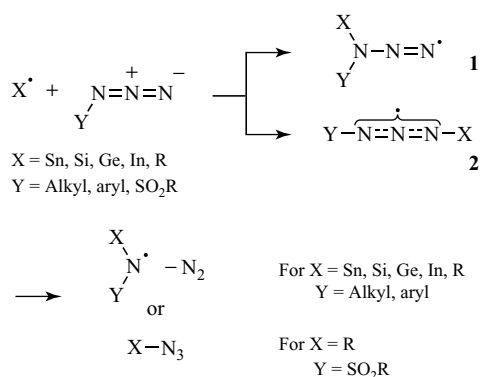


Figure 1 Homolytic addition to azides and generation of aminyl radicals.

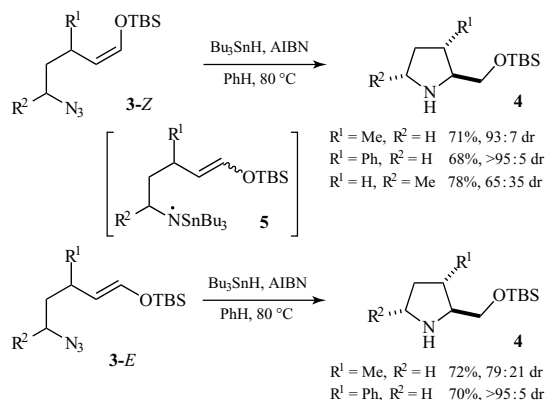


Figure 2 Generation of *N*-stannylaminyl radicals and intramolecular addition onto enol ethers.

Intermolecular addition of stannyl radicals to alkyl azides provides transient stannylaminyl radicals which can cyclize onto C=C double bonds to form heterocyclic rings. Recently, Sammis reported diastereoselective cyclizations of aminyl radicals **5**, generated from azides **3**, onto electron-rich silyl enol ethers for the preparation of polysubstituted pyrrolidines **4**. In this transformation, the nature of the substituent in allylic position and the configuration of the vinyl ether turned out to be critical for controlling the diastereoselectivity (Figure 2).^{4,5}

Stannylaminyl radicals can add intramolecularly to electrophilic cyano groups to form aminoimidyl radicals, which can undergo further cyclizations onto suitably positioned alkenes and aromatic rings. Leardini and Spagnolo showed that radical domino

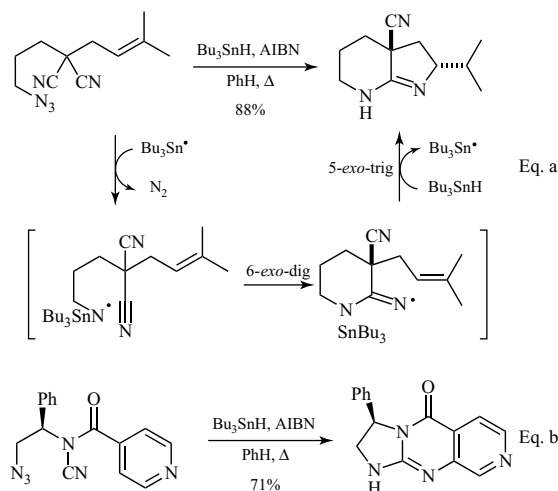


Figure 3 Intramolecular addition of *N*-stannylaminyl radicals onto nitriles or cyanamides.

reactions involving unsaturated azidoethyl- and azidopropylmalononitriles proceed in good yields and generate a variety of pyrro- and pyrrolopyridine derivatives (Figure 3, equation a).⁶ A similar strategy was adopted for the first radical preparation of bi- and tricyclic guanidines using cyanamides as relay partners. In this case, the final step of the cascade is achieved by a radical aromatic substitution of the iminyl-type radical intermediate (Figure 3, equation b).⁷

Stannylaminyl radicals also undergo rapid intramolecular 3-*exo*-trig cyclizations to the ketone carbonyl of β -keto esters. The resulting alkoxy radicals can β -fragment to generate lactams. For example, cyclic α -azido β -keto esters **6** treated in the presence of Bu_3SnH /azobisisobutyronitrile (AIBN) provide the corresponding ring-expanded lactams **7** in high yields (Figure 4).⁸

The tin hydrides could be replaced by a combination of silanes and catalytic amounts of a thiol under polarity reversal catalysis (PRC). The triethylsilane/*tert*-dodecanethiol system can promote the reduction of aromatic azides **8** to anilines **9**. The use of Bu_3GeH as a reductant in lieu of Et_3SiH has been reported too. However, both reductive systems failed to reduce aliphatic azides (Figure 5).⁹

Another synthetically useful mediator for radical chain reactions is indium hydride (InCl_2H), which is generated *in situ* from $\text{Et}_3\text{SiH}/\text{InCl}_3$ or $\text{NaBH}_4/\text{InCl}_3$. This reagent can substitute tin

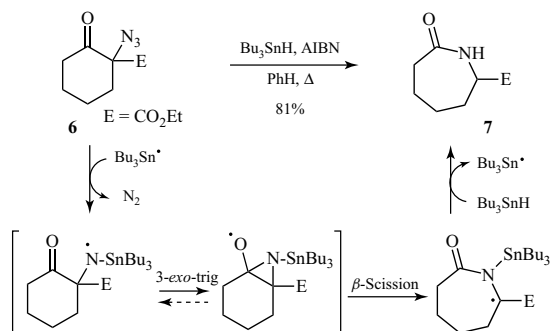


Figure 4 Intramolecular addition of *N*-stannylaminyl radicals onto carbonyl groups/ β -fragmentation.

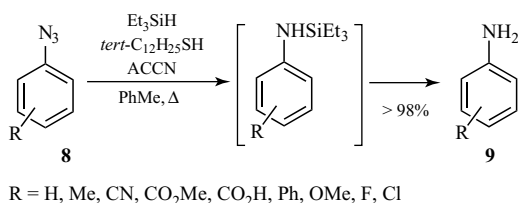


Figure 5 Radical reduction of aromatic azides with triethylsilane under polarity reversal catalysis.

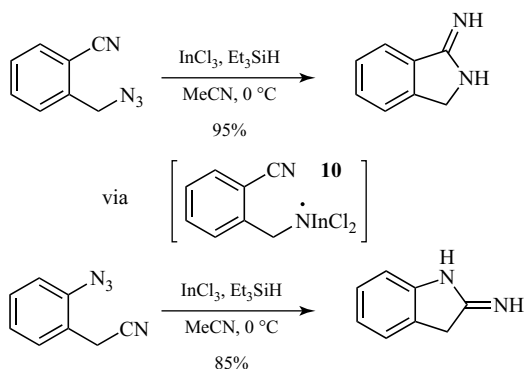


Figure 6 Generation of indium-aminyl radicals and intramolecular addition onto nitriles.

hydrides in various transformations, first and foremost the reduction of halides. InCl_2H can also reduce aromatic and aliphatic azides at low temperature. The *N*-indium-substituted aminyl radical intermediate **10** can subsequently participate in intramolecular cyclization onto nitriles (Figure 6).¹⁰

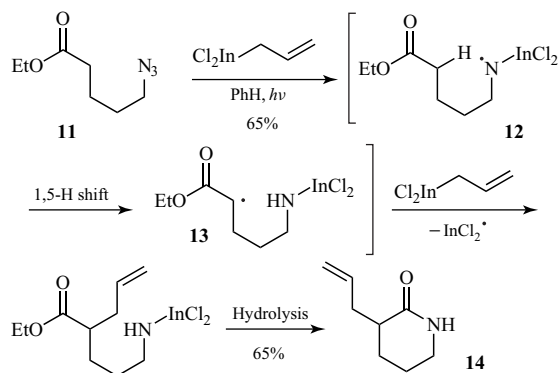


Figure 7 Radical allylations by reaction of alkyl azides with allylindium dichloride.

Allylindium dichloride proved to be a valuable reagent for promoting radical allylation of azido compounds. Under UV light irradiation, photolysis of allylindium dichloride leads to the dichloroindyl radical, which can react with alkyl azide **11** to generate indium-aminyl radical **12**. The latter can then undergo intramolecular 1,5-H abstraction followed by allylation of the resulting radical **13**. Allyllactam **14** was obtained in good yield after hydrolysis (Figure 7).¹¹

Reduction of organic azides to *N*-centered radicals can in some cases be promoted by iron(II) complexes. Treatment of acyl and oxycarbonyl azides with a catalytic amount of FeCl_2 and trimethylsilyl chloride (TMSCl) in ethanol (or isopropanol) results in the formation of lactams and oxazolidinones, respectively. A radical pathway is proposed that involves the formation of an iron amidyl-type radical as intermediate and its subsequent cyclization to either alkene or alkyne functionalities. The sequence ends by the incorporation of a chlorine atom, which differs from the indium case (Figure 8).^{12,13}

In contrast, carbon-centered radicals react with organic azides exclusively in an intramolecular manner, providing cyclic aminyl radicals. Murphy designed radical cascades for the construction of the aspidospermidine, vindoline, and horsfiline cores, which included this key step (Figure 9).^{14–16}

An extension to the generation of amidyl radicals from acyl radicals was proposed by Benati, Spanolo, and Strazzari. Tin-mediated aryl radical cyclization onto thioester **15** derived from an iodoarylthiol led to the formation of acyl radical **16**, which underwent intramolecular addition to the azido group. In the presence of allyltriphenylstannane, the

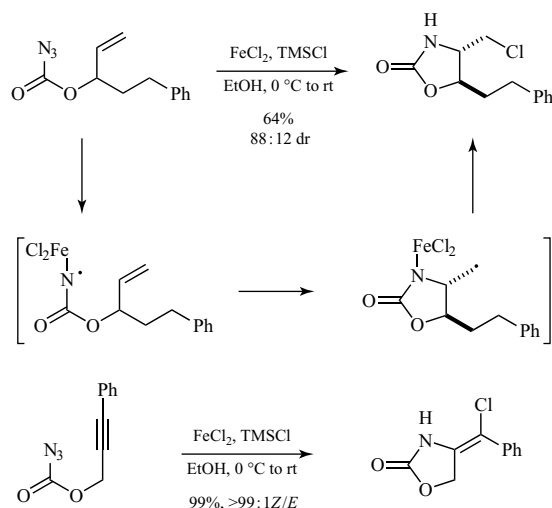


Figure 8 Iron(II)-catalyzed intramolecular chloroamination of 2-alkenyloxycarbonyl azides and 2-alkynyloxycarbonyl azides.

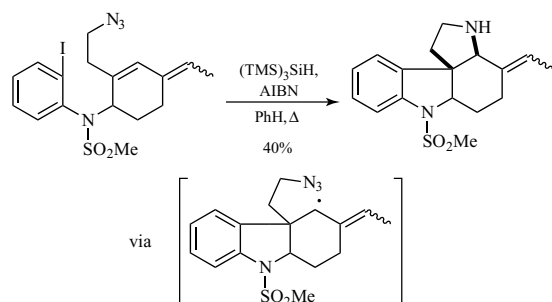


Figure 9 Intramolecular addition of alkyl radicals onto alkyl azides.

transient amidyl radical **17** could be allylated and the corresponding indolinone derivative **18** was isolated in 60% yield (Figure 10).¹⁷

Vinyl azides are of particular interest because they are precursors of iminyl radicals. In 1997, Montevocchi reported the addition of the thiophenyl radical to α -azidostyrene and suggested that the α -azidobenzyl radical intermediately and spontaneously β -eliminated nitrogen to deliver an iminyl radical.¹⁸

Chiba later used it as a partner in manganese(III)-catalyzed tandem reactions with 1,3-dicarbonyl compounds. This sequence provides access to polysubstituted NH pyrroles. The best results were obtained with β -keto esters and Mn(OAc)₃·2H₂O as oxidative catalyst. This may

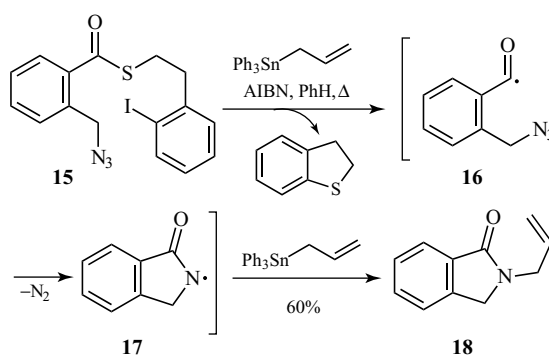


Figure 10 Intramolecular addition of acyl radicals onto alkyl azides and subsequent allylation.

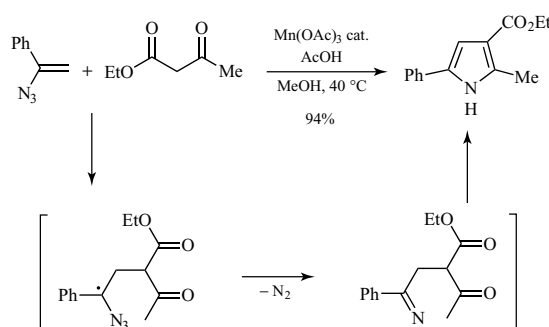


Figure 11 Manganese(III)-mediated reaction of 1,3-dicarbonyls with vinyl azides.

involve sequential addition of β -keto ester radical—generated by Mn(III) enolate oxidation—to the vinyl azide, followed by evolution of N₂, cyclization of the resulting iminyl radical onto the ketone carbonyl and final dehydration to the pyrrole (Figure 11).¹⁹ Similar experiments were carried out with cyclopropanols, which led to either substituted pyridines or 2-azabicyclo[3.3.1]non-2-en-1-ols in excellent yields (Figure 12).²⁰ By analogy, Spagnolo examined the behavior of aryl azides toward carbon-centered radicals. Intramolecular ipso cyclization of aryl radicals of anilide derivatives at the para position of aromatic azides led to cyclohexadieniminyl radical intermediates which provided indolones and quinolones bearing either spirocyclohexadienimine or spirocyclohexadienone rings (Figure 13).²¹

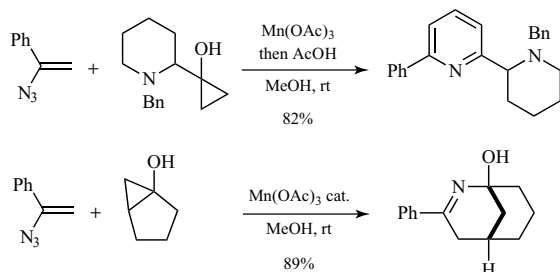


Figure 12 Manganese(III)-mediated reaction of cyclopropanols with vinyl azides.

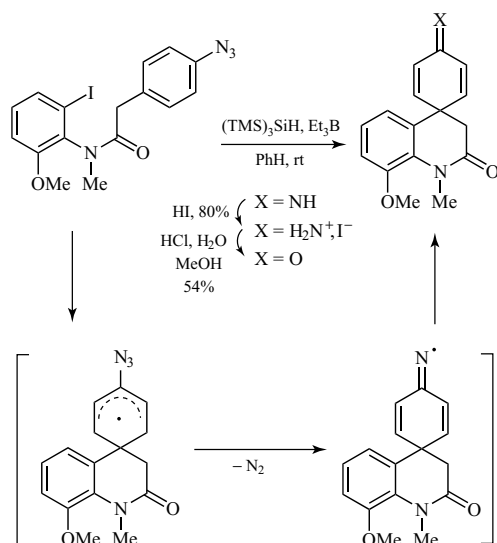


Figure 13 Intramolecular ipso addition of aryl radicals onto aromatic azides.

2.1.2 From Hydrazine Compounds

Hydrazine derivatives can also serve as precursors to nitrogen-centered radicals. As illustrated by Studer, carbamoyl radicals can be generated from N-aminated Hantzsch esters under conditions of PRC, and were shown to participate in anti-Markovnikov hydroamination of alkenes. This process takes advantage of the ability of the thiophenyl radical to activate the C–H bonds of dihydropyridines owing to polarity matching and then to generate carbamoyl radical (BocNH $\cdot$) after subsequent N–N bond cleavage. Finally, the liberated radical could be trapped by terminal and 1,2-disubstituted double bonds in moderate yields (Figure 14).²² Thiosemicarbazide derivatives also

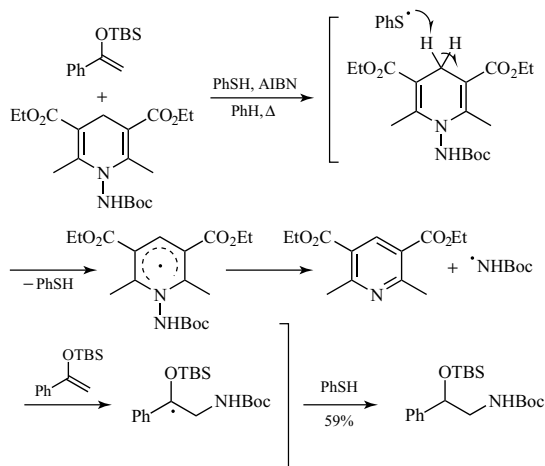


Figure 14 Radical hydroamination of olefins with N-aminated dihydropyridines under PRC.

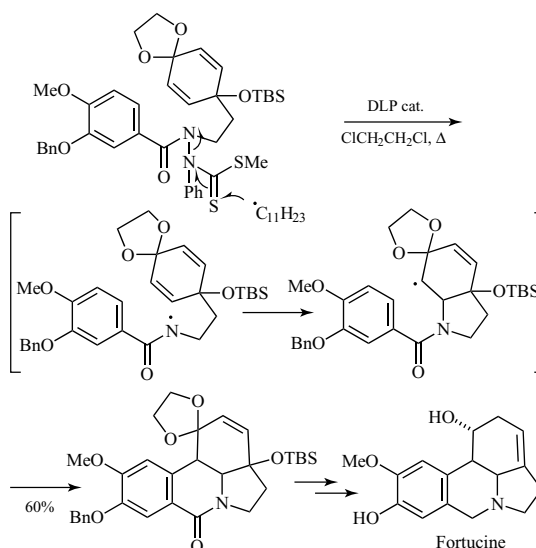


Figure 15 Synthesis of the forticine core through an amidyl radical cascade reaction.

showed a propensity for providing amidyl radicals. An elegant application to the synthesis of the natural product forticine was proposed by Zard (Figure 15).^{23,24}

2.1.3 From Triazene Compounds

Another class of functional groups for the generation of N-centered amidyl radicals includes

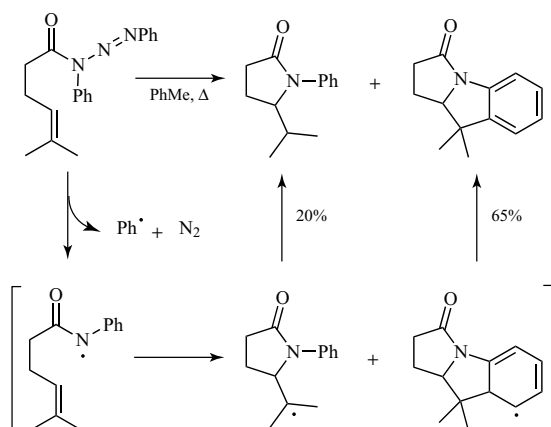


Figure 16 Cyclization of amidyl radicals generated from *N*-acyltriazenes.

N-acyltriazenes whose reactivity has been briefly examined. Thermolysis of unsaturated *N*-acyltriazenes in toluene releases amidyl radicals, which undergo intramolecular 5-*exo* cyclizations to form γ -lactams. With more substituted substrates, a cascade radical cyclization involving sequential 5-*exo* cyclization/homolytic aromatic substitution led to tricyclic lactams (Figure 16).²⁵

2.2 N-Centered Radicals by Homolytic N–S Bond Cleavage

2.2.1 From *N*-Thioaryl Compounds

Sulfenamine and sulfenylamide derivatives have been successfully employed for the generation of N-centered radicals by homolytic cleavage of the N–S bond. As reported by Li, treatment of *N*-(benzenesulfonyl)pent-4-enylamines with the Bu₃SnH/AIBN system affords the corresponding aminyl radicals which can cyclize onto the alkene moiety providing a mixture of pyrrolidines and piperidines. As usual, the nature of the substituents on the alkene is critical for controlling the product distribution. For instance, cyclization of pent-4-enylaminyl and 4-methylpent-4-enylaminyl radicals gave preferentially the 5-*exo* products, while the 4-chloro-substituted radical gave the 6-*endo* adducts. It is also worthy of note that the cyclization of primary aminyl radicals is much more

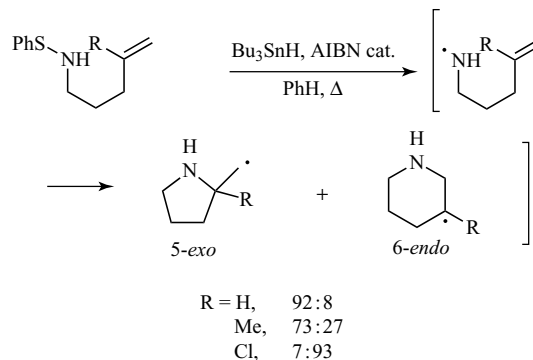


Figure 17 5-*exo* versus 6-*endo* cyclization of primary 4-substituted pent-4-enylaminyl radicals.

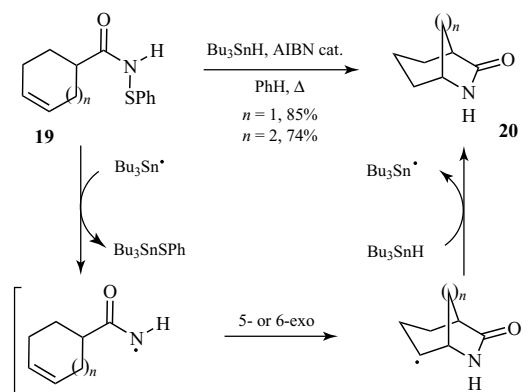


Figure 18 Intramolecular addition of primary amidyl radicals to C=C double bonds.

efficient than that of secondary aminyl radicals (Figure 17).²⁶

Lessard examined the intramolecular addition of primary amidyl radicals to olefins. Under standard tin hydride conditions, *N*-(phenylthio)amide precursors **19** underwent 5-*exo*-trig cyclizations exclusively to give γ -lactams **20** (Figure 18).²⁷ The behavior of 5-hexenamidyl radicals has been studied by Li. Theoretical calculations and deuteration experiments showed that the reaction of primary amidyl radicals favors the formation of the 6-*endo* products while its *N*-*tert*-butyl counterpart undergoes 1,5-hydrogen abstraction.²⁸ Additional studies examined the effect of the substitution of the vinylic function on the regioselectivity of *N*-(4-pentenyl)aminyl radical cyclization. The presence of heteroatoms (Cl, OMe, SEt) in the internal position results in the exclusive formation of the 6-*endo* products.²⁹

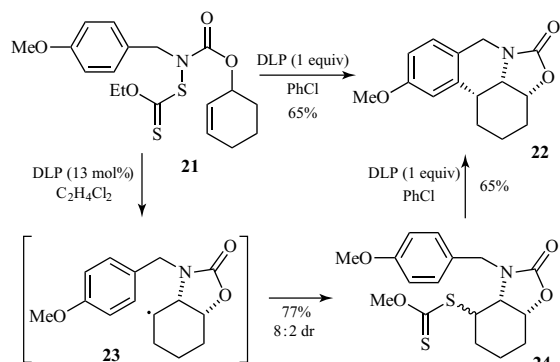


Figure 19 Cyclization of amidyl radicals generated from *N*-(*O*-ethyl thiocarbonylsulfanyl)amides.

2.2.2 From *N*-Thiocarbonylsulfanyl Compounds

N-(*O*-Ethyl thiocarbonylsulfanyl)amides are of particular interest because they are both precursors of amidyl radicals and able to perform xanthate transfer reactions. As reported by Zard, a catalytic amount of lauroyl peroxide (DLP) can initiate the homolysis of the N–S bond of **21** and generate an amidyl radical. The latter adds intramolecularly to a double bond. Then, the resulting cyclized radical **23** reacts with another molecule of *N*-(*O*-ethyl thiocarbonylsulfanyl)amide and propagates the radical chain process. The addition of an extra equivalent of DLP to the pyrrolidinone derivative **24** triggers an intramolecular homolytic aromatic substitution (see **Radical Arylations**) to form the tetracyclic product **22**. The same compound can also be obtained directly, starting from a stoichiometric amount of DLP (Figure 19).³⁰

2.2.3 From *N*-Allylsulfonyl Compounds

N-Allylsulfonylamides also lead to amidyl radicals. Sequential xanthate radical addition to the allyl moiety followed by β -fragmentation led to the *N*-amidosulfonyl radical. Depending on the substitution at N, extrusion of SO₂ can follow. With *N*-phenyl derivatives, the amidyl radical can be formed and then undergo a 5-*exo*-trig cyclization. In turn, the newly formed radical can add to the xanthate, regenerate the tertiary alkyl radical, and then propagate the chain. When *N*-allylsulfonylamides

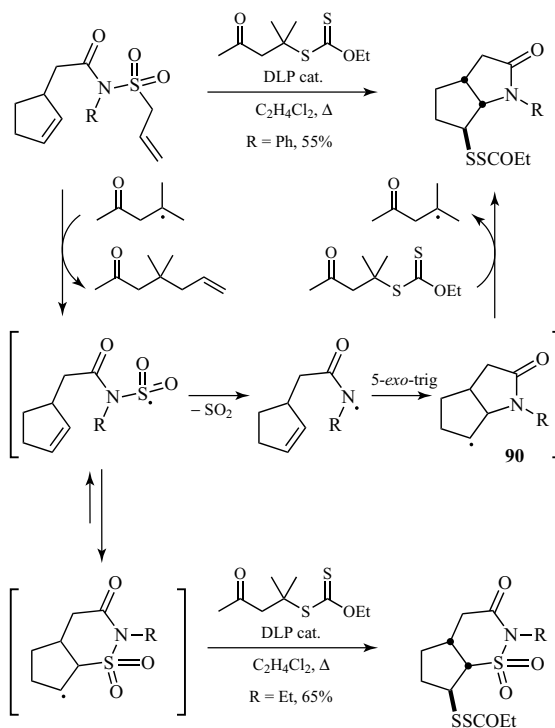


Figure 20 Generation of *N*-amidosulfonyl and amidyl radicals from *N*-allylsulfonyl compounds and subsequent cyclization reactions.

are substituted by an ethyl group instead of a phenyl, ring closure of *N*-amidosulfonyl radicals occurs more rapidly than the loss of sulfur dioxide (Figure 20).³¹

2.3 N-Centered Radicals by Homolytic N-Halogen Bond Cleavage

Photochemical activation can allow the cleavage of N-halogen bonds, which constitutes one of the most efficient ways to generate N-centered radicals. The formation of substrates bearing N-halo bond has been achieved by electrophilic halogenations of amines, amides, or sulfonamides. These substrates are sufficiently stable to be isolated, and they can also be generated *in situ*. A one-pot N-halo bond formation/homolysis reaction has been applied to the formation of aziridiny radicals (Figure 21).³² The reaction of aziridine **25** with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) yields the corresponding *N*-bromo or *N*-iodo aziridine **26** which undergoes N–X bond homolysis

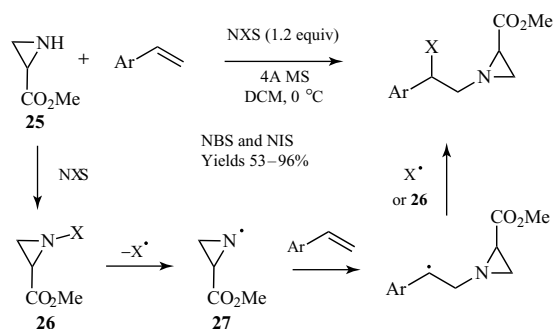


Figure 21 Aziridiny radical formation and addition onto alkenes.

to form aziridiny radical **27**, which adds onto styrenes. Termination occurs by either bromination or by iodination. By using *N*-chlorosuccinimide (NCS) as the halogenation reagent, no reaction was observed, which can be indicative of a less favorable homolysis of a N–Cl bond compared to N–Br or N–I. A cationic process was excluded, since the addition of galvinoxyl radicals resulted in complete inhibition. The same effect has been observed in the absence of light, providing further strong evidence for a radical process.

Aminyl radicals can also be generated by reduction processes of the N–X bond. In the presence of copper(I) salts, the *N*-chloramine **28** has been converted to piperidiny derivatives **29** (Figure 22).³³ Single-electron transfer (SET) from copper(I) catalyst allows the reduction of the N–Cl bond to generate the radical cation **30**, which undergoes a 5-*exo*-trig cyclization to afford the pyrrolidiny intermediate **31** and release the copper(II) complex. The primary radical formed reacts through a second SET process, leading to the formation of the corresponding chlorinated pyrrolidine **32** and the regeneration of the catalyst. The primary chloride **32** undergoes a subsequent stereoselective ring expansion to yield compound **29**.

Cyclizations have also been reported to adopt a chair-like Beckwith–Houk transition state. The copper(II) center not only allows the activation of the aminyl radical but also coordinates to the alkene to access a more rigid transition state and thus ensures better stereoselectivity. The stereoselectivity increased further in the presence of a stronger Lewis acidic complex (CuPF₆ vs CuCl) and more sterically demanding ligands (e.g., *N,N,N',N'*-tetramethylethylenediamine

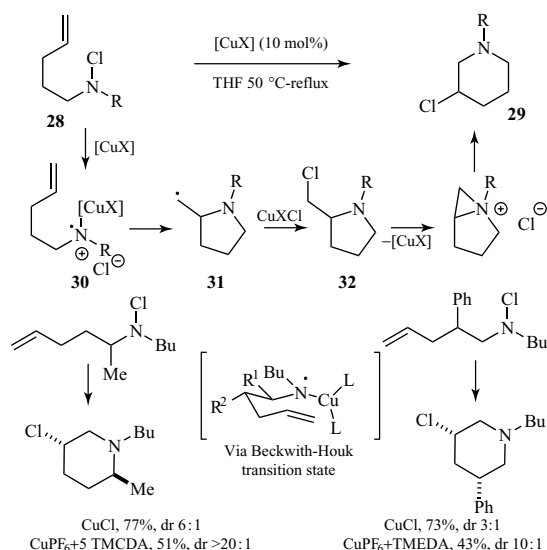


Figure 22 Copper(I)-mediated formation of aminyl radical.

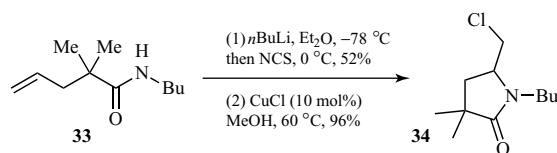


Figure 23 Copper(I)-mediated formation of amidyl radical.

(TMEDA) or *N,N,N',N'*-tetramethylcyclohexanediamine (TMEDA)). Diversely substituted piperidiny compounds can be obtained with selectivity up to 20 : 1.

The same type of transformation has been applied to the cyclization of amidyl radicals (Figure 23).³⁴ The *N*-chloramide substrate was prepared by deprotonation of amide **33** to form the corresponding amidyl anion, followed by quenching with NCS. Subsequent heating in methanol with a catalytic amount of copper(I) chloride allowed the formation of the chlorinated pyrrolidone **34** in 96% yield. Attempts to extend this methodology to the formation of *N*-centered carbamoyl radical led to low yields of the cyclized products.

Amidyl radicals are also generated by spontaneous homolytic cleavage of N-halogen bond. A two-step reaction sequence has been reported by Li starting from iodoacetamide **35** (Figure 24).³⁵ Atom transfer radical addition (ATRA, see **Halo-**

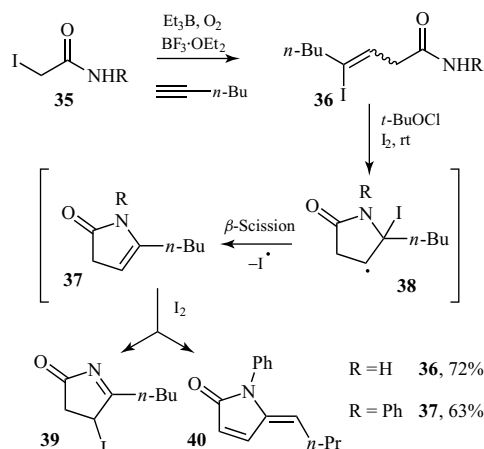


Figure 24 Reactivity of amidyl radical in atom transfer radical addition.

Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications) reaction initiated by triethylborane has been conducted with 1-hexyne in the presence of $\text{BF}_3\cdot\text{OEt}_2$ to afford the vinyl iodide derivatives **36**. Subsequent treatment with $t\text{-BuOCl}/\text{I}_2$ system allows the *in situ* formation of the corresponding *tert*-butyl hypoiodite, which generates the N–I bond. Homolytic cleavage of this bond yields the amidyl radical, which cyclizes through a 5-endo-trig mode. Radical **38** evolves through a β -scission reaction to form lactam **37**, which reacts with iodine to afford either iodide **39** or diene **40**, depending on the nitrogen substituent (R).

N-Chlorosulfonamide derivatives exhibit good ability as sulfonamidyl radical precursors. The irradiation of *N*-chlorosulfonamide **41** by a 125-W high-pressure mercury lamp allowed the homolytic cleavage of the N–Cl bond and the subsequent cyclization of the resulting *N*-tosyl aminyl radical (Figure 25).³⁶ The 5-*exo*-trig and 6-*endo*-trig cyclization products, **42** and **43** respectively, were obtained in favor of the six-membered ring due to the internal substitution of the olefin. The incorporation of a chlorine atom in the products is the result of an atom transfer step in the radical chain process. The same transformation was also reported under chemical initiation with the triethylborane (cat.)/ O_2 system, providing strong evidence for a radical chain reaction.

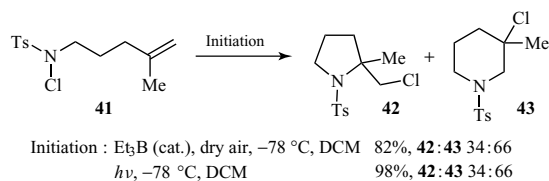


Figure 25 Reactivity of sulfonamidyl radical in atom transfer radical addition.

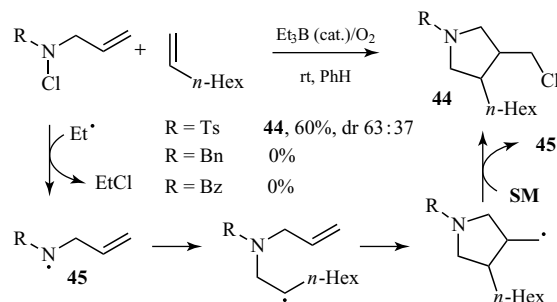


Figure 26 [3 + 2] Annulation sequence through sulfonamidyl radical.

A [3 + 2] annulation sequence has been reported by Oshima for the *N*-allyl-*N*-tosylamidyl radical (Figure 26).³⁷ Chlorine abstraction from triethylborane/ O_2 enables a radical cascade of N-centered radical **45** featuring an intermolecular addition followed by 5-*exo*-trig cyclization to the pyrrolidinyl derivative **44**. The primary radical formed undergoes chlorine transfer to regenerate **45**. Aminyl and amidyl radicals were not suitable, since they were reduced by hydrogen transfer from the allylic position prior to cyclization.

An interesting use of *N,N*-dichlorosulfonamide **46** as a diradical equivalent has been reported for the preparation of disubstituted pyrrolidine derivatives (Figure 27).³⁸ Using triethylborane as radical initiator, *N*-chloro-*N*-sulfonamidyl radical was formed to add onto 1,3-dienes to yield the corresponding chlorinated *N*-chloro-*N*-allylsulfonamide resulting from an atom transfer process. The second radical addition can be performed with the isolated intermediates or in a one-pot two-step sequence. For the second reaction step, the second olefin and a catalytic amount of triethylborane were directly added to the crude mixture. Then, a second atom transfer process (ATP) proceeded leading to the formation of 1,2-dichlorinated compounds. This sequence was applied to a variety of radical acceptors. For

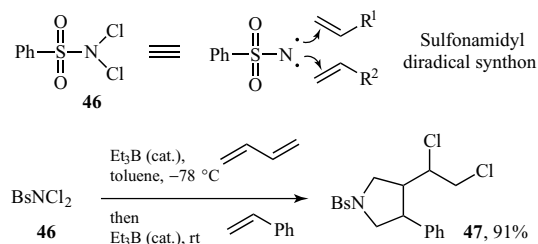


Figure 27 *N,N*-Dichlorosulfonamide as a diradical equivalent.

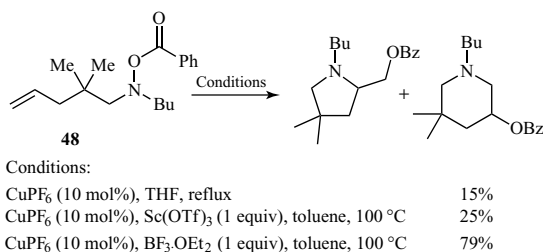


Figure 28 Copper(I)-catalyzed N–O homolysis for the formation of aminyl radical.

example, 1,3-butadiene and styrene reacted in these conditions to afford **47** in 91% yield.

2.4 N-Centered Radicals by Homolytic N–O Bond Cleavage

Aminyl radical can enter group transfer reactions initiated by copper(I)-catalyzed reduction of N–O bonds in *N*-benzoyloxyamines such as **48** (Figure 28).³⁹ The copper(II)–benzoyl complex formed during the reduction step transfers the acyl group to the primary C radical obtained after cyclization, which allows the regeneration of the catalyst. No reaction was observed without Lewis acid, indicating that the acyloxy group must be activated to weaken the N–O bond. Boron trifluoride is the best activator (79% yield).

Similarly, the *N*-benzoyloxyamidyl group has been used for the formation of amidyl radicals in the total synthesis of alkaloids. In this case, a tributylstannyl radical added onto the oxygen atom of the benzoyl group, leading to fragmentation of the N–O bond of **49** (Figure 29).⁴⁰ The resulting amidyl radical **50** underwent a radical cascade which provided an entry toward (±)-deoxyserratine. Note that a second equivalent of tributyltin hydride

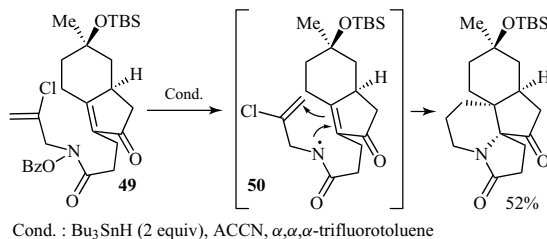


Figure 29 Amidyl radical formation by addition of tributylstannyl radical onto *N*-benzoyloxyamidyl group.

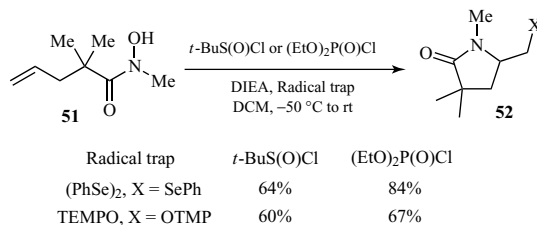


Figure 30 Fragmentation of sulfinate and phosphonate derivatives of hydroxamic acids as precursor of the amidyl radical.

is needed to remove the chlorine atom used to direct the final 6-*endo*-trig cyclization. The same concept has been applied to the total synthesis of (±)-aspidospermidine.⁴¹

The formation of amidyl radicals has been also induced by the fragmentation of sulfinate and phosphonate derivative of hydroxamic acids (Figure 30).⁴² The *in situ* formation of such intermediates has been performed by the treatment of **51** with *tert*-butylsulfinyl or diethylphosphonyl chloride in the presence of diisopropylethyl amine at –50 °C. Upon increase of the reaction temperature, a spontaneous homolytic cleavage of the N–O bond gave the corresponding amidyl radical.

This transformation has been applied to oxime substrates to generate iminyl radicals. The primary C-centered radicals resulting from 5-*exo*-trig cyclizations were trapped with either diphenyl diselenide or 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) to obtain the pyrrolidones **52** in good yields. β-Tosylethylhydroxylamine was subjected to the same conditions to afford the analog amidyl radicals, which allowed a facile deprotection of the amide function.⁴³

Iminyl radicals are certainly the most studied nitrogen-centered radical and can be obtained under a variety of experimental conditions.⁴⁴

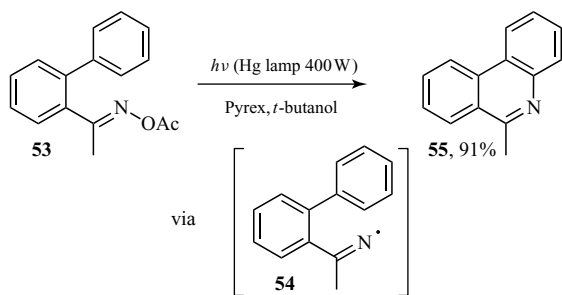


Figure 31 Photochemical formation of iminyl radical by activation of acyloxime derivatives.

With photochemical activation, the N–O bond of biphenyl acyloxime **53** is cleaved to generate the corresponding iminyl radical **54** (Figure 31).⁴⁵ An intramolecular arylation delivered phenanthridine derivative **55** in high yield. Intermolecular and intramolecular addition onto various unsaturated acceptors such as arenes, alkenes, or alkynes have been reported. Some theoretical and photochemical studies have been made on such systems.⁴⁶ This convenient transformation has found applications in natural product synthesis.⁴⁷ An analogous transformation involving dioxime oxalates as radical precursors has been reported by Walton.⁴⁸

Redox processes have proven to be highly efficient in the context of iminyl radical formation, allowing experimental conditions to be compatible with organic synthesis. This type of transformation mainly involves reduction steps of the N–O bond either by organic or organometallic compounds. *O*-Acyl and *O*-methyloxime **56** were allowed to react under photochemical irradiation in the presence of a catalytic amount of 1,5-dimethoxynaphthalene (DMN) and 1,4-cyclohexadiene (1,4-CHD) to yield the corresponding cyclic imine **57** in good yield (Figure 32).⁴⁹ The photoactivated DMN reduced **56** by an SET process to generate the radical anion $[56]^{*-}$. Then, the fragmentation of the N–O bond gave the iminyl radical, which cyclized by a 5-*exo*-trig pathway to afford the radical intermediate **58**. By a hydrogen transfer from the 1,4-CHD, the final product **57** was obtained and the reduction of $[DMN]^{*+}$ occurred to regenerate the photosensitizer DMN. No reaction was observed without the DMN, indicating that these N–O bonds cannot be cleaved at wavelengths above 300 nm. Extensions of this reaction are possible with other photosensitizers and radical acceptors.^{50,51}

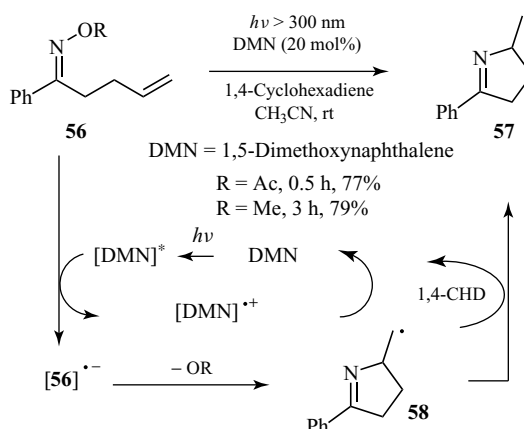


Figure 32 Photochemical/single-electron transfer sequence for iminyl radical formation.

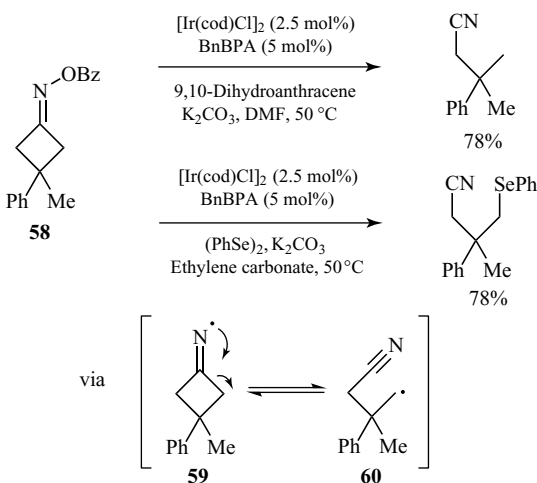


Figure 33 Single-electron transfer process for the formation of the iminyl radical.

SET was also investigated under transition-metal catalysis. Ir(I) complex in the presence of pyridinyl ligands was able to reduce the N–O bond of **58** to afford the corresponding iminyl radical **59** (Figure 33).⁵² Strain release evolved through a fast β -scission reaction and gave rise to the resulting nitrile function. In the presence of 9,10-dihydroanthracene, the radical intermediate **60** has been reduced by hydrogen transfer. Besides, diphenyl diselenide $(PhSe)_2$ was used as a radical trap for **60** to form a C–Se bond.

The homolytic cleavage of the N–O bond can also be triggered by microwave irradiation. This works

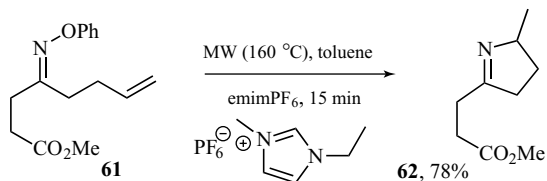


Figure 34 Microwave-assisted homolysis of N–O bond of *O*-phenyl oxime.

best with weak bonds such as *O*-phenyl oxime ethers (bond dissociation energy (BDE) ($R_2C=N-OPh$) = 140 kJ mol^{-1} for $R = \text{Me}$ or Ph).⁵³ The substrate **61** was used as the iminyl radical precursor, which was able to cyclize and afford the imine derivative **62** in good yield (Figure 34).⁵⁴ The reaction was conducted in toluene, which allowed the reduction of the phenoxyl radical by hydrogen transfer. One equivalent of ionic liquid emimPF_6 was necessary to increase the microwave absorbance level of the reaction medium. This reaction was extended to other radical acceptors that trapped the iminyl radical in an intra- or intermolecular manner. The syntheses of quinazolines and dihydroquinazolines derivatives were reported by using imines as radical acceptor.^{55,56} Conversely, one can also look at this process as an efficient pathway to generate aryloxy radicals.⁵⁷

2.5 N-Centered Radicals by Homolytic N–C Bond Cleavage

Cleavage of N–C bonds is an interesting yet rare path to nitrogen-centered radicals. Such bonds are generally too strong to lead to efficient homolytic cleavage, and β -amino radicals thus do not undergo radical β -elimination easily. However, Taguchi and coworkers took advantage of the ring strain in aziridines to generate N-centered radicals via such a process. The opening is regioselective and favors the formation of electrophilic *N*-tosylamino radicals rather than the α -amino ones.

Primary radical **63** underwent strain-release-driven C–N radical β -elimination. The N radical **64** was engaged in a [3 + 2] cycloaddition manifold with electron-rich alkenes to form the corresponding substituted pyrrolidine in good yield (Figure 35).⁵⁸ A similar radical pathway was later applied by Speybroeck,⁵⁹ Prévost,⁶⁰ and Shipman,⁶¹ to intramolecular processes.

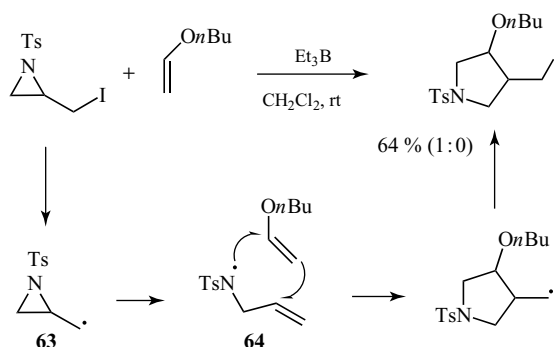


Figure 35 Formation of *N*-tosylamino radical by opening of aziridines.

In 2002, Prévost and Shipman showed that N-centered radical can also be generated from 2-methyleneaziridines by intramolecular addition of alkyl radical onto *exo*-methylene and subsequent β -elimination.^{59,60} Here again, the relief of the high ring strain was the promotor of the cleavage of the nitrogen–carbon bond, leading to an aminyl radical. In fact, the ring strain of the 2-methyleneaziridine is $12\text{--}13 \text{ kcal mol}^{-1}$ higher than for the aziridine; however, these species are still very stable.

In this article,⁶⁰ the 2-methyleneaziridine produced an alkyl radical in the presence of Bu_3SnH and AIBN, which cyclized only on the *exo* mode (Figure 36). This was then followed by the opening of the aziridine and the formation of the nitrogen-centered radical. Piperidines were synthesized with good yields, even in the case where the intermediate was a stable tertiary radical. This new method offered the possibility to synthesize piperidines and bicycles using radical rearrangements with total regioselectivity.

Alternatively, rearomatization can be harnessed to bring the energy required to cleave the C–N bond.⁶² Hydrogen atom abstraction from 1,4-cyclohexadiene derivative **65** enables the C–N bond fragmentation by releasing an aromatic by-product (Figure 37). Nitrogen radical addition to norbornene followed by H-atom transfer from **65** allows the formation of the hydroaminated norbornane and the propagation of the radical cycle. It was later shown that unactivated and electron-rich olefins can be hydroaminated under these conditions.⁶³ Better yields were obtained when thiophenol was used as a catalyst and a high anti-Markovnikov selectivity was observed. Besides, one of the most important advantages of

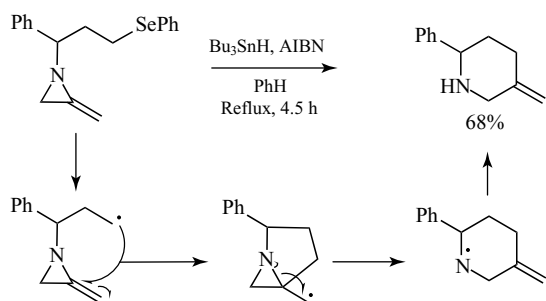


Figure 36 Formation of an aminyl radical from a 2-methyleneaziridine.

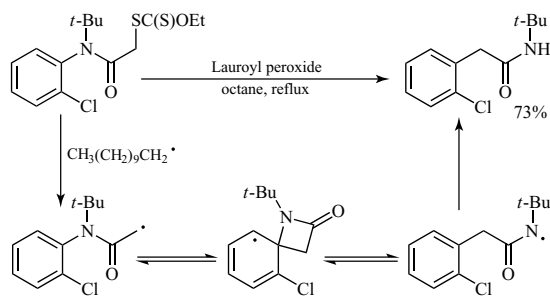


Figure 38 Radical Smiles rearrangement starting from a xanthate.

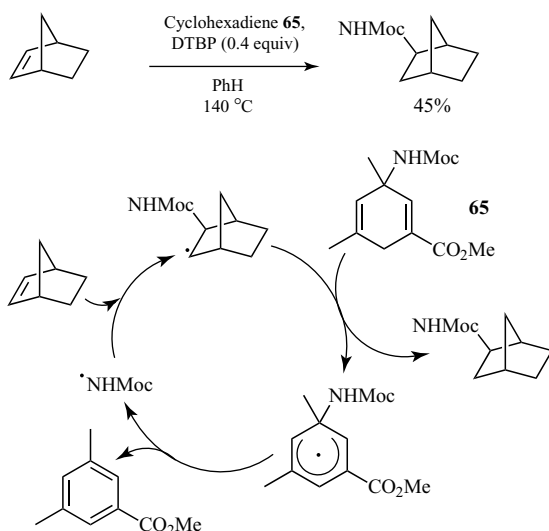


Figure 37 Synthesis of hydroaminated norbornane by rearomatization of 1,4-cyclohexadiene derivative **65**.

this synthesis was the good tolerance toward functional groups such as bromides, imides, alcohols, or amides.

A last example of the rupture of a nitrogen–carbon bond was reported by Zard *et al.*, when they observed an unusual radical Smiles rearrangement starting from a xanthate (Figure 38).⁶⁴

2.6 N-Centered Radicals by Homolytic N–H Bond Cleavage

The generation of N-centered radicals can be achieved through formal N–H bond cleavage of

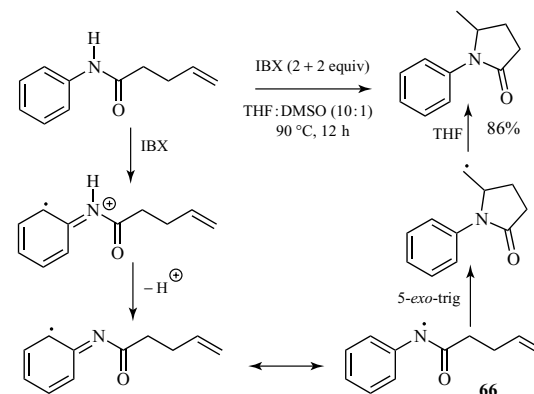


Figure 39 Oxidation of anilnamides mediated by IBX.

aminyl, amidyl, or similar functional groups. It is in fact an electron coupled to a proton transfer carried out with hypervalent iodine oxidants. For example, Nicolaou *et al.* reported the oxidation of anilnamides by 2-iodoxybenzoic acid (IBX), which generates an anilnamidyl radical **66** that can undergo 5-*exo*-trig cyclizations to δ -lactams (Figure 39). As shown by the authors in mechanistic studies, the solvent plays an important role in the termination step. However, some steps of the mechanism are still not clear. But the method offers a convenient way for the synthesis of various compounds such as cyclic urethanes, hydroxylamines, and sugars.⁶⁵

Following a similar principle, Suarez presented the formation of amidyl radicals using $\text{PhI}(\text{OAc})_2$ and I_2 (see **Radicals and Carbohydrates**). In a sugar, this N radical **67** undergoes 1,6-intramolecular hydrogen transfer to re-form the amide and the anomer radical **68**. Oxidation of the latter generates an oxonium which is trapped by

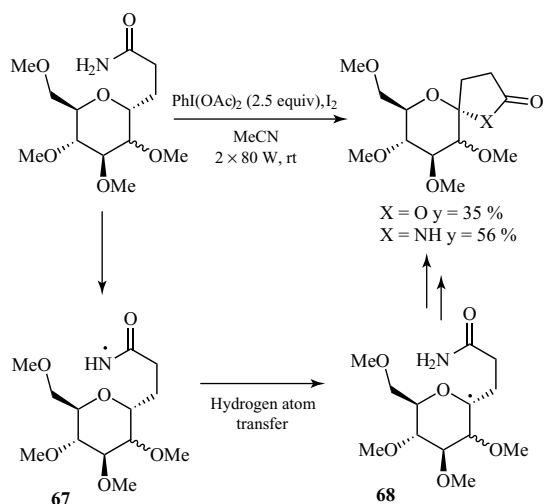


Figure 40 Formation of amidyl radicals using $\text{PhI}(\text{OAc})_2$ and I_2 .

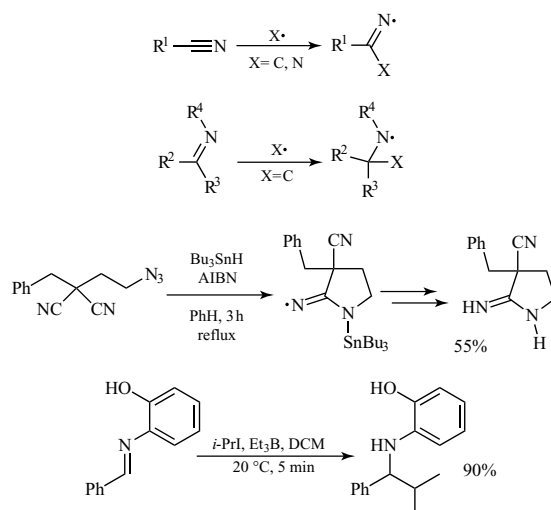


Figure 42 Addition of nitrogen and carbon radicals onto nitriles and imines.

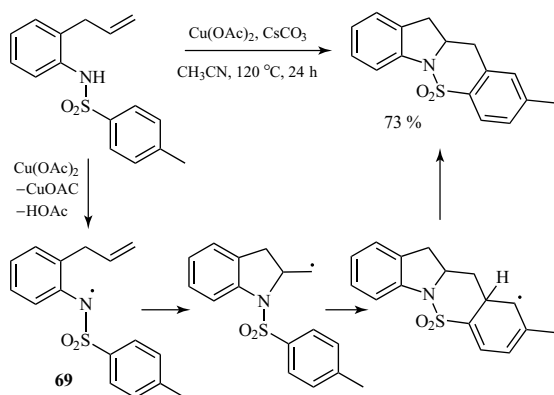


Figure 41 Intramolecular carboamination of alkenes.

the amide to form spirolactams (Figure 40).⁶⁶ Similarly, 2-amino-*C*-glycosides can be transformed into oxa-aza spirobicycles.^{67,68}

The oxidation of tosyl-*o*-allylanilines has also been investigated by using $\text{Cu}(\text{OAc})_2$ and Cs_2CO_3 at 120°C . As a result, tosylaniliny radicals **69** were formed and cyclized in a 5-*exo*-trig mode.⁶⁹ This intramolecular carboamination of alkenes can be used for the synthesis of hetero-polycyclic compounds (Figure 41).^{70–73}

2.7 N-Centered Radicals by Radical Addition onto Nitrile or Imine Derivatives

Iminyl or aminyl radicals can be generated by radical addition to cyano or imino functional groups, respectively. As shown below, either a carbon- or nitrogen-centered radical can add at the carbon atom of the cyano or imino moiety, producing a new nitrogen radical.⁷⁴ This is illustrated by the two examples shown below in which radical ring closure onto nitriles forms cyclic amidines,⁶ while the addition of isopropyl radical to imines leads to amines (Figure 42).⁷⁵

In addition, radical fragmentation (retroaddition) can also take place and result in the re-formation of the starting functional group (Figure 43). Interestingly, cyano group transfer can be observed to occur through a 5-*exo* or 6-*exo* cyclization/ring-opening sequence.^{76,77}

Most of the examples in the literature report cascade reactions of iminyl radicals formed through intramolecular radical addition to cyano groups.^{7,78–83} These cascades can be initiated either by reducing agents—such as SmI_2 -initiated reduction of aryl halides—(Figure 44a),⁸⁴ or by radical mediators (Figure 44b and c, respectively).^{76,85} Radicals formed under these conditions undergo cyclization cascades that are intermediated by either iminyl or aminyl radicals.

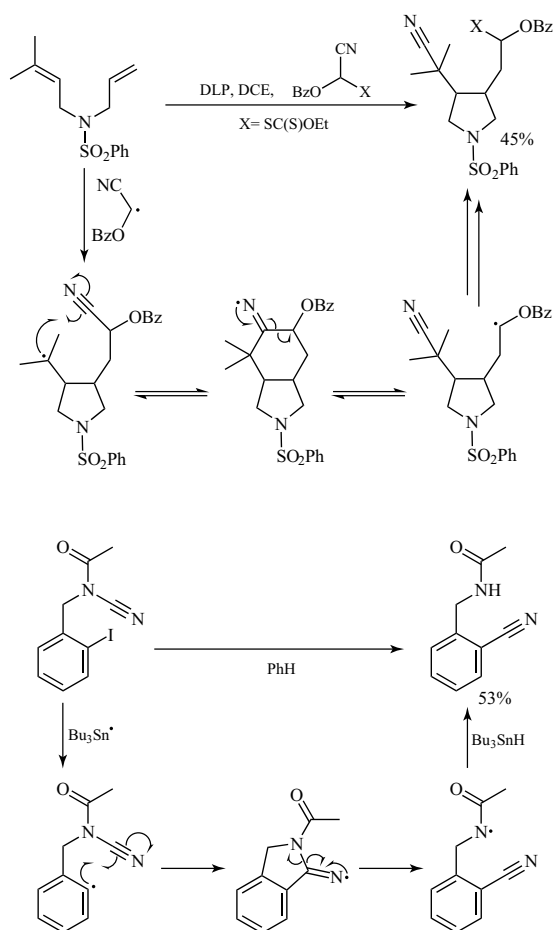


Figure 43 Cyano group transfer through radical cyclization/ring-opening cascade.

3 OXYGEN-CENTERED RADICALS

Formation of oxygen-centered radicals has been widely described in the literature for almost 50 years.^{86,87} They have been generally generated from many R–OX species under different conditions (Figure 45).

It is also known that alkoxy radicals are very reactive and can be used as strategic intermediates in organic synthesis. Indeed, these radicals exhibit three major reactivities, namely, hydrogen atom transfer (HAT), β -scission, and additions onto unsaturations. The following sections will attempt to describe recent advances in the generation of alkoxy radicals and their reactivities in the order given above.

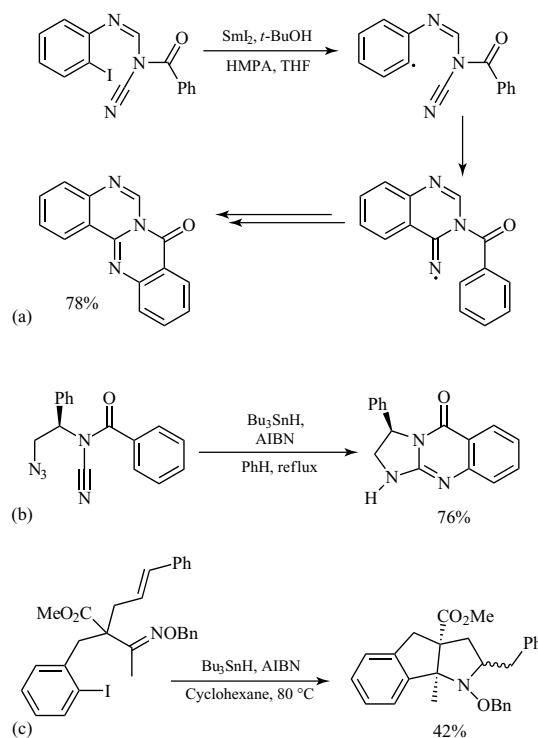


Figure 44 Radical cyclization cascades where iminyl and aminyl radicals occur as intermediates.

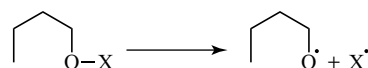


Figure 45 Formation of oxygen-centered radicals.

3.1 Formation of Alkoxy Radicals from RO–X Compounds

More than a dozen methods to generate alkoxy radicals before 2000 have been described and summarized by Čeković in a review.⁸⁸ The wide variety of conditions and substrates allow this method to be applied to organic synthesis. Indeed, we can find families of precursors such as alkyl hypohalites, nitrites, peroxy compounds (hydroperoxides, dialkylperoxides, and peroxyacetates), and *N*-alkoxy phthalimides. The conditions used can be photolysis, thermolysis, or oxidation. A main advance in this field was made by Beckwith, who showed in 1988 that *N*-alkoxy-pyridine-2(1*H*)-thiones were clean sources of alkoxy radicals.⁸⁹ Hartung

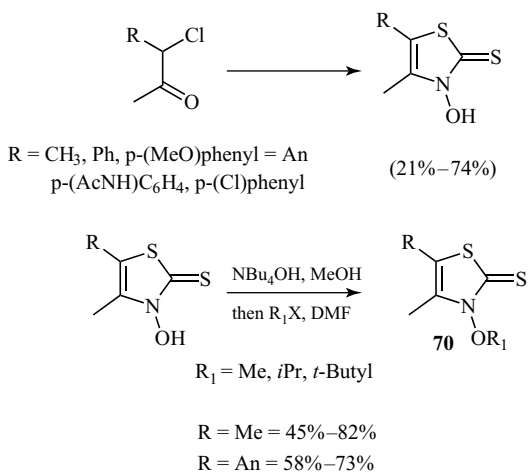


Figure 46 Two steps to alkoxy-4-methylthiazole-2(3)-thiones.

followed up on this chemistry by first using these derivatives and then proposed the valuable alternative alkoxy radical precursors.^{90,91} Indeed, he has recently developed a method to access alkoxy-4-methylthiazole-2(3)-thiones **70** in good yields in two steps (Figure 46). On this occasion, he studied the influence of substituents on the absorbance wavelength and also made spin-trapping experiments using the nitron 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole-1-oxide (DMPO), monitored by electron paramagnetic resonance (EPR).^{92,93}

This method has also been used by the same team to form precursors that were engaged in reactions to show classical reactivities of alkoxy radicals such as 5-*exo* cyclization, 1,5 HAT, or β -scission.⁹⁴

Newcomb has also proposed 4-nitrobenzenesulfonate esters (such as **71**) as precursors of alkoxy radicals.⁹⁵ Indeed, these compounds can easily perform an O–S bond homolysis to give the desired alkoxy radical using laser flash photolysis by irradiation at 355 nm (Nd:YAG third harmonic) (Figure 47).

More recently, methods have been described using catalytic amounts of metal salts. For instance, the formation of alkoxy radicals from 1-phenylcyclopropanols has been described with catalytic amounts of complexes of manganese(III)²⁰ silver(I),⁹⁶ or cobalt(II) in each case, in the presence of an oxidant.⁹⁷ Applications of these procedures are discussed.

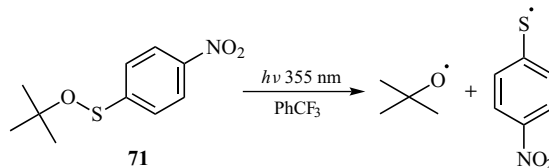


Figure 47 O–S bond homolysis.

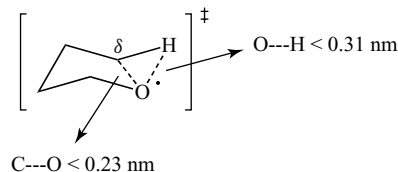


Figure 48 Six-membered ring chair-like conformation.

3.2 Reactivity

3.2.1 Hydrogen Atom Transfer

As mentioned earlier, HAT is a prominent reaction of alkoxy radicals.⁸⁸ While this has been known for a long time, the main questions remain: What factors are leading this reactivity? What conditions should be used? Can this process be useful in organic synthesis? The most common abstraction in the literature is the 1,5 HAT,⁹⁸ which requires, as modeled by Houk,⁹⁹ a six-membered ring in the lowest energy chair-like conformation of Figure 48.

Other HATs such as 1,6 and 1,4 are not favored. In the case of a 1,6 HAT, a seven-membered ring is involved, which is entropically disfavored. We can nevertheless find, in the literature, this HAT applied to rigid systems, with the right distance between the O-radical, the hydrogen, and the carbon in the δ position.¹⁰⁰

Recently, Sammis *et al.* have highlighted the use of 1,5 HAT to form cyclopentyl, tetrahydrofuran, and pyrrolidine derivatives through the homolysis of *N*-alkoxy phthalimides in the presence of AIBN and tributyltin hydride.¹⁰¹ The reaction is interesting because it involves two key radical steps in one reaction. First, the alkoxy radical reacts via 1,5 HAT to give a secondary carbon-centered radical **72**. Then, this new radical performs a 5-*exo*-trig cyclization giving five-membered ring substrates as a mixture of diastereomers, the *cis* being the major

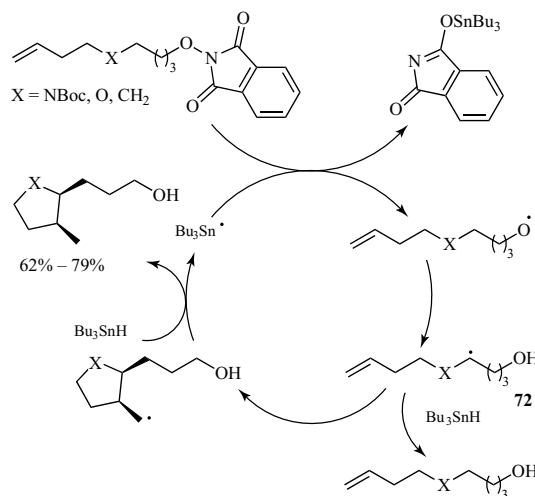


Figure 49 Hetero five-membered rings from *N*-alkoxy phthalimides homolysis.

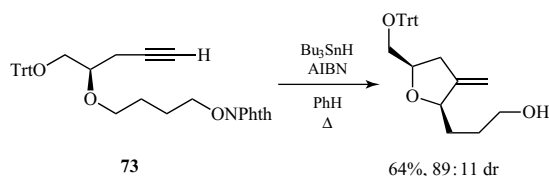


Figure 50 Application to a fragment of (–)-amphidinolide K.

one in accordance with the Beckwith–Houk model (Figure 49).

This principle could be applied to the synthesis of a fragment of (–)-amphidinolide K, starting from enantiopure precursor **73** (Figure 50).

HAT is also a very powerful tool if it is well controlled. As an example, Suarez *et al.* used a very rare 1,8 HAT between glucopyranose units in a disaccharide template such as **74** (Figure 51).¹⁰² The conformational restriction of this system minimizes the entropic cost associated with the assembly of a transient nine-membered ring. Conversely, the C6–O···H–C5' distance has been estimated to 2.5 Å. Thus, in the presence of 1.5 equiv of (diacetoxyiodo)benzene (DIB) and 0.7 equiv of iodine, an alkoxy radical (**75**) is generated that performs the 1,8 HAT, which engenders a tertiary C-centered radical (**76**) in the β -position of an acetate group. That proximity affords the reversible formation of a five-membered ring by creating a C–O bond through a quite unusual 5-*endo*-trig radical cyclization. The

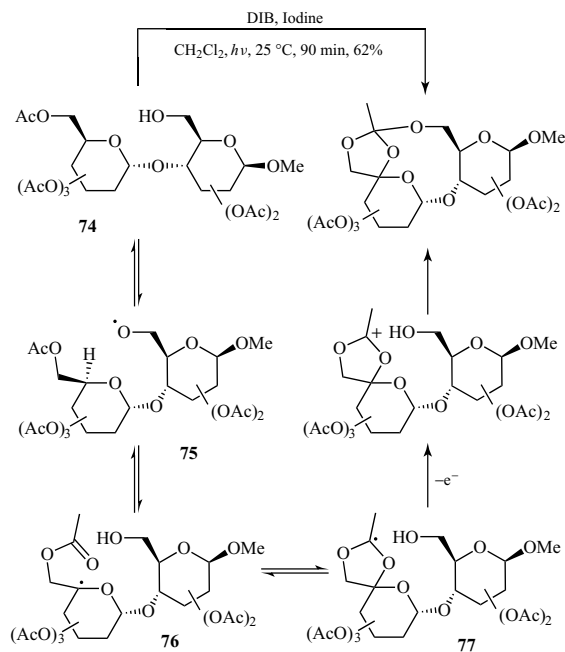


Figure 51 Example of 1,8 HAT.

resulting radical intermediate **77** is oxidized to give the corresponding oxonium cation, which is subsequently trapped by the pendant alcohol to give the desired compound. This access to 4-D-Glc disaccharides can be of interest in the chemistry of heparin analogs.

As seen previously, HAT requires a hydrogen at the right distance from the alkoxy radical to be efficient. If not, we can observe another reactivity called β -scission, which is discussed in the next subsection.

3.2.2 β -Scission

β -Scission consists in a homolytic bond breaking following an alkoxy radical formation and can be influenced by reaction conditions such as solvent or temperature. Indeed, as recently compiled by Ingold in a review, solvents play a role in the β -scission kinetics (see Figure 52).¹⁰³ For instance, hydroxylated solvents accelerate the β -scission compared to aromatic ones.

The β -scission acceleration can be explained by the fact that the solvation of the carbonyl species

Solvent	$T(K)$	$k (10^6 \text{ s}^{-1})$
$\text{PhCMe}_2\text{O}^\bullet \rightarrow \text{PhC(=O)Me} + \text{Me}^\bullet$		
{ Benzene	303	0.4
{ H ₂ O	303	10
$\text{PhCCH}_2\text{CH}_2\text{O}^\bullet \rightarrow \text{H}_2\text{C=O} + \text{PhCH}_2^\bullet$		
{ PhCl	238	1.9
{ PhCl + 0.4 M EtOH	238	10.7

Figure 52 Solvent effect in the β -scission kinetics.

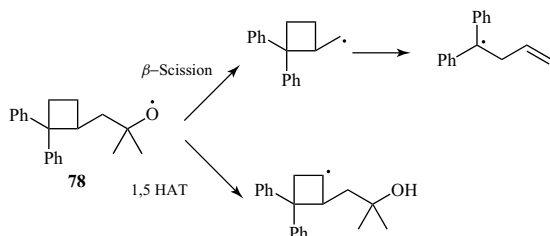


Figure 53 Competitive reactions.

that are formed is better than the solvation of its alkoxy radical precursors.

Despite the solvent effect, the stability of the product radical matters in the rates of radical loss. In the first reaction (Figure 52), if we have the R radical (with R = Et, *i*-Pr, *t*-Bu, PhCH₂), instead of the Me one we can notice that the reaction speed increases with the substitution. The rate constant is estimated at $5 \times 10^6 \text{ s}^{-1}$ for propyl versus $2 \times 10^8 \text{ s}^{-1}$ for benzyl.

Logically, Newcomb *et al.* highlighted in 2000 that temperature has an influence on the rates of β -scission and of 1,5 HAT and compared both reactivities.⁹² They showed that the rate of β -scission decreases with temperature. They also observed the same phenomenon with 1,5 HAT but noticed that $k_{1,5 \text{ HAT}}$ decreases more slowly than $k_{\beta\text{-scission}}$. For example, the alkoxy radical **78** can undergo 1,5 HAT or β -scission (Figure 53). Measurements show that 40% of products come from the β -scission at 50 °C instead of 21% at 10 °C. A prototypical case of 1,5 HAT involving an alkoxy radical and a secondary alkyl position gave a value of $2.7 \times 10^7 \text{ s}^{-1}$.

This reactivity can be used in intramolecular reactions such as ring expansions. The following example by the Hasegawa group in 2007 shows

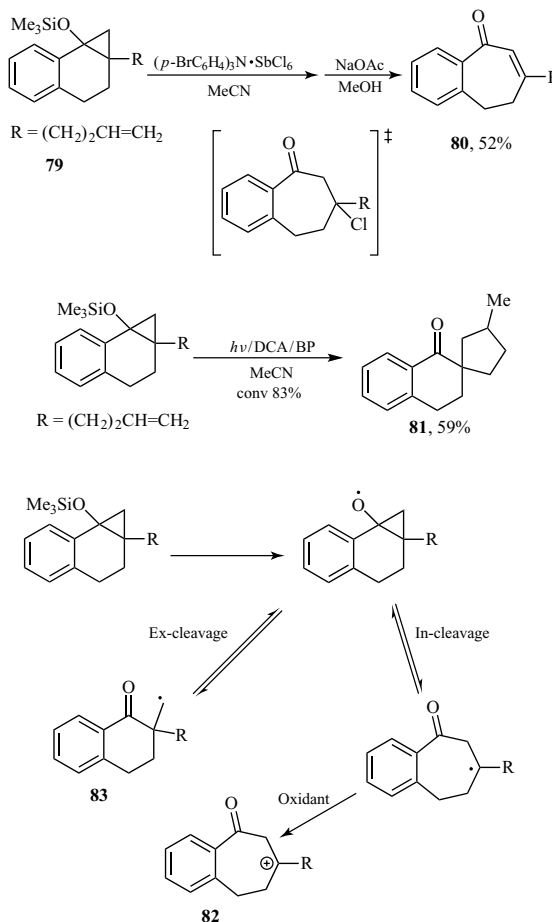


Figure 54 Example of intramolecular reactions.

some possibilities of β -scission which depends on the substrate structure (ring size, *n*) and reaction conditions.^{104,105} Thus, when cyclopropyl silyl ether **79** is treated with 2 equiv of tris-*p*-bromophenylaminium hexachloroantimonate (TBPA), a well-known hole catalyst, the chloro derivative is formed. Subjecting this crude product to NaOAc in MeOH provides cycloheptenone **80** in 52% overall yield. In contrast, upon treatment with 0.1 equiv of 9,10-dicyanoanthracene (DCA) and 1.2 equiv of biphenyl (BP) in MeCN under irradiation (Photoinduced electron transfer (PET) conditions, $\lambda > 340 \text{ nm}$), bicyclic ketone **81** is obtained in 59% yield (Figure 54).

This difference of outcome is rationalized by external or internal bond cleavage. In the presence of an oxidant (second equivalent of TBPA), the

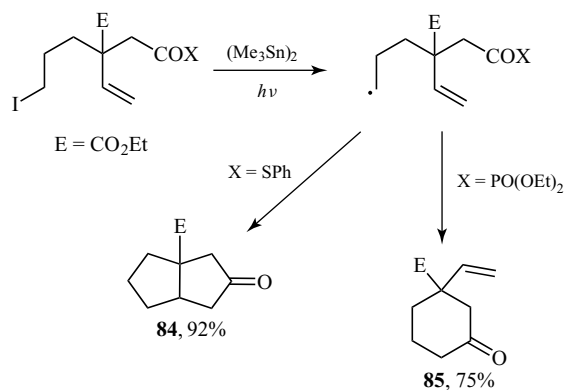


Figure 55 Alkoxy radicals involving heteroatomic partners.

formation of a tertiary carbocation **82** will drive the reaction to the internal cleavage; on the contrary under PET conditions, oxidizing species have short lifetimes and radical processes from the external cleavage such as 5-exo cyclization can take place (**83**).

β -Scissions from alkoxy radicals can also involve heteroatomic partners such as phosphorus- or sulfur-centered radicals.¹⁰⁶ This study brought to light an interesting dependence of a tandem process on the nature of the leaving group. Thus, in the case of an acylsulfide precursor, the first reaction that occurs is a 5-exo cyclization followed by the addition on the acyl group to form the corresponding alkoxy radical intermediate. Homolytic cleavage of the C–S bond gives the final product **84**. In the case of the acyl phosphonate, however, the 5-exo cyclization does not occur. The major product **85**

corresponds to the addition on the acyl phosphonate (6-exo cyclization) and the leaving of the phosphonate group. The difference of reactivity can be explained by the fact that the acyl phosphonate is a better radical acceptor than acyl sulfide (Figure 55).

Recently, the β -scission of diversely substituted cyclopropanols has triggered interest in the synthetic community. Narasaka has shown that various β -keto radicals were generated in the presence of a catalytic quantity of AgNO_3 and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as a reoxidant and pyridine. Good yields of addition products to enolethers such as **86** have been observed. Even more versatile is the possibility to accomplish three-component couplings with electron-deficient and electron-rich alkenes as in **87**, in this order because of the nucleophilic character of the initial β -keto radical (Figure 56).

Chiba nicely followed up on this by devising a Mn(III)-catalyzed or mediated synthesis of pyridine and 2-azabicyclo[3.3.1]non-2-en-1-ol derivatives from cyclopropanols and vinylazides (Figure 57).

This formal [3 + 3] annulation of vinyl azides and cyclopropanols proved useful for the total synthesis of the indole alkaloid of ($\pm$)-melinoline E (Figure 58).¹⁰⁷

3.2.3 Brook Rearrangement

Paredes and Alonso used α -silyl alcohols and α -silyl alcohol nitrite esters in the presence of lead tetraacetate.¹⁰⁸ In the case of alcohols, subsequent to the corresponding alkoxy radical generation, a

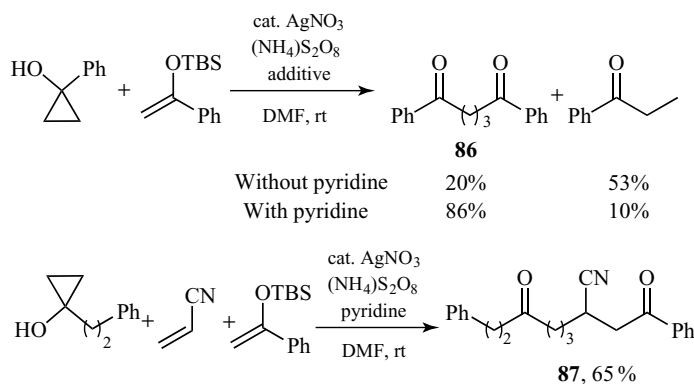


Figure 56 β -Scission of diversely substituted cyclopropanols.

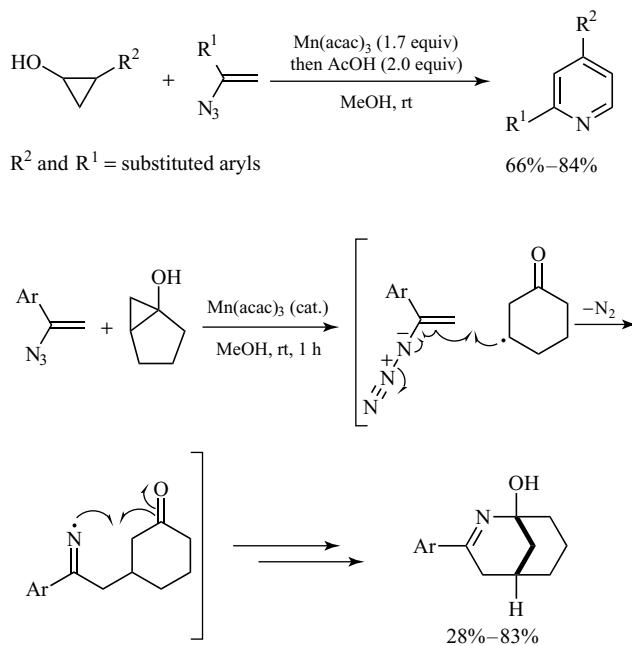


Figure 57 Mn(III)-catalyzed synthesis of pyridine.

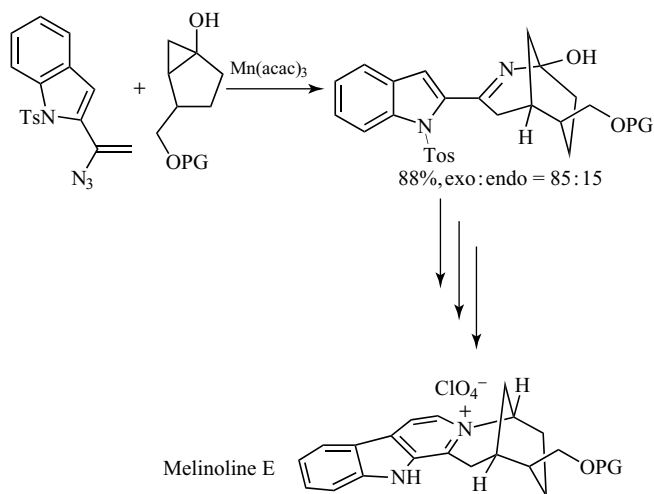


Figure 58 Synthesis of the indole alkaloid of (±)-melinoline E.

radical Brook rearrangement occurred, resulting in the formation of a secondary or tertiary C-centered radical which was reoxidized by lead triacetate. Finally, the cation was trapped by an acetate to deliver the final products (Figure 59).

It is also interesting to note that acylation is faster than 5-exo cyclization even if an electron

withdrawing group such as an ester is present in alkene α -position (Figure 60).

In the case of nitrites under light irradiation, with alkyl derivatives, formation of carbonyl species prevails. With aromatic substrate, no light is even required. Several mechanistic scenarios have been proposed (Figure 61).

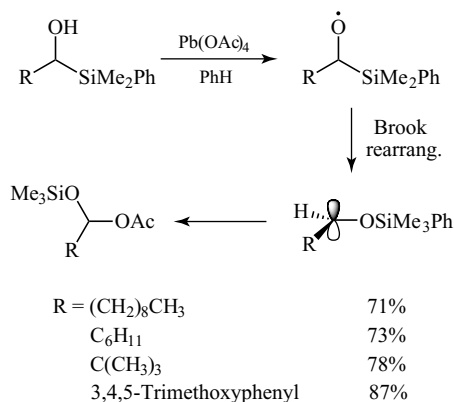


Figure 59 Radical Brook rearrangement.

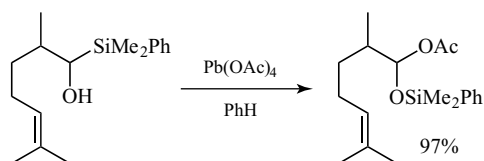


Figure 60 Faster acylation than cyclization.

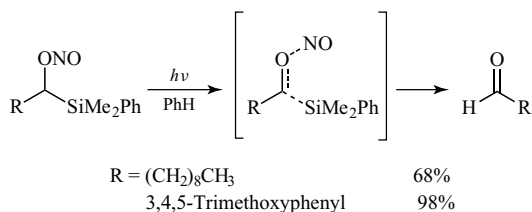


Figure 61 Proposal for a mechanism for O–N bond breaking.

3.3 Addition of Oxygen-Centered Radicals to π Systems

3.3.1 Intermolecular Reactions

The manipulation of oxygen-centered radicals for synthetic applications, especially in an intermolecular context, is particularly delicate because these types of intermediates are presumably just too reactive and can potentially give rise to undesired pathways. The work of Wille has certainly provided a good solution to circumvent this issue by developing the concept of self-terminating radical

cyclizations. It relies on the additions of O–X[•] radicals featuring spin density centered on the oxygen atom, X[•] being an easy radical to generate. First examples along these lines were given with the NO₃[•] radical, which can be conveniently formed by anodic oxidation of the nitrate anion or photolysis of ammonium cerium(IV) nitrate. Medium-sized cycloalkynes ($n = 8\text{--}12$), because of their intrinsically strong transannular interactions favoring subsequent intramolecular steps, were anticipated to be substrates of choice for these studies, which proved to be a good intuition. Thus, upon treatment of cyclodecyne with the electrochemically generated NO₃[•] radical, transannular cyclization took place and provided the formation of cis-fused bicyclic ketone **88** and the trans-fused one **89** in 70% yield in a 3:1 ratio.¹⁰⁹ Intermolecular addition of the NO₃[•] radical generates a highly reactive vinyl radical intermediate that is prone to undergo transannular hydrogen transfers. Not surprisingly, 1,5-H transfer prevails and gives rise to a secondary alkyl radical that further adds onto the vinyl ester function. Final fragmentation liberating the NO₂[•] radical completes the cascade of events and delivers the bicyclo[5.0.3]decanone system **88** as major product and as a single diastereomer. The other minor component originates from an initial 1,6-H transfer followed by the same type of elementary steps (Figure 62).

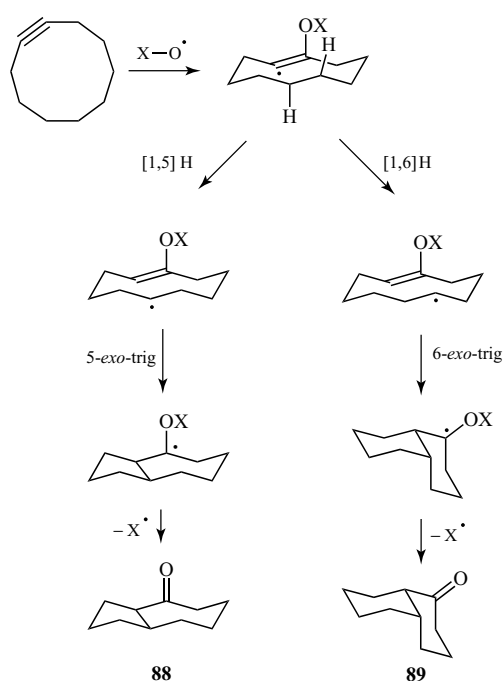
Other sources of <<O:>> synthon were tested with the Fenton-generated SO₄^{•-} radical and provided the same mixture of **88** and **89** in 80% yield in a 1.9:1 ratio¹¹⁰ and with acyloxy radicals¹¹¹ (RCO₂[•], R = Me, Ph, 4-OMe-Ph, etc.) resulting in yields up to 89%. The precursors used for the generation of the acyloxy radicals were *O*-acyl thiohydroxamate esters. Other O-centered radicals such as (alkoxycarbonyl)oxyl, ROC(O)O[•], [(alkoxycarbonyl)-acyl]oxyl, ROC(O)C(O)O[•], (carbamoyl)oxyl R₂N C(O)O[•], alkoxy radical, RO[•],¹¹² and nitroxyl radicals R₂NO[•]¹¹³ have been tested and have proved to be operative for the formation of **88** and **89**. Interestingly, even the hydroxy radical could be engaged (Table 1).¹¹⁴

Though beyond the scope of this article, it should be mentioned that N-centered (aminium and amidyl) and S-centered radicals have also been used in the context of self-terminating radical cyclizations.¹¹⁵

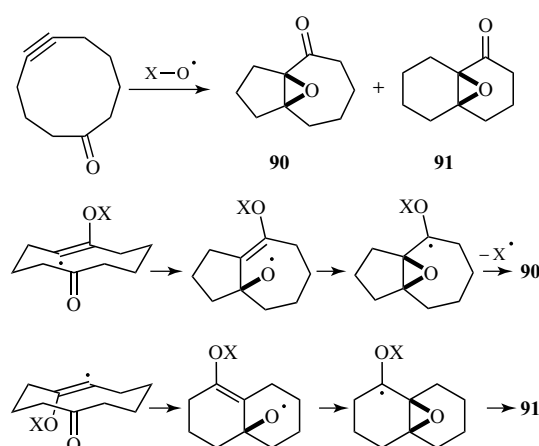
Interestingly, 5-cyclodecyne also proved to be an interesting substrate to study, since in that case further complexity is obtained thanks to the

Table 1 Influence of the O-centered radical source on the formation of **88** and **89**.

Entry	X	Yield	Ratio (88 : 89)
1	NO ₂	70 ^a	53:17 ^a
2	SO ₃ ⁻	79 ^a	52:27
3	MeC(O)	66 ^b	35:31
4	PhC(O)	81 ^b	42:39
5	4-MeOC ₆ H ₄	89	47:42
6	MeOC(O)	94	—
7	allylOC(O)	89	—
8	Et ₂ NC(O)	69 ^a	—
10	EtOC(O)C(O)	82	—
11	Me	32	—
12	N(C(O)CH ₂ CH ₂) ₂	50	—

^aYield and ratio determined by GC.^bYields are given with respect to the radical precursor.**Figure 62** Formation of cis-fused bicyclic ketone.

presence of the reacting carbonyl function as an acceptor of the vinyl radical (Figure 63). The resulting highly reactive alkoxy radical undergoes a reversible 3-*exo*-trig cyclization whose driving force is the fast β -elimination of the X[•] radical which restores a C=O function. Logically, two regioisomeric vinyl radicals can be initially formed with possible evolution for both of them, resulting generally in a mixture of **90** and **91** in ratios close to 1:1 to 1:3 with the cis form as the major product.

**Figure 63** Oxidative radical cyclizations of 5-cyclodecynone with inorganic and organic oxygen-centered radicals of type XO[•].

Finally, open-chain alkynes bearing a cyclic template could be cyclized in the presence of NO₃[•], providing annelated tetrahydrofurans derivatives such as **92** in moderate to good yields and in good diastereoselectivity (Figure 64).^{116–118}

This reactivity could be extended to annelated pyrrolidines (**93** and **94**) by introducing a pendant nitrogen arm (Figure 64).¹¹⁹ Some calculations have come to the support of all these findings.^{120–122}

It should also be mentioned that the NO₃[•] radical has been shown to oxidize aromatic amino acids such as phenylalanine and tyrosine. Two mechanisms have been proposed, which consist of hydrogen transfer or electron transfer followed by proton loss.¹²³

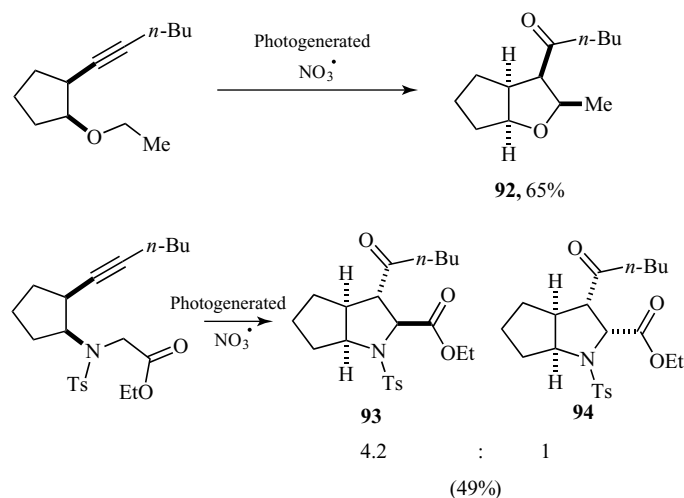


Figure 64 Anellated tetrahydrofurans and pyrrolidines derivatives formation.

3.3.2 Intramolecular Reactions

The work of Hartung has established the cyclization of alkoxy radicals as a very reliable method for the synthesis of tetrahydrofuran systems.^{90,91,124} This chemistry could be extended to a halocyclization process. Thus, bis-homoallylic alcohols were converted to the *N*-alkenoxythiazole-2(3*H*)-thiones or pyridine-2(1*H*)-thiones. Upon photolysis, in the presence of BrCCl_3 and either *N*- $\text{C}_4\text{F}_9\text{I}$ or diethyl 2-iodo-2-methyl malonate serving as radical trapping agents, the corresponding bromo- or iodo-tetrahydrofuran derivatives were obtained in high yields and diastereoselectivities.¹²⁵

The stereoselectivity of the 4-penten-1-oxyl radical 5-*exo*-trig cyclization has been computationally (density functional theory, DFT) addressed by Hartung, who proposed a new transition state model as an alternative to the classical Beckwith–Schiesser–Houk–Spellmeyer model.¹²⁶ More recently, the Hartung group has concentrated on cobalt-catalyzed alkenol cyclizations. Thus, bis-homoallylic alcohols were shown to undergo oxidative cyclizations upon bis{2,2,2-trifluoromethyl-1-[(1*R*, 4*S*-1,7,7-trimethyl-2-(oxo- κ O) bicyclo[2.2.1]hept-3-ylidene]ethanolato- κ O} cobalt (II) catalysis in the presence of O_2 (Figure 65).⁹⁷ Further work showed that the stereoselectivity of the (5-phenyltetrahydrofur-2-yl)alkan-1-ol formation from the corresponding pentenols was

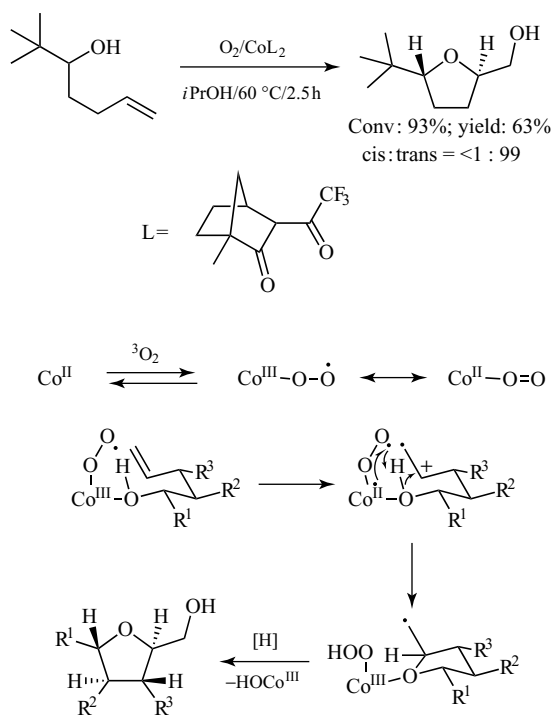


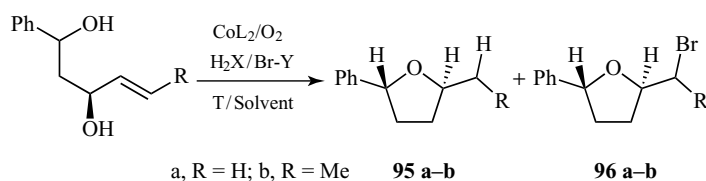
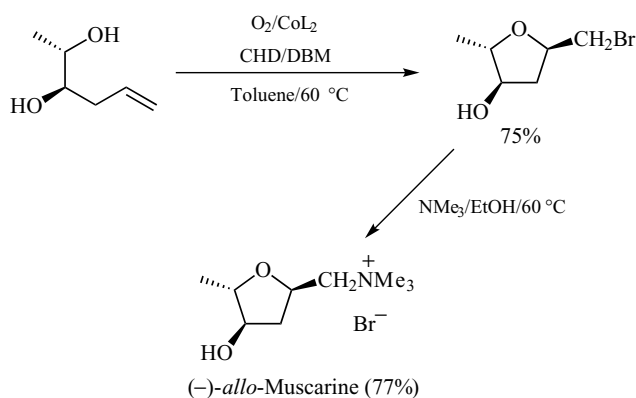
Figure 65 Tetrahydrofuran formation using cobalt catalysis.

independent of the configuration of the alkene, confirming the initial assumption of a radical mechanism, which is depicted in Figure 65.¹²⁷

On the basis of these findings, reductive and brominative terminations of the alkenol

Table 2 Tetrahydrofuran formation using cobalt catalysts.

Entry	R	CoL ₂ (mol%)	H ₂ X (equiv)	Br– Y (equiv)	T (°C)	95 (%)	96 (%)
1	H	1	CHD (20)	—	60	85	—
2	H	4 × 5	CHD (30)	Br–CCl ₃ (10)	60	—	85
3	Me	2 × 2	CHD (20)	—	75	80	—
4	Me	4 × 10	CHD (30)	Br–CCl ₃ (10)	75	—	87

**Figure 66** Reductive and brominative terminations of the alkenols cyclizations.**Figure 67** Efficient synthesis of (–)-*allo*-muscaine.

cyclizations were devised by the simple addition of cyclohexadiene, BrCCl₃, or DBM (Table 2 and Figure 66).

This protocol could be applied to the total synthesis of (–)-*allo*-muscaine (Figure 67) and extended to intra–inter–intra domino processes (Figure 68).^{128,129}

4 PHOSPHORUS-CENTERED RADICALS

The principal features of P-centered radicals up to 2004 have been reviewed previously.^{130,131} The present account is an update of our 2004 review. For clarity, we decided to use a similar order here.

4.1 Physical Organic Background

Several P-centered radicals and radical ions have been studied both theoretically and experimentally.

The Coote group calculated the effect of substituents on the stabilities of phosphonyl radicals and their hydroxyphosphinyl tautomers, because of the central role of the former in free-radical chemistry.¹³² It was found that the main factor for radical stabilization is the σ -effects of the substituents. The phosphorus atom is polarized with a high positive charge and is pyramidal. Thus σ -donation is stabilizing and the π -effects are minimal.

Phosphorus can go hypervalent also for radicals. Phosphoranyl radicals have been intensely studied for their properties and as intermediates of synthetic processes. Two reports illustrate this fact well.

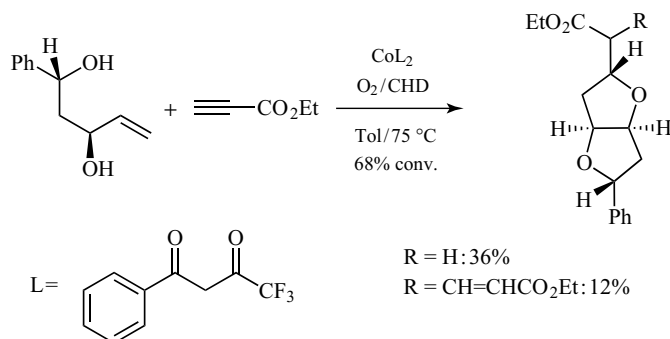


Figure 68 Application to intra–inter–intra domino processes.

Using time-resolved kinetic studies, the Bietti group has examined the addition of alkoxy radicals to phosphites, as well as the behavior of the phosphoranyl radicals obtained.¹³³ The addition is controlled by steric factors on both the phosphite and the alkoxy radicals, while the β -scission step is controlled by the stability of the carbon radical formed.

Persilylation of the oxygen substituents in phosphoranyl radicals of the type $(\text{RO})_4\text{P}^\bullet$, where $\text{R} = \text{SiAlk}_3$, led to the first acyclic persistent P radical.¹³⁴ This opened perspectives for controlled radical polymerization and dynamic nuclear polarization.

SET from phosphines through either photosensitization or pulse radiolysis, as well as quenching of the phosphine radical cations with oxygen, has been thoroughly studied by Yasui, Majima, and others.^{135–137} Further insight was given by photoelectron spectroscopy.¹³⁸

Several new inorganic and organometallic P-centered radicals and radical ions have been prepared over the last few years. They were generally characterized by approaches employing EPR, X-ray diffraction, and modeling.

Ito and Yoshifuji reported an air-tolerant 1,3-diphosphacyclobuten-4-yl radical (**97**, Figure 69a), whose structure was solved.¹³⁹ However, in-depth EPR characterization showed that the spin was mostly away from the P atom, so **97** should be best described as a stable C-centered radical.

Insertion of metals on specific position can help stabilize new radicals. Cummins introduced resonance-stabilized monomeric P radicals (**98**, Figure 69b).¹⁴⁰ In this case, two nitridovanadiums

act as redox-active ligands, which can tune the reactivity of the complex. The latter exhibited “substantial radical character on the phosphorus atom,” which was shown experimentally by regioselective selenation and other radical reactions, all taking place at P.

Complexation by tungsten helped stabilize a triphosphaallyl radical generated from addition/rearrangement of a photogenerated $\text{P}^\bullet$ -bis-W complex to a diphosphene derivative (**99**, Figure 69c).¹⁴¹ The authors were also able to isolate the triphosphaallyl cations and anions.

Along related lines, van Gastel, Neese, and Streubel got insight into the reactivity of the P-chlorophosphanyl radical–tungsten complex (characterized by electron spin resonance ESR).¹⁴² One-electron oxidation of P-chlorophosphinoid complex of W **100** with a tritylium cation delivered the radical pair **101**, which recombined to generate a C–P bond in the transient complex **102**. Further, the reactivity of **102** depends on the substituent on phosphorous atom (Figure 69d).

The Bertrand group recently obtained the structure of a stable crystalline phosphinyl radical cation.¹⁴³ The key stabilization of the radical cation stabilization was introduced by a cationic substituent derived from a cyclic (alkyl) (amino) carbene (CAAC) (Figure 70). Radical cation **104** was obtained via one-electron oxidation of phosphalkene **103**. Compound **104** exhibits spin density mostly at the phosphorus center (0.67e), which was demonstrated experimentally via Bu_3SnH reduction to cationic phosphine **105**. Dimerization through radical recombination is prevented by the bulky and cationic substituent. P_2 Radical ions were also characterized.^{144,145}

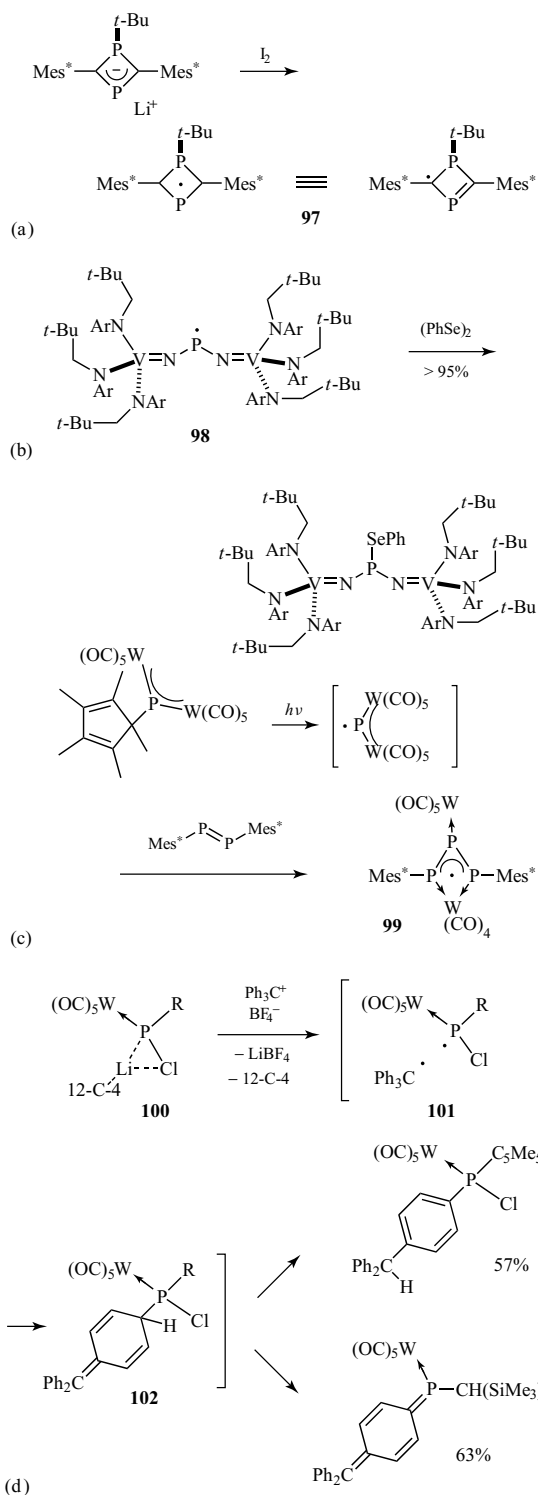


Figure 69 Transient P-chlorophosphanyl radical complexes.

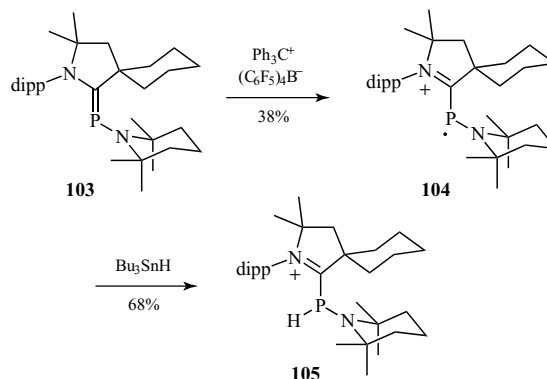


Figure 70 Synthesis of a stable phosphinyl radical cation.

4.2 Phosphorus-Based Mediators

The use of P-H compounds as radical reductants did not really catch up, and no new concept or mediator emerged during the last 6 years. Interesting applications have been reported. These are the new radical arylation of **106** to **107** as a key step leading to horsfiline (Figure 71),¹⁴⁶ cyclizations leading to medium-sized rings—for example, via 8-*endo*-trig cyclization¹⁴⁷—and intermolecular radical additions of dihaloalditol derivatives to acrylonitrile.¹⁴⁸ Both diethylphosphine oxide (DEPO) and *N*-ethylpiperidine hypophosphite (EPHP) were generally applicable.

4.3 Additions of P-Centered Radicals to Unsaturations

Several reports have focused on the addition of phosphorus radicals to unsaturated compounds, olefins, and alkynes, as well as aromatic derivatives. The addition can be the only radical event, leading to hydrophosphination or hetero-phosphination of olefins, or it can be part of a more complex process involving several unsaturations.

4.3.1 Hydrophosphination and Hetero-phosphination

Various P-H-containing derivatives could be added to olefins under radical conditions. The Parsons group reported hydrophosphination from

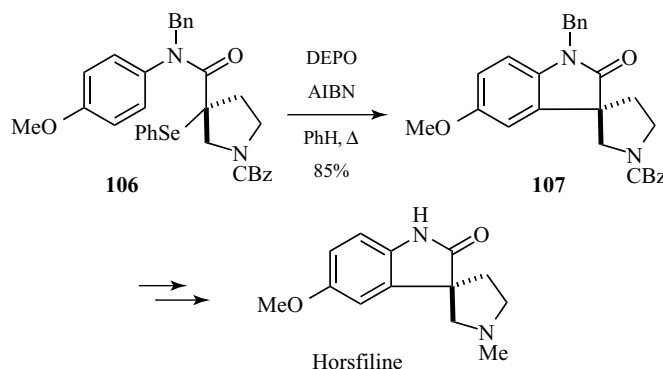


Figure 71 Application of P-based mediators to radical arylation.

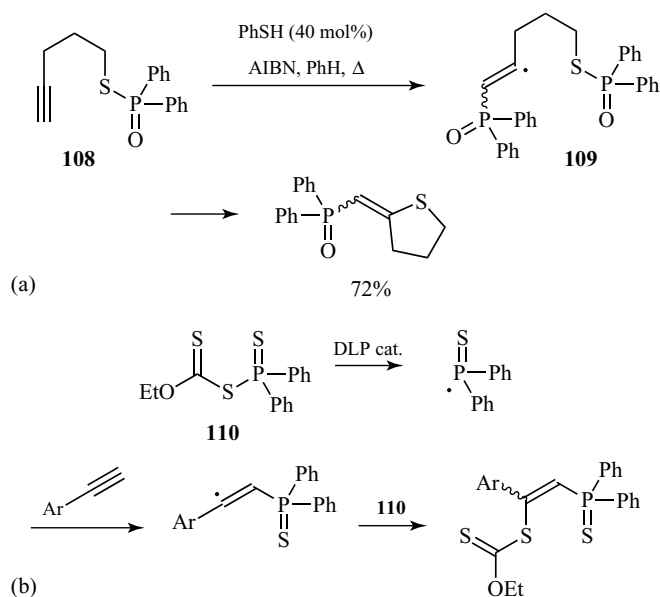


Figure 72 Alkyne radical 1,2-thiophosphinoylation: (a) intramolecular and (b) intermolecular.

diethylthiophosphites—(RO)₂P(=S)H—¹⁴⁹ and diphenylphosphine sulfides—Ph₂P(=S)H.¹⁵⁰ Han *et al.* published the air-induced radical addition of phosphine oxides—R₂P(=O)H—and phosphinates—(RO)R'P(=O)H.¹⁵¹ The same group had previously published the AIBN-initiated addition of chiral phosphinates.¹⁵² Phosphinoyl radicals were also generated under irradiation¹⁵³ or via homolytic substitution (which also worked for phosphonyl and diaminophosphonyl radicals).^{154,155}

All the above-mentioned methods used P(V) derivatives. Trofimov reported the controlled hydrophosphanation of vinylimidazoles by secondary

phosphines.¹⁵⁶ This was initiated either by AIBN or UV irradiation and had to be carried out in the absence of air to avoid oxidation of the phosphorus atom.

The radical resulting from the addition of the initial P-centered radical could be further functionalized beyond a simple reduction. We reported the first 1,2-bis-functionalization of alkynes. Addition of the P-centered radical to the ω -functionalized alkyne **108** generated an intermediate vinyl radical (**109**), which underwent the S_H2 leading to a P,S-substituted *exo*-methylene cyclohexane (Figure 72a). The Oshima/Yorimitsu group devised

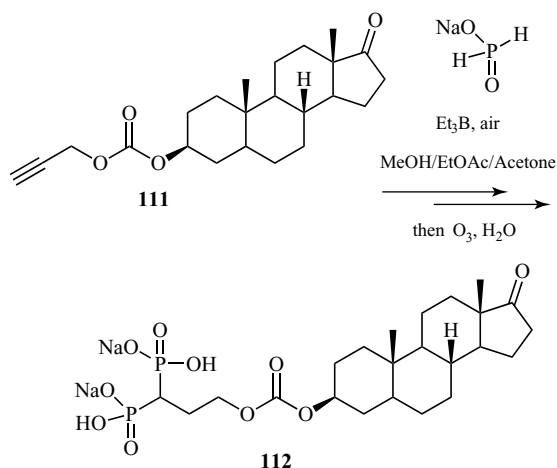


Figure 73 Preparation of bioactive bis-phosphinates via $P^\bullet$ bis-addition to an alkyne.

the intermolecular version of this process upon introducing an *S*-thiophosphinoyl xanthate (**110**), which was the source of both the P and S ends of the olefins, via a xanthate transfer reaction (Figure 72b).¹⁵⁷

Other studies on thiophosphination of terminal alkynes that delivers products with *E*-selectivity are reported using a mixture of diphenyldisulfide and diphenyldiphosphide through irradiation by a xenon lamp¹⁵⁸ with AIBN employed as initiator to activate arylthiodiphenylphosphines.¹⁵⁹

4.3.2 Hydrophosphination Step in Cascade Processes

The Parsons group has been active to extend the $P^\bullet$ addition to polyunsaturated compounds. The cascade is triggered by the initial radical C–P bond formation. This generates a carbon radical β to the phosphorus atom, which can add to suitably positioned unsaturations. This provides a synthetic route to heterocyclic Horner–Wadsworth–Emmons reagents,¹⁶⁰ as well as the cannabinoid¹⁶¹ and quinuclidine¹⁶² frameworks. This approach was also suitable for bidirectional functionalization.¹⁶³

Montchamp has reported the bis-addition of sodium hypophosphite to alkynes. Air-initiated $P^\bullet$ -radical addition takes place at the same carbon,

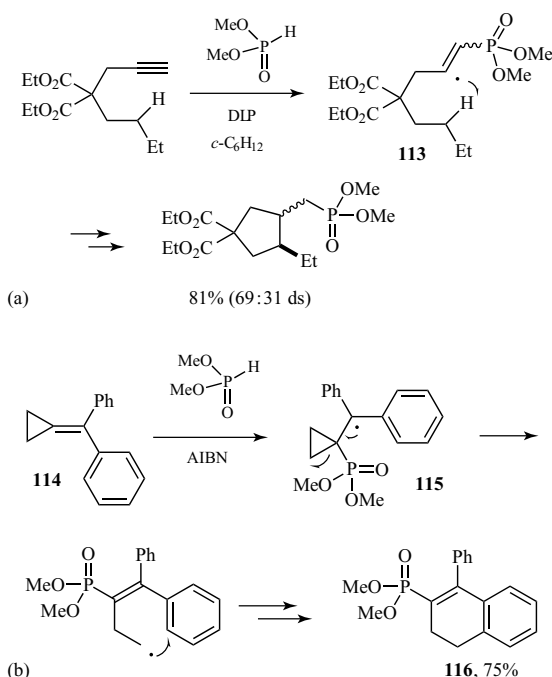


Figure 74 Cascade processes involving phosphonyl radicals featuring (a) a 1,5-H translocation and (b) an α -cyclopropyl radical opening.

delivering 1,1-bis-*H* phosphinates in good yields, maybe because of spontaneous precipitation of the 1,1-bis adduct.¹⁶⁴ Simple ozone oxidation delivers biologically important bis-phosphonates, such as **112** (obtained in two steps and 38% overall yield from alkyne **111**, Figure 73). Steroid conjugate **112** is a potential prodrug for delivery of the hormone to the bone for treatment of osteoporosis.

Renaud has devised a process featuring H transfer from the initially formed β -phosphonyl vinyl radical **113** and rebound cyclization to generate phosphonyl-substituted cyclopentanes (Figure 74a).¹⁶⁵

Huang and Yu reported the synthesis of dihydronaphthylphosphonates via a domino process featuring an initial addition of phosphonyl radicals onto vinylcyclopropanes such as **114**. The resulting radical **115** ring opens, thus generating a radical suited for aromatic addition to deliver the desired **116** (Figure 74b).¹⁶⁶

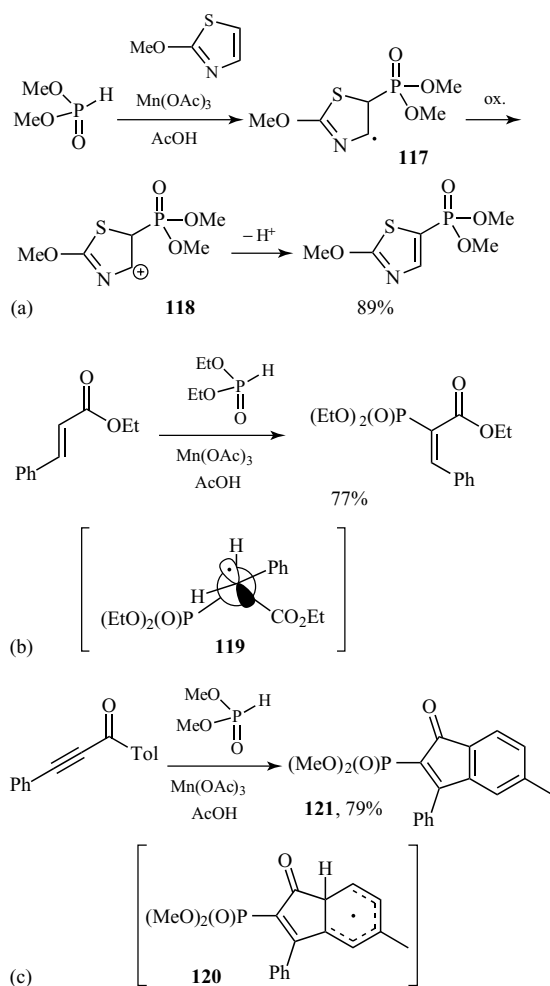


Figure 75 Oxidative phosphorylations (a) of heteroaryls and (b) of alkenes and alkynes.

4.3.3 Hydrophosphination Followed by Single-Electron Oxidation

Radical phosphonation of heteroaryls (Figure 75a),¹⁶⁷ as well as aryl alkenes and alkynes (Figure 75b),¹⁶⁸ can also be achieved under oxidative conditions. In these cases, radical addition is followed by single-electron oxidation of **117**, **119**, and **120** (Figure 75) to the corresponding cations (e.g., **118**, Figure 75a).

For 2-substituted thiazoles, the addition is regioselective, and leads to the α -N radical (such as

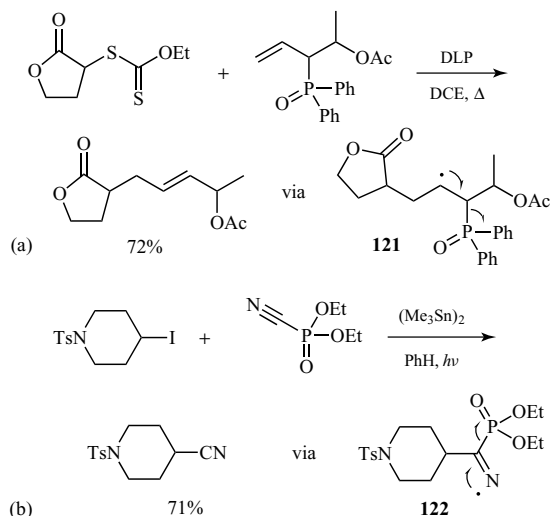


Figure 76 Key $\text{P}^*\beta$ -elimination for (a) allylations and (b) cyanations.

117, Figure 75a), possibly because it is more stabilized. In the case of aryl alkenes, the *E* diastereomers were obtained, which was explained by decreased nonbonding interactions in the intermediate radicals (such as **119**, Figure 75b). Finally, aryl alkynes deliver substituted indenones (such as **121**, Figure 75c) via a tandem addition (i) on the alkyne and (ii) on the aryl group. Rearomatization occurs after oxidation of radical **120**.

4.4 Phosphorus Radicals as Leaving Groups

4.4.1 β -Eliminations

Two new reports have used the β -elimination of P-centered radicals we uncovered in 1995,¹⁶⁹ which have been inserted into varied cascade processes.^{106, 170–172} Allyl phosphine oxides were proposed as allylating agents by Zard and coworkers via the key fragmentation of radical **121** (Figure 76a).¹⁷³ The corresponding β -phosphonyl radical was not conducive to allylation, which parallels our own observations for vinylations.

On the other hand, the phosphono-iminyl radical **122** underwent efficient fragmentation (Figure 76b).¹⁷⁴ This allowed the authors to devise a radical cyanation.

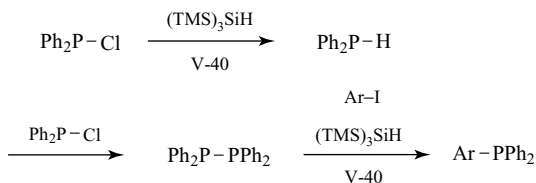


Figure 77 Radical phosphination.

4.4.2 Homolytic Substitutions

The most significant advance in synthetic phosphorus radical chemistry has been in the homolytic substitution field. Homolytic substitutions are covered in depth in another article of this encyclopedia (see **Intramolecular Homolytic Substitutions in Synthesis**), so we give only the main points of this particular reactivity here.

Ogawa introduced a photochemical variant of Yorimitsu and Oshima's¹⁷⁵ radical bisphosphination.¹⁷⁶ By replacing the alkynes with halides or xanthates, the latter authors have devised a highly elegant radical phosphination in which a P[•] is released upon substitution at P in a temporarily formed diphosphinyl derivative (Figure 77).¹⁷⁷

Coote has examined *in silico* the polymerization of strained phosphorus heterocycles. She calculated different elementary steps, involving the homolytic substitution releasing P-centered radicals, the homolytic substitution at P, as well as P[•]-releasing β -eliminations.¹⁷⁸ She concluded that radical ring-opening polymerization of small P-heterocycles should be feasible.

Studer introduced sila- and stannaphosphanes as reagents for homolytic substitutions at P.¹⁷⁹ DFT calculations indicated that the homolytic substitution likely proceeded through an associative mechanism featuring an intermediate phosphoranyl radical **123** rather than via an S_H2 pathway (Figure 78).

Studer and Curran determined the rate for the S_H involving the stannaphosphane at $\sim 9 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.¹⁸⁰ Using the axial chirality of *o*-halo anilides, the authors reported a very nice example of chemodivergent phosphanylations of atropoisomers.

Finally, chalcogen phosphinylation of alkynes was studied by the Oshima/Yorimitsu (for sulfur¹⁵⁷) and Nomoto/Ogawa groups (for S,¹⁵⁸ Se,¹⁵⁶ and Te¹⁵⁷).

The P-chalcogen reagents needed can be prepared before the reaction,¹⁵⁷ or *in situ*.^{156–158} In the

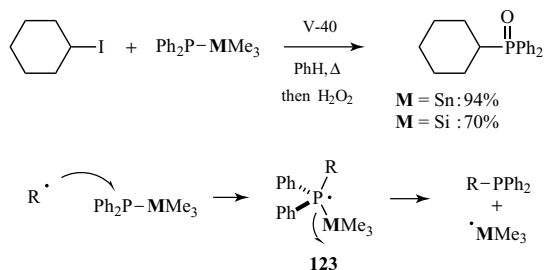


Figure 78 Radical phosphination from sila- and stannaphosphanes.

latter case, it builds up in the initial stages of the reaction via homolytic cleavage of the S–S, Se–Se, or Te–Te bonds and, probably, homolytic substitution at P. Then bis-functionalization of the alkyne follows. Interestingly, the regioselectivity is directed by the relative rates of additions of radicals Ph₂P[•] and Ph-chalcogen[•] to the triple bond. The PhTe[•] addition rate is very slow, resulting in the preferred initial addition of the phosphinyl radicals leading to **128**, while the reverse is true for S and Se (radicals **124**, **125**, **126**, **127**). This induced a regioselectivity switch (Figure 79).

5 SULFUR-CENTERED RADICALS

The study of the properties and the reactivity of S-centered radicals (and of their relative radical ions) has attracted a vast number of research groups owing to the relevance of these species in a wide range of domains, ranging from organic synthesis to biochemistry. Intense theoretical and experimental efforts have been carried out on this subject, and we present in the next section recent advances in the field. Xanthate chemistry and homolytic substitutions are covered extensively in this encyclopedia (see **Xanthates and Related Derivatives as Radical Precursors** and **Intramolecular Homolytic Substitutions in Synthesis**), so we have included these where necessary only briefly.

5.1 Sulfur-Based Mediators

S-Centered radicals, in particular aromatic thiyl ones, represent a well-known group of radical

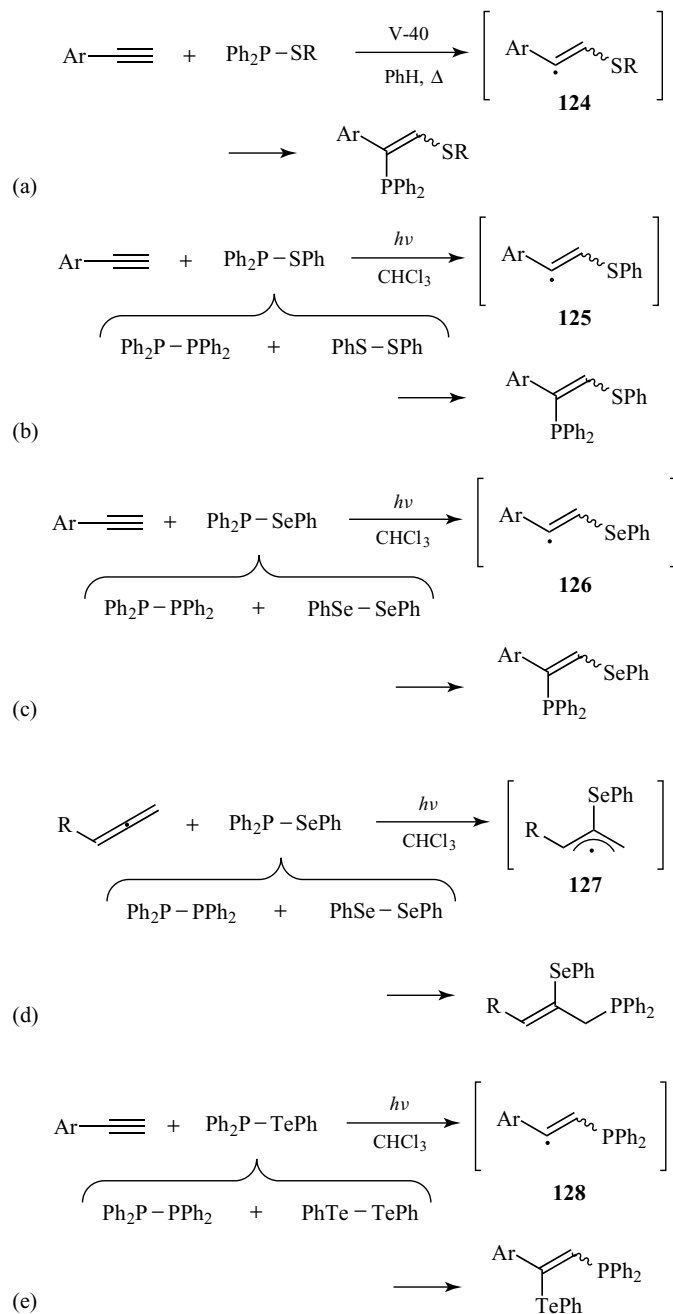


Figure 79 Intermolecular bis-functionalization (P-chalcogen) of alkynes and allenes. (a) Thiophosphinylation of alkynes from preformed P–S compound; (b) thiophosphinylation of alkynes from P–S derivatives obtained *in situ* through homolytic substitution; (c) selenophosphinylation of alkynes; (d) selenophosphinylation of allenes; (e) tellurophosphinylation of alkynes.

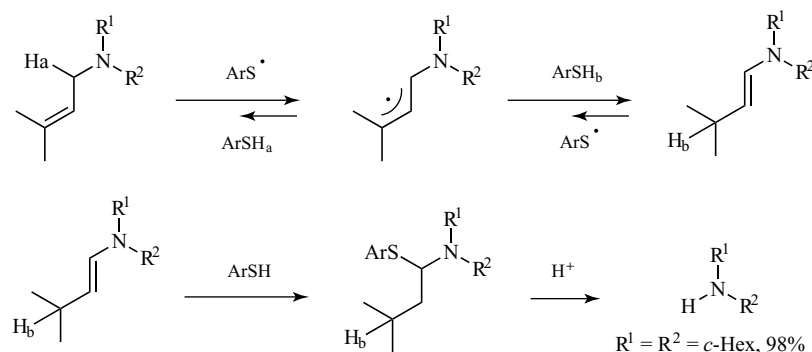


Figure 80 Thiol-mediated cleavage of allylic C–N bonds.

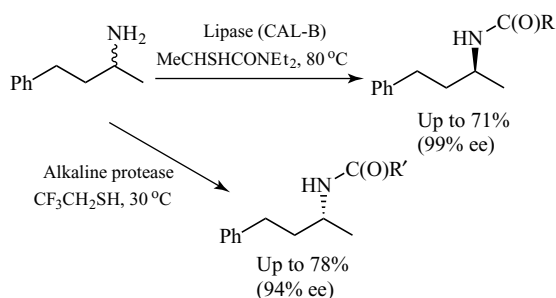


Figure 81 Tandem racemization–DKR of amines yielding either (*R*)- or (*S*)-enantiomers.

mediators as a result of the relative reversibility of their addition onto C–C multiple bonds. In the last decade, no new mediator has been found, although interesting applications have been reported, which will be briefly presented here. Main advances have been in the field of PRC, pioneered by Roberts.¹⁸¹ The key feature of this approach is related to the relative ease for an *electrophilic* thiyl radical to abstract hydrogen atoms to generate *nucleophilic* carbon-centered radicals.

In this context, new applications for arylthiols came from the group of Gastaldi and Bertrand, who reported the thiyl-radical-mediated cleavage of allylic C–N bonds.¹⁸² Detailed mechanistic and theoretical investigations suggested that thiyl radicals are responsible for the isomerization of the allylic amines to the enamines, which are cleaved by means of acidic work-up (Figure 80).¹⁸³

Applications were reported for the racemization of tertiary amines, either benzylic or nonactivated.^{184,185} The authors later combined an enzymatic kinetic resolution of primary amines

with a thiyl-radical-mediated racemization to obtain optically pure aliphatic amides from the corresponding racemic amines with excellent enantiomeric excess.¹⁸⁶

Further development allowed performing these racemization reactions at temperatures as low as 30 °C under near-UV irradiation instead of the traditional heating protocol, thus expanding the practical applications of the method otherwise limited by the relative thermal instability of dynamic kinetic resolution (DKR) enzymes at high temperatures. Through this approach, it has been possible to achieve either (*R*)- or (*S*)-selective DKR of chiral aliphatic amines.^{187,188} To date, this is the most efficient and mildest existing DKR of amines (Figure 81).

Through the PRC approach, benzenethiol has also been successfully employed as a catalyst for the radical reduction on aromatic azides to amines with tributylgermanium hydride.¹⁸⁹

Yamada and Tomioka used alkyl thiol PRC for the intramolecular acyl radical cyclization of alkenals.¹⁹⁰ This approach was later extended by the authors to the formal synthesis of (+)-allokainic acid and by Stoltz in its approach to (–)-cyanthiwigin F (Figure 82).^{191,192}

5.2 Addition of Sulfur-Centered Radicals onto Multiple Bonds

The most recent review on thiol-mediated radical cyclizations was published in 2008.¹⁹³ Addition of thiyl radicals to olefin can be the first step of radical-based olefin isomerizations. The β -thiyl radicals obtained from addition to a *Z* alkene undergo

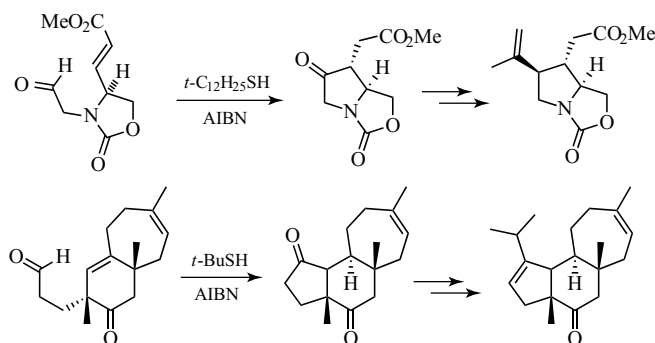


Figure 82 Synthesis of natural products through thiol-mediated acyl radical cyclization.

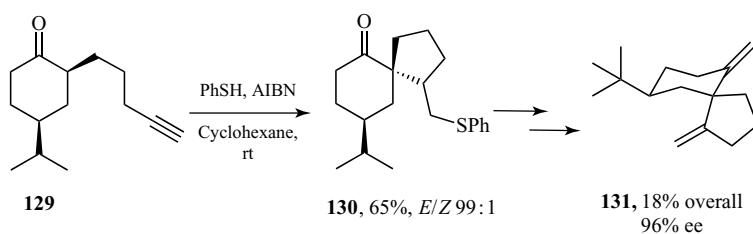


Figure 83 Access to (–)-erythrodiene through sequential radical addition/cyclization.

β -elimination to give the less sterically congested *E* alkene after rapid rotation. This is highly relevant in several fields, first and foremost that of lipid isomerization, which has been thoroughly studied by Chatgililoglu and Ferreri,^{194–202} and is reviewed elsewhere in this encyclopedia (see **Lipid Isomerization**).

Radical addition of thiols to alkenes and alkynes is an efficient method to introduce a sulfanyl moiety onto these multiple bonds. Because of the sensitivity of radical additions to steric hindrance on the carbon undergoing addition, the reaction works generally better on terminal rather than internal alkynes. Also, alkynes are better than alkenes.

Renaud reported an efficient procedure for running cascade reactions involving 1,5-hydrogen abstraction followed by a radical cyclization in which alkenyl radicals are generated through reaction between terminal alkynes and thiophenol.^{203–205} This approach allowed an elegant synthesis of (–)-erythrodiene **131** in seven steps from cyclohexanone **129**, the key issue being represented by the control of the stereochemistry at the spiro center of **130** (Figure 83).

Renaud's group later expanded these method featuring thiol-mediated 1,5-hydrogen transfer to the

preparation of 1-azabicyclic alkanes belonging to the class of pyrrolizidines and indolizidines from *N*-substituted caprolactams.²⁰⁶

Spagnolo and Nanni studied the addition of thiyl radical on terminal alkynes tethered to thioethers and carbamothioates as a mild protocol for the tin-free generation of alkyl and acyl carbon-centered radicals (via homolytic substitution).^{189,207,208}

Alonso reported the cyclization of γ -alkynyl ketimines through addition of $\text{PhS}^\bullet$.^{209,210} Interestingly, he found that substitution of the alkyne moiety at the ε -position is crucial to determine the favored cyclization pathway. 6-Exo (resp. 5-endo) manifolds are favored with phenyl (resp. carboxymethyl) substituents.

Yorimitsu and Oshima recently reported the radical addition of thiyl radicals onto ynamides and enamides.²¹¹ A particular hydrothiolation of the former class of substrates has been achieved by Castle.²¹² Interestingly, the addition is fully regioselective, delivering the β -thioenamides, but the stereoselectivity depends on the amount of thiol used. With 1 equiv of thiol, formation of the *cis* compound was observed (reduction governed by the approach of the reductant on the kinetic product), while the *trans* adduct was obtained with excess

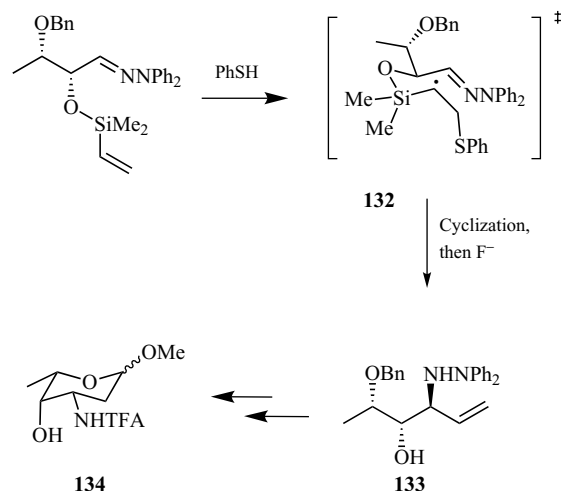


Figure 84 Tandem addition/cyclization and subsequent ring opening, yielding aminosugars.

thiol (thiyl-radical-mediated isomerization leads to the thermodynamic product).

Radical addition of benzenethiol on silicon-tethered vinyl groups was investigated by the group of Friestad. These radical reactions could be performed as a two-step sequence, in which $\text{PhS}^\bullet$ adds to a double bond and the resulting alkyl radical undergoes cyclization with the $\text{C}=\text{N}$ bond of an hydrazone.^{213–216} The favored anti relative configuration is consistent with a chair-like Beckwith–Houk transition state such as **132**. The resulting cyclized compounds delivered the desired products **133** after treatment with fluoride anions, which regenerated the alkene. The method was applied to the synthesis of protected amino sugars, such as L-daunosamine (**134**, Figure 84).^{217,218}

Addition of S-centered radicals on vinylidenecyclopropanes has been investigated by Shi.²¹⁹ Interestingly, the regioselectivity of the reaction could be switched completely upon changing the nature of the sulfur derivative. Diphenylphosphinodithioic acid smoothly delivered 1,2 addition products where the S atom was introduced on the cyclopropyl ring (**135**), while thioacetic acids led to addition to the central atom of the allene (**136**, Figure 85).

The group of Majumdar actively investigated radical cyclizations triggered by initial addition of $\text{PhS}^\bullet$ to alkenes and alkynes.^{220–222} It recently reported that propargylamino-substituted uracils reacted with thiophenol to yield the corresponding

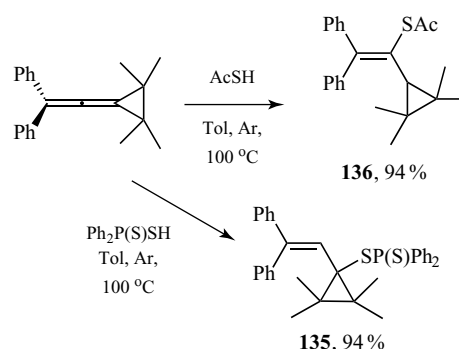


Figure 85 Reversal of regioselectivity in the addition of thiyl radical on vinylidenecyclopropane.

pyrrolopyrimidines, whereas in the presence of an allyl group ortho to the propargylamino motif, 8-*endo*-trig cyclization delivered the corresponding azocines.

In most cases, sulfur radicals are generated by AIBN or Et_3B . Switching to disulfides led to alkyne and enyne hydrothiolation (**137** and **138**, respectively, Figure 86) through an amine-mediated SET process.²²³

Thiyl radical additions are uniquely suited for the 1,2 bis-functionalization of multiple bonds. Mixed thiophosphinations, thioselenations, and thiotellurations are presented in Sections 4 and 6 of this article.

Hydroxysulphenylations usually require electron-rich olefins as radical acceptors. Electron-poor olefins lead to competitive Michael additions of the nucleophilic thiols. Bachi used this reaction on substituted 1,5-dienes to access endo peroxides with promising *in vitro* antimalarial activity via a very elegant cascade (Figure 87).^{224,225} 1,2,4-Trioxanes were obtained from substituted allylic alcohols.²²⁶

An interesting exception to the electron-rich olefin rule has been reported by Naito. α,β -Unsaturated oxime ethers and hydrazones gave good yields of hydroxysulphenylated compounds **139** after reduction of the hydroperoxide (Figure 88). The preferential formation of the *trans* isomer was proposed to be due to steric effects on the radical intermediate, the C–S bond being eclipsed by the p orbital of the carbon radical.²²⁷

The authors later expanded this method to the reaction of vinylcyclopropyl oxime ethers.²²⁸ In this case, the initial thiyl radical addition is followed by

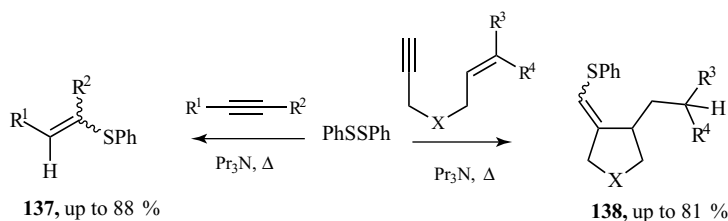


Figure 86 Amine-mediated activation of disulfides followed by addition or addition/cyclization.

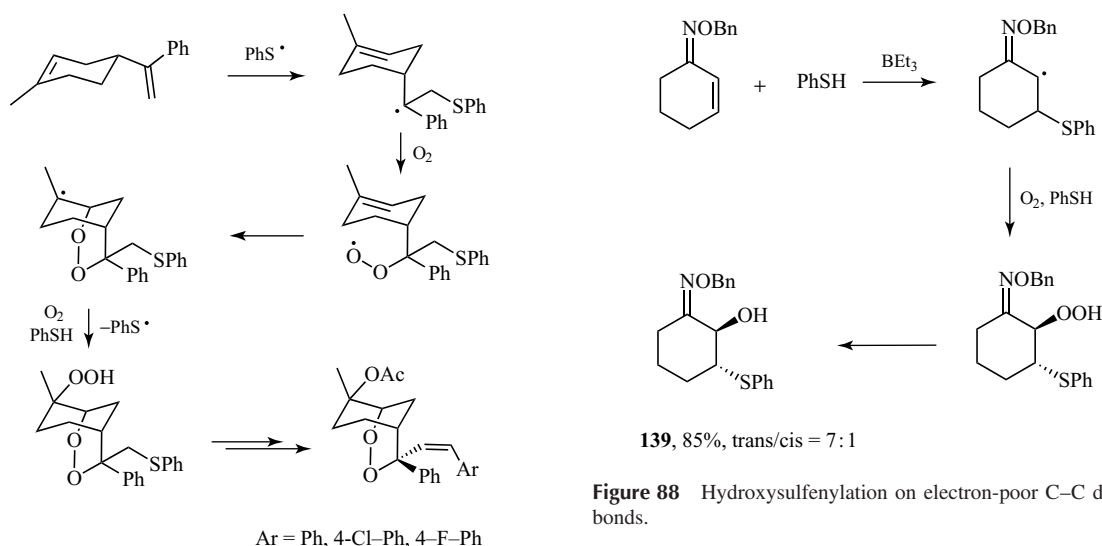


Figure 87 Hydroxysulfenylation of 1,5-dienes affording endoperoxides.

ring-opening of the cyclopropyl motif. The resulting carbon-centered radical reacts with oxygen as in the previous case to deliver a linear α -hydroxyl ω -thiyl imine.

Jugé has coupled free-radical peroxy sulfidations of aryl- and alkyl-substituted olefins with a catalytic decomposition of the resulting hydroperoxide adduct (such as **141**, Figure 89) with several metal–salen complexes (**140**).²²⁹ This is a very clever way of achieving oxidative cleavage of the olefins with molecular oxygen. Evidence for a radical mechanism was deduced from the rapid isomerization of *cis*- to *trans*-stilbene before consumption of the thiol and the concomitant formation of the carbonyl derivatives.

Wille reported that thiyl radical can activate molecular oxygen, and through this approach developed a new method for the oxidative conversion of

disubstituted alkynes to α -diketones.²³⁰ Mechanistic studies indicate that this process, which proceeds without full cleavage of the alkyne bond, is initiated by intermediately formed thiylperoxyl radicals.

Wille has recently extended her examination of the self-terminating radical cyclization to thiyl radicals,²³¹ which fared poorly or not at all in that context. Thus, thiols might be useful partners for studying the crucial H-atom translocation step of the self-terminating process.

Addition onto carbon–heteroatom multiple bonds of thiyl radical has been extended to isocyanides. The group of Ogawa reported methods for the bithiolation, thiotelluration, and thioselenation of these derivatives.^{232,233} Upon visible light irradiation, very selective reactions are achieved, and the former method was applied to the synthesis of heterocycles belonging to the class of indoles (resp. quinolines) using *o*-vinyl (resp. *o*-allyl) substituted phenylisocyanides.

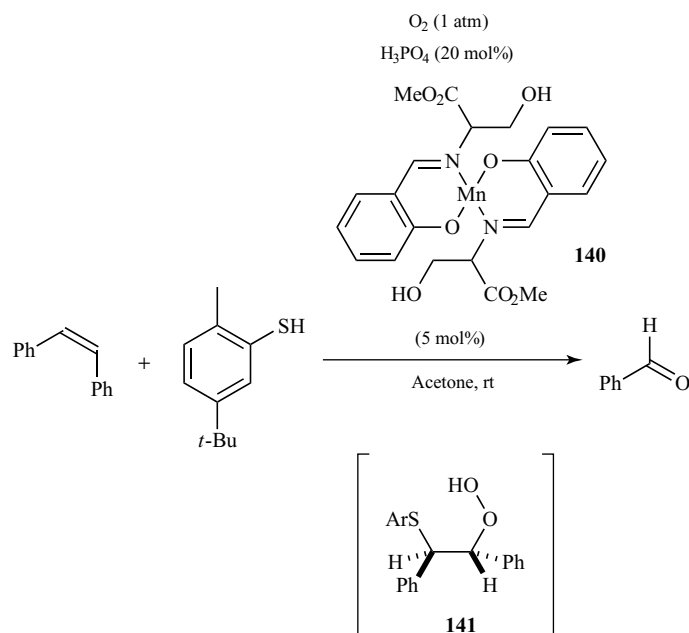


Figure 89 Thiyl-radical-promoted oxidative cleavage of olefins.

Manganese salts were used as catalysts for free-radical thiocyanation of indoles and anilines by Zou and Zhang.²³⁴ Ligand exchange on $\text{Mn}(\text{OAc})_3$ by a thiocyanate anion followed electron transfer to the metal-center-generated S-centered radicals, which added to electron-rich double bonds. On anilines, the reaction showed exclusive para-regioselectivity.

Wu reported manganese-catalyzed free-radical cyclizations of thioformanilides.²³⁵ Microwave irradiation was required to access the corresponding 2-substituted benzothiazoles. The synthesis of benzothiazoles (**142**) from the corresponding *N*-arylthioamides has been achieved in several other ways to exploit the reactivity of thiyl radicals. Various oxidants, such as halides,²³⁶ hypervalent iodine derivatives,^{237,238} and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),²³⁹ have been successfully employed. A recent approach introduced a photoinduced electron transfer by chloranil.²⁴⁰ The best results were obtained with electron-rich *N*-aryl rings. Conversely, Wang has shown that the reaction of electron-poor thioamide derivatives favors dimerization to the corresponding disulfides (**143**, Figure 90).²⁴¹

Similarly, the reaction of acyl thioformanilides and activated methylene nucleophiles—such as

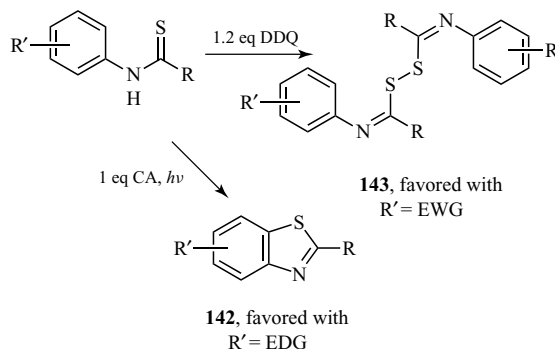


Figure 90 Cyclization versus dimerization upon radical activation of thioformanilides.

malononitriles or cyanoacetates—delivered penta-substituted dipyrrole disulfides.²⁴²

Naumov and Schöneich have investigated *in silico* the addition of cysteine thiyl radicals to phenylalanine (Phe) and tyrosine (Tyr).²⁴³ DFT calculations showed that this highly important bioradical may add intramolecularly to neighboring aromatic rings in Phe and Tyr, but that the π complexes are more stable in water than the fully formed cyclohexadienyl adduct radicals.

Photoinduced thiol–ene coupling is a tool widely used in polymer and bioorganic chemistry because it allows convergent coupling of two subunits via photoinduced radical hydrothiolation (see **Radical Thiol–X Click Chemistry**).^{244,245} A full review of these topics exceeds the scope of this review. Nonetheless, this approach has also been successfully applied to molecular synthesis, for example, for the synthesis of thiodisaccharides.²⁴⁶

In the context of thiyl radical reactions, xanthates and Barton's ester represent a well-known tool in synthetic organic chemistry. The former topic is examined in detail in another part of this encyclopedia (see **Xanthates and Related Derivatives as Radical Precursors**), while the latter has been highlighted in a very recent review.²⁴⁷

5.3 Elimination and Fragmentation of Sulfur-Centered Radicals and Radical Ions

Sulfur-centered radical cations can also fragment. This has been studied extensively by the Baciocchi/Lanzalunga group because of their relevance for the understanding of enzymatic redox processes. Thus, the physical organic parameters of the fragmentation of sulfide radical cations to carbocations and thiyl radicals^{248,249} as well as that of sulfoxide radical cations to carbocations and sulfinyl radicals²⁵⁰ have been determined. The latter is two orders of magnitude faster than that of the corresponding sulfides. Therefore, the general rule of reactivity that is valid for β -eliminations of β -sulfur radicals to form alkenes can be extended to radical cations, probably for the same reason (higher stability of the sulfinyl radicals).

Radiolysis-produced carbon dioxide radicals could efficiently reduce sulfonium salts through one-electron reduction in aqueous media.²⁵¹ The resulting sulfur-centered radical fragments to the most stable radical, in the reactivity order benzyl > substituted alkyl > methyl > phenyl.

Studer has reported a (moderately) atroposelective radical aryl migration involving sulfonates.²⁵² The key step in this process is a β -fragmentation of an alkoxysulfonyl radical which regenerates aromaticity.

Kampmeier and Lund have examined the regioselectivity of the bond cleavage of 9-*S*-3-sulfuranyl radicals in extraordinary depth.²⁵³ Selectivity for the fragmentation derives not only from the structure of the hypervalent radicals but also from the potential of the reductant.

Minozzi and Nanni investigated the selective C–S β -scission of thioimidoyl radicals as an effective tool for reductive defunctionalizations and intermolecular additions to electron-rich olefins.^{254,255} They propose that a sulfanyl radical—generated from a thiol and AIBN—adds to an isocyanide to yield an alkyl radical by fast β -fragmentation of the above-mentioned thioimidoyl radical **144**. This method delivers an isothiocyanide together with the desulfurated product **145** from the reacting isocyanide (Figure 91).²⁵⁶

Renaud has proposed a novel method for the efficient formation of carbon–nitrogen bonds via reaction of carbon radicals with sulfonyl azides.^{257–260} The success of the protocol—which relies on a key β -elimination of a sulfonyl radical—lies in the electrophilic character of azides (see **Unusual Radical Acceptors**). Thus, the azidonation process is particularly efficient with nucleophilic (alkyl) radicals, whereas it is slow with ambiphilic or electrophilic ones. The authors expanded these findings by coupling this process with intramolecular and intermolecular C–C bond-forming steps. They applied their method to the synthesis of several alkaloid skeletons: pyrrolidinones (**146** and **147**,²⁶¹ Hyacinthacin A₁,²⁶² and spirolactams²⁶³) (Figure 92).

Homolytic substitutions, which can be seen formally as α -elimination events, are a staple of sulfur radical chemistry. They are covered in depth in the corresponding article (see **Intramolecular**

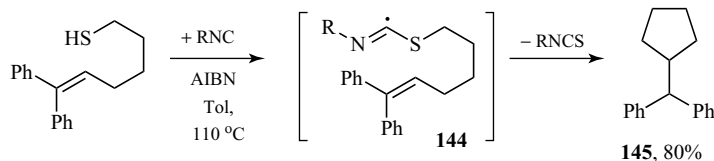


Figure 91 C–S bond cleavage triggered by isocyanides.

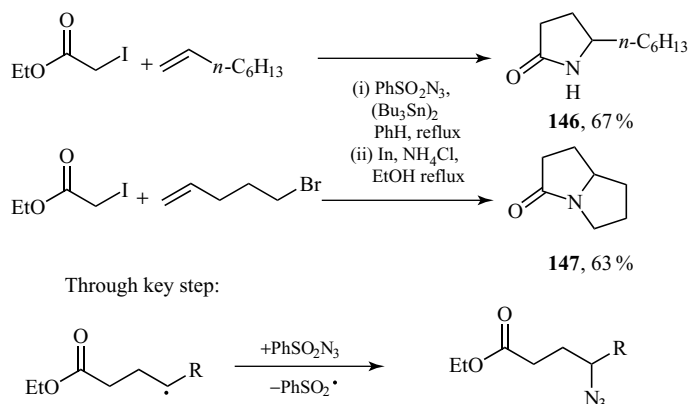


Figure 92 Introduction of an azide functional group on alkyl radicals and one of its selected synthetic applications delivering pyrrolidinones.

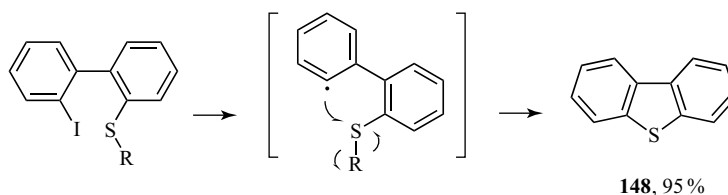


Figure 93 Homolytic substitution at sulfur atom in the synthesis of dibenzothiophenes.

Homolytic Substitutions in Synthesis), so only a brief presentation is given here.

One of their relevant applications is the synthesis of fused aromatic polycyclic compounds. The group of Maruoka employed *o*-(*o*-iodophenyl)phenylthioethers to trigger the formation of the corresponding dibenzothiophenes (**148**, Figure 93) using BET_3 as initiator.²⁶⁴

More recently, Ila reported the synthesis of substituted benzothiophenes.²⁶⁵ We extended this reactivity to the more oxidized sulfoxides and sulfinamides.^{266,267}

6 SELENIUM-CENTERED RADICALS

Discovered in 1817, selenium has long been avoided by organic chemists owing to its high toxicity. However, for the last 50 years the element has demonstrated unexpected and multifaceted properties which have found soaring applications.^{268–271} Indeed, selenium was shown to be an essential trace element for mammalian life, and selenocystein, present in the active site of glutathione peroxidase,

was recognized as the 21st natural amino acid. In the field of radical chemistry, selenium precursors are particularly attractive as will be illustrated in this review. Radical reactions using selenium precursors have been reviewed in depth by Renaud²⁷² in 2000, so only the literature starting from this year will be covered here.

6.1 Physical Organic Background

Over the past decades, many organoselenium compounds designed to mimic the activity of selenoenzyme glutathione peroxidase (GPx) have shown promising antioxidant activities, consequently attracting the attention of the pharmaceutical industry.²⁷³ However, the exact mechanism of the redox processes involved is still unknown. Several theoretical and experimental studies on selenium radicals have been performed to make sense of the chemistry.^{274–276} The selenocysteinyl radicals were generated by laser flash photolysis, using a photolabile protecting group, and characterized by

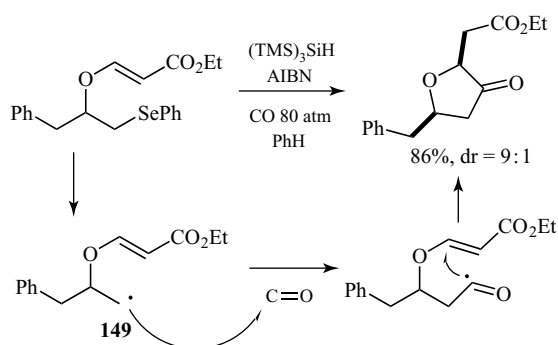


Figure 94 Synthesis of tetrahydrofuran-3-ones by tandem radical carbonylation/cyclization.

time-resolved UV–Vis, EPR, and Fourier transform infrared spectroscopy.²⁷⁷

Using photomodulated voltammetry, Daasbjerg measured the reduction and oxidation potentials of a set of parasubstituted phenylselenanyl radicals.²⁷⁸ The values obtained were $E^{\text{ox}}_{1/2} = 0.70$ V versus saturated calomel electrode (SCE) and $E^{\text{red}}_{1/2} = -0.06$ V versus SCE for the unsubstituted phenylselenanyl radical. For the substituted compounds, both the reduction and oxidation potentials correlated linearly with the Hammett substituent coefficients.

6.2 Homolytic Substitutions at Selenium

6.2.1 Substitution by Tin- or Silicon-Centered Radicals: Phenylselenium as a Leaving Group for the Generation of Carbon-Centered Radicals

Organo selenium compounds are readily available precursors for the generation of carbon radicals. Furthermore, unlike the tin halide residues obtained from tin hydrides, the seleno-tin side products generated are usually stable on silica gel,

and easily removed from the reaction products. Carbon-centered radicals can also be generated by the homolytic cleavage of the carbon–selenium bond under irradiation,^{279,280} or by photoinduced SET.²⁸¹

The group transfer reactions of PhSe derivatives will not be detailed in this section since they are covered in another part of this Encyclopedia (see **Halogen and Chalcogen Transfer Chemistry**).

The selenium atom in phenylselenium groups can undergo homolytic substitution from tin or silyl radicals to generate alkyl radicals (even primary). In new installations, those were employed, for example, in *5-exo-trig*^{282,283} or *7-endo-trig*²⁸⁴ cyclizations. Adding a further level of complexity, Engman described a cascade where the radical **149** generated is carbonylated by carbon monoxide before the *5-exo-trig* reductive cyclization^{285,286} (Figure 94).

Alkoxy-substituted alkyl radicals were also successfully generated starting from stable O,Se-acetals. Vidal treated (phenylseleno)methyl aryl ethers with tri(trimethylsilyl)silane (TTMSS) and AIBN to form arylmethoxy radicals that added intramolecularly onto ketimines.²⁸⁷ Anomeric radicals can easily be generated by this approach.^{288–290} Thus, Shuto has reported the synthesis of β -C-glucoside **151** via the radical cyclization of silicon-tethered 1- β -phenylseleno-D-glucose derivative **150** (Figure 95).²⁹¹ Owing to the presence of bulky protecting groups, the substrate is restricted in a 4C_1 conformation. Generation of the anomeric radical through treatment with Bu_3SnH and AIBN leads to an uncommon β -selective *9-endo-trig* cyclization because of the anomeric effect. An oxidative Si–C bond fission was finally performed to obtain the desired β -C-glucoside **151** in 44% overall yield.

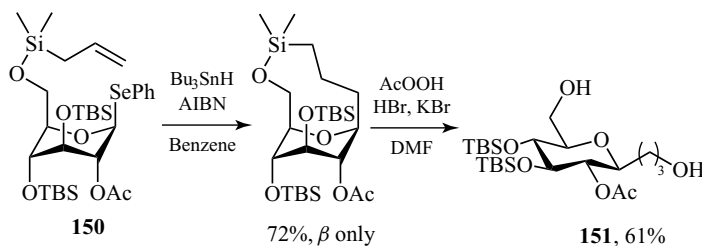


Figure 95 β -Selective radical C-glycosylation using a conformationally restricted 1-phenylseleno-D-xylose derivative.

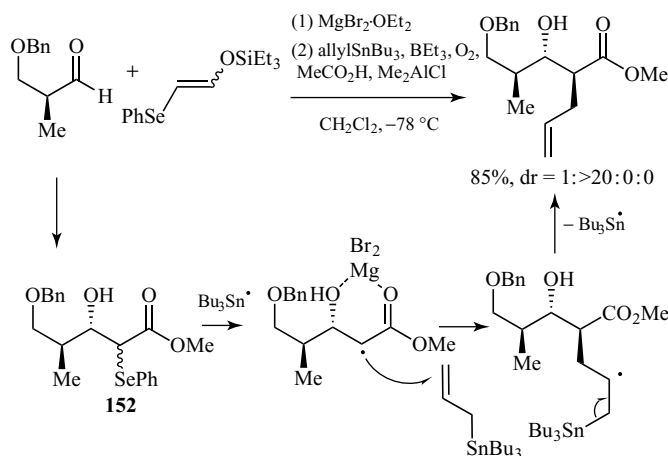


Figure 96 α -Selenoester intermediate in diastereoselective tandem Mukaiyama/radical allylation.

α -Carbonyl seleno compounds have been widely used in radical synthesis because they are readily synthesized and provide a convenient access to tertiary or quaternary stereogenic centers.^{292,293} Thus, Guindon has developed a tandem Mukaiyama reaction/free-radical allylation where the intermediately formed α -selenoester **152** is reduced in the presence of allyltributyltin, Et_3B , and a Lewis acid to form stereo-defined quaternary centers via diastereoselective intermolecular radical allylation (Figure 96).^{294,295}

Unlike acyl halides, acyl selenoesters are very efficient precursors for the formation of acyl radicals. This property has been extensively exploited in the radical synthesis of polyheterocyclic compounds.²⁹⁶ It has been newly illustrated by Takahashi, who reported the 5-*exo*-trig cyclization of selenocarbonates to diastereoselectively form γ -lactones.²⁹⁷ Bennasar especially studied the generation of 2-indolylacyl radicals from the corresponding acylselenium precursors under hexabutyltin-*h* ν or Bu_3SnH -initiator conditions.^{298–301} She recently described a new route to the alkaloid isodasycarpone from the key 6-*exo*-trig cyclization of selenoester **153** (Figure 97).³⁰²

Imidoyl phenylselenanides are also efficient precursors for the generation of imidoyl radicals, as demonstrated by Bowman.³⁰³ He successfully used this approach to prepare the anticancer alkaloid Ellipticine through a radical cascade (Figure 98).³⁰⁴

Yoshimura has reported the radical synthesis of *C*-cyclonucleosides by treatment of

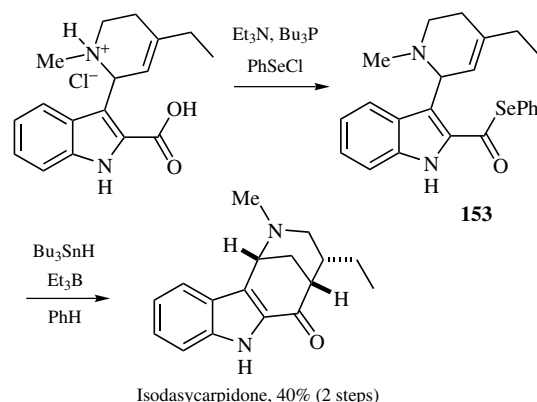


Figure 97 Synthesis of isodasycarpone by 6-*exo*-trig cyclization of a selenoester.

6-phenylselenouridine derivatives with TTMSS and AIBN.³⁰⁵ The reaction proceeded via a vinyl radical, which underwent hydrogen transfer and rebound cyclization.

6.2.2 Homolytic Substitution by Carbon-Centered Radicals

Diselenides possess an efficient carbon-radical capturing ability. The rate constant for the $\text{S}_{\text{H}}2$ reaction of a 5-hexenyl radical with $(\text{PhSe})_2$ was estimated to be $1.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, compared to $7.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ for $(\text{PhS})_2$. Ogawa beautifully exploited the differences of reactivity between disulfides and

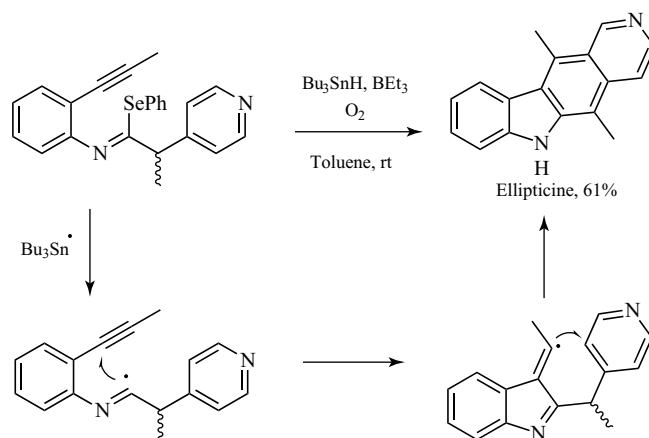


Figure 98 Radical synthesis of Ellipticine.

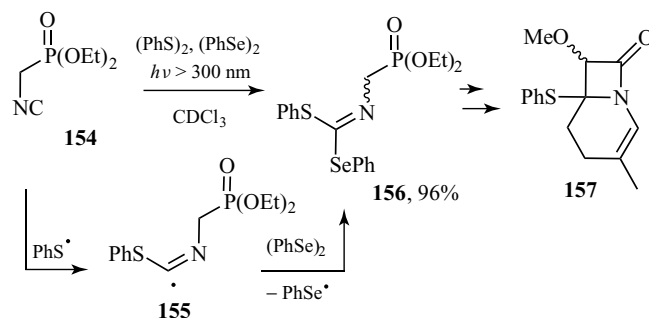


Figure 99 Selective thioselenation of isocyanide **154**.

diselenides to perform the selective thioselenation of aromatic isocyanides.²³³ A mixed system of $(\text{PhS})_2$ and $(\text{PhSe})_2$ was irradiated in the presence of an isocyanide such as **154**. *In situ*-formed thiyl radical added to the isocyanide carbon, generating intermediate **155**, which was selenylated by $\text{S}_\text{H}2$ reaction from diphenylselenide. The thioselenated product **156** was carried forward to the carbacephem **157** (Figure 99). The same approach was used to perform the selenoperfluoroalkylation of acetylenes from a mixed system of perfluoroalkyl iodide and diphenyl diselenide under irradiation.³⁰⁶

Zard reported an interesting procedure in which a triphenylmethylhydrazide precursor is oxidized by phenylselenenic acid in the presence of a catalytic quantity of diphenyl diselenide.³⁰⁷ The oxidation generated diphenyldiselenide and the corresponding triphenylmethyl diazo derivative which spontaneously fragmented to deliver an acyl radical. The latter cyclized to an internal olefin to form

a carbon-centered radical which was captured by diphenyl diselenide.

Homolytic substitution at selenium is possible when the radical extruded is stabilized. Thus, ring closure of aryl radicals at selenium with extrusion of benzyl radical proceeds at a rate constant of $\sim 3 \times 10^7 \text{ s}^{-1}$ at 80°C , which is 2–4 times faster than the same reaction at sulfur.³⁰⁸ In-depth mechanistic studies were carried out by Schiesser,³⁰⁹ as well as the efficient synthesis of biologically active heterocycles.^{310–317} A recent example details the synthesis of selenochromanes via tandem intermolecular addition/intramolecular homolytic substitution at selenium.³¹⁸ Benzylic xanthates such as **158** led to the stabilized, weakly nucleophilic benzyl radical **159** under irradiation and thermal conditions. This latter added to an electron-poor olefin, and the radicals thus obtained cyclized to quantitatively deliver the six-membered selenium-containing rings (Figure 100). This reaction was also possible by

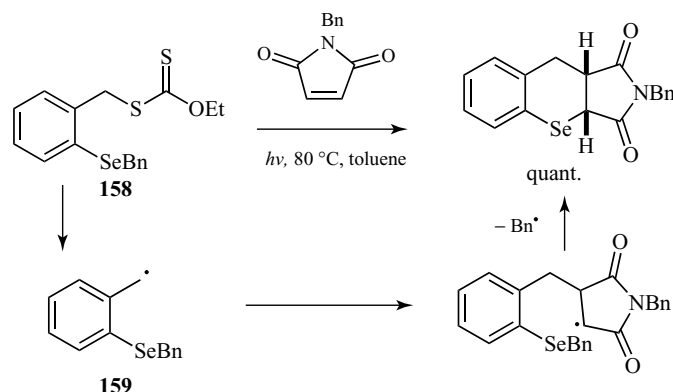


Figure 100 Tandem intermolecular addition/intramolecular homolytic substitution at selenium.

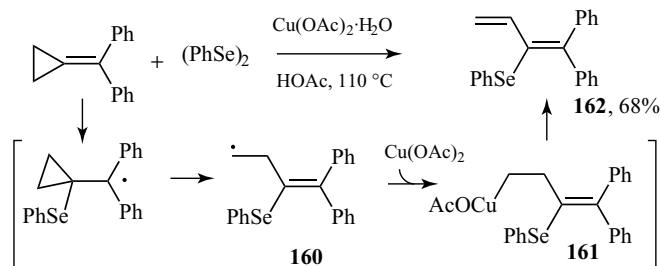


Figure 101 Formation of 2-phenylselenylated butadienes.

treatment of the reagents with triethylborane and O_2 at $0^\circ C$.

6.3 Additions of Selenium-Centered Radicals to Insaturations

Selenium radicals are more stable than their sulfur counterparts, but are less reactive toward insaturations. For example, the rate constant of addition of $PhSe^\bullet$ to vinyl monomers is 10–50-fold smaller than that of $PhS^\bullet$ to the same olefin.³¹⁹ Nevertheless, several interesting reactions triggered by intermolecular additions of $PhSe^\bullet$ to multiple bonds have been reported. Since the addition of selenium radicals is a reversible process, a radical trap must be used to pull the equilibrium.

Huang described the addition of the phenylselenium radical to methylenecyclopropane in the presence of copper acetate.³²⁰ Ring-opening of the cyclopropane led to homoallyl radical **160**, which was presumably converted to the organocopper intermediate **161**. Final β -H elimination gave

phenylselenyl-substituted buta-1,3-diene **162** (Figure 101).

Several tandem reactions initiated by addition of $PhSe^\bullet$ and terminated by S_H2 selenylations have been reported. They provide diselenated compounds that can be easily further functionalized.^{321–323} Ogawa developed a highly selective four-component coupling radical reaction of an alkyne, two differently polarized olefins, and diphenyl diselenide.³²⁴ Irradiation generated $PhSe^\bullet$, which added to the alkyne. Owing to polar effects, electrophilic vinyl radical **163** was selectively trapped by electron-rich 2-methoxypropene, affording a new nucleophilic radical **164**. Reaction of the latter with the electron-poor olefin produced 5-hexenyl radical **165**, which underwent 5-*exo*-trig ring closure. The final α -seleno radical **166** ultimately performed the S_H2 termination to give the desired product after six elementary steps (Figure 102).

$PhSe^\bullet$ can also be generated from sources other than diselenides. Yao related the 1,4-radical addition of benzeneselenenol to α,β -unsaturated ketones under (oxidizing) SET conditions (ceric(IV)

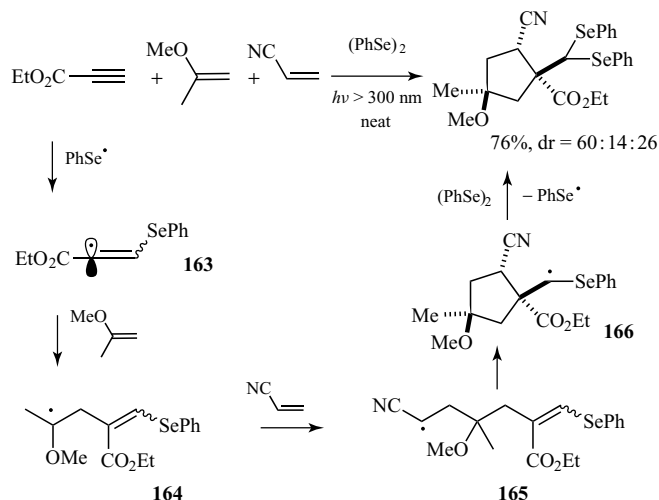


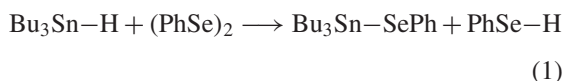
Figure 102 Four-component coupling cascade.

ammonium nitrate, CAN).³²⁵ Alternatively, Huang described the reductive formation of $\text{PhSe}^\bullet$ from *N*-(phenylseleno)phthalimide and $(\text{NH}_4)_2\text{S}_2\text{O}_8$.³²⁶

6.4 Benzeneselenenol as Radical Mediator

Benzeneselenenol is an especially fast reducing agent. Newcomb has measured that 6,6-diphenyl 5-hexenyl primary alkyl radical was trapped by PhSeH with a rate constant of $1.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, close to diffusion control, compared to $1.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for PhSH and $2.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for Bu_3SnH .³²⁷

The catalysis of stannane-mediated radical chain reactions by PhSeH was introduced in 1995 by Crich and has since led to numerous synthetic applications.³²⁸ In this strategy, benzeneselenenol is generated *in situ* by reduction of diphenyl diselenide with tributyl tin hydride (1). It rapidly reduces the early radical intermediates before they can react further, which regenerates tin radicals by hydrogen abstraction. This approach is often designated as *PRC* since the polarity-mismatched reduction of the nucleophilic alkyl radical by Bu_3SnH is substituted by two polarity-matched steps involving PhSeH .



This catalysis can block radical rearrangements and other less rapid transformations, such as the

rearomatization of arenes^{329–332} or heteroaromatic rings.³³³ For example, Crich reported the reductive radical arylation of benzene as the key step for the synthesis of phenolic cyclitol derivatives. In this key step, phenolic iodide **167** was treated with Bu_3SnH , AIBN, and a catalytic amount of diphenyl diselenide. The aryl radical **168** generated added to benzene forming cyclohexadienyl radical **169**, which was trapped by benzeneselenenol and led to cyclohexadiene **170** (Figure 103).³³⁴

Schiesser reported that the yield of the hydrostannylation of a silyl enol ether increased from 20% to 95% when 10 mol% of diphenyl diselenide was added, because the reduction steps became faster than the reverse β -fragmentation of the stannyl radicals.³³⁵

Clive reported that the yield of the cyclization of alkyl radicals onto *O*-trityl oximes rose sharply in the presence of $(\text{PhSe})_2$ (Figure 104). In that case, benzeneselenenol was thought to rapidly reduce the persistent trityl radical and thus prevent the disruption of the chain propagation.³³⁶

7 CONCLUSIONS AND PERSPECTIVES

For the last five decades, radical transformations have progressively merged into the mainstream synthetic chemistry. In that evolution, radical chemistry based on the main-group elements has occupied a

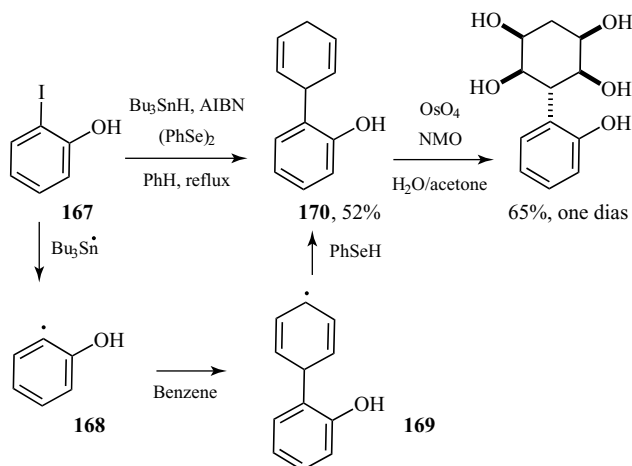


Figure 103 Synthesis of a *meso*-tetraol via radical dearomatization and osmylation.

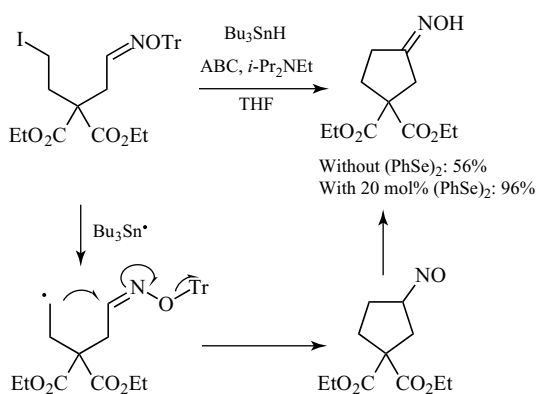


Figure 104 Effect of diphenyl diselenide on the radical closure onto *O*-trityl oximes.

prominent position. This is certainly due to the fact that main-group elements are at the origin of very unique and intriguing opportunities.

In this review, we have discussed the recent advances, over the last 10 years, in homolytic processes involving nitrogen-, oxygen-, phosphorus-, sulfur-, and selenium-centered radicals which have constituted extremely rich sources of molecular innovation. Modes of generation of these highly reactive entities, mechanistic considerations in multistep sequences, as well as stereoselectivity issues have been thoroughly addressed. Playing with heteroatoms and their connected functionalities has given rise to tremendous developments, and their

various applications in terms of substrates and finality perfectly illustrate the good health of main-group radical chemistry. Thus, just to name a few, total synthesis of natural products, glycochemistry, and even material sciences or bioorganic chemistry based on thiol–ene coupling processes, for instance, have benefited from all these advances.

A notable feature of the last decade's progress is the invention of catalytic processes to generate radical intermediates, so that, based on a variety of metal complexes or pure organic agents, very versatile transformations have been devised. It is obvious that besides the neat advantage to escape from toxic and stoichiometric mediators, catalysis constitutes a reliable entry into selectivity and, if relevant, asymmetric synthesis, by simply adjusting the electronic nature as well as the steric environment of the ligands. It is most likely the area where we can anticipate the best crop of novel findings.

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Organic Electron Donors

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1 INTRODUCTION

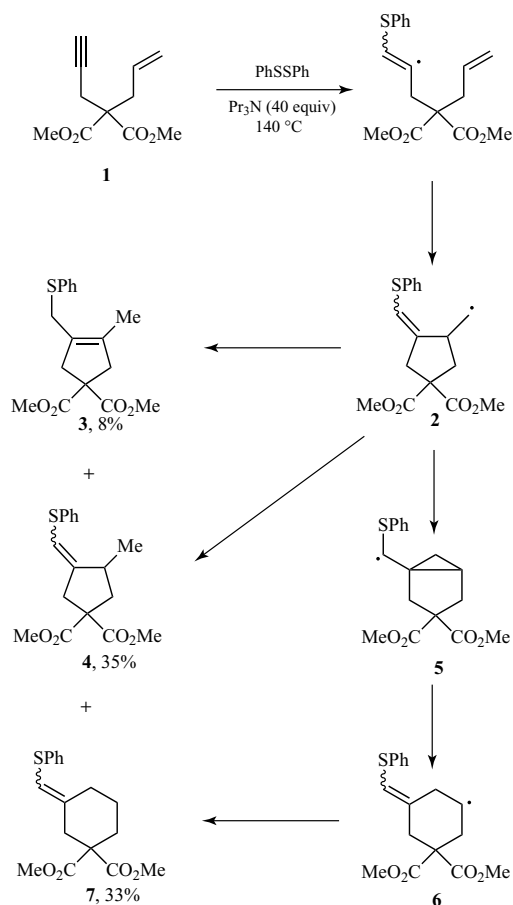
Organic molecules can behave as electron donors to form radical cations¹ and, subsequently, radicals under many conditions. They can do so spontaneously through encountering (i) a reagent or (ii) a partner substrate that has sufficient oxidizing power, or they can be induced to donate an electron photochemically, electrochemically, or under exposure to radiation conditions (including mass spectrometry). This article focuses on neutral organic molecules that are prone to oxidation by electron transfer, either intrinsically or under the conditions of the reaction, whether in intermolecular or intramolecular manner. The coverage will certainly be selective rather than comprehensive. This article forms part of the Volume on Chemical Synthesis and so deals with reactions that may be used in synthetic studies, rather than a stricter definition of reactions that have been used in the synthesis of a natural or unnatural product. The article does not set out to cover reactions in biology or materials chemistry; those topics are for other authors. There is undoubtedly some overlap with other articles in this work, and at such instances the reader is referred to those; however, it is also useful to see something of the broad scope of organic molecules that can act as electron donors in one article.

2 SPONTANEOUS OR THERMAL ELECTRON TRANSFER TO PARTNER SUBSTRATES

This section describes reactions that occur at various temperatures including room temperature and

below, but they do not require activation by photochemical, electrochemical, or other methods. Molecules with nonbonding electrons are prime candidates for such reactions. Recently, Ishibashi *et al.*² have shown that tripropylamine reacts with diphenyldisulfide at 140 °C to give reactions with all the hallmarks of radical chemistry (Scheme 1), and it is proposed that the radicals are generated by single electron transfer (SET) to the disulfide by the amine. The thiyl radicals then add to alkenes and alkynes—thus enyne **1** affords the cyclopentenenes **3** (8%) and **4** (35%), and the cyclohexene **7** (33%); a cyclopropylcarbinyl radical rearrangement (**2** → **5** → **6**) is proposed to account for the formation of the six-membered ring. This builds on earlier examples using 1,4-dimethylpiperazine as the electron donor.³

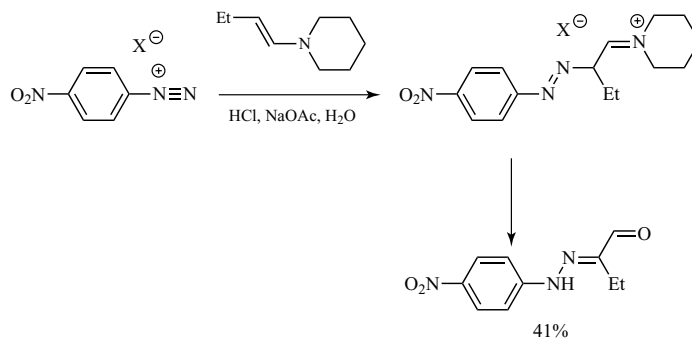
Heteroatom-substituted alkenes have featured prominently in electron transfer reactions. The ground-state SET chemistry of enamines, enols, and their derivatives with various oxidizing reagents is considered later in this article. In general, they do not undergo electron transfer with organic acceptors in the ground state; for example, with good organic electron acceptors such as arenediazonium salts, enamines undergo a simple nucleophile–electrophile reaction.^{4,5} (Scheme 2). However, when additional heteroatoms are present on the alkene, the nature of the reaction can change. The chemistry of electron-rich olefins has been reviewed.⁶ Tetrathia-alkenes are widely known and their electron transfer chemistry is dominated by the special case of tetrathiafulvalene and its analogs.



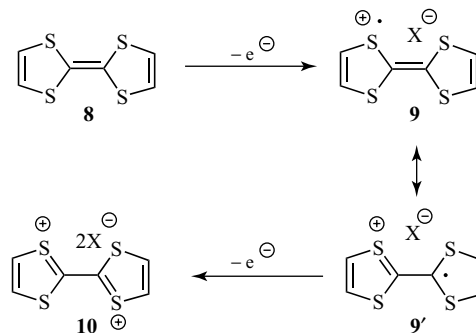
Scheme 1

2.1 Tetrathiafulvalenes

Wudl synthesized the parent tetrathiafulvalene (TTF) **8**, and characterized its radical-cation salts



Scheme 2

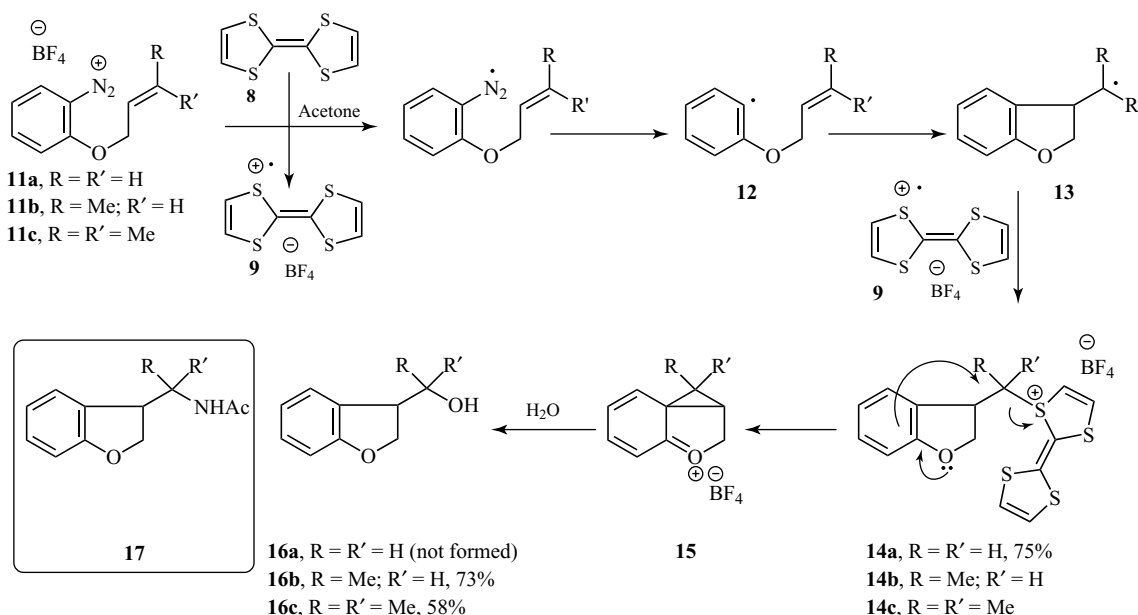


Scheme 3

9 in 1970;⁷ substituted analogs of **8** had been prepared earlier.^{8,9} The credentials of TTF in electron transfer, particularly in materials chemistry and supramolecular chemistry, are reflected in the 30 000 citations for “TTF” currently on the ISI Web of KnowledgeSM.

TTF is easily oxidized in the presence of appropriate substrates, but relatively stable to air unless photoactivated, and this stability is reflected in its availability from commercial chemicals suppliers. The oxidation potentials for TTF have been determined as $E_1^0 = +0.32\text{ V}$; $E_2^0 = +0.71\text{ V}$ versus saturated calomel electrode (SCE) in MeCN,¹⁰ involving sequential oxidation to a radical cation **9** and to a dication **10**. In the dication **10**, the aromaticity can be fully expressed (Scheme 3).

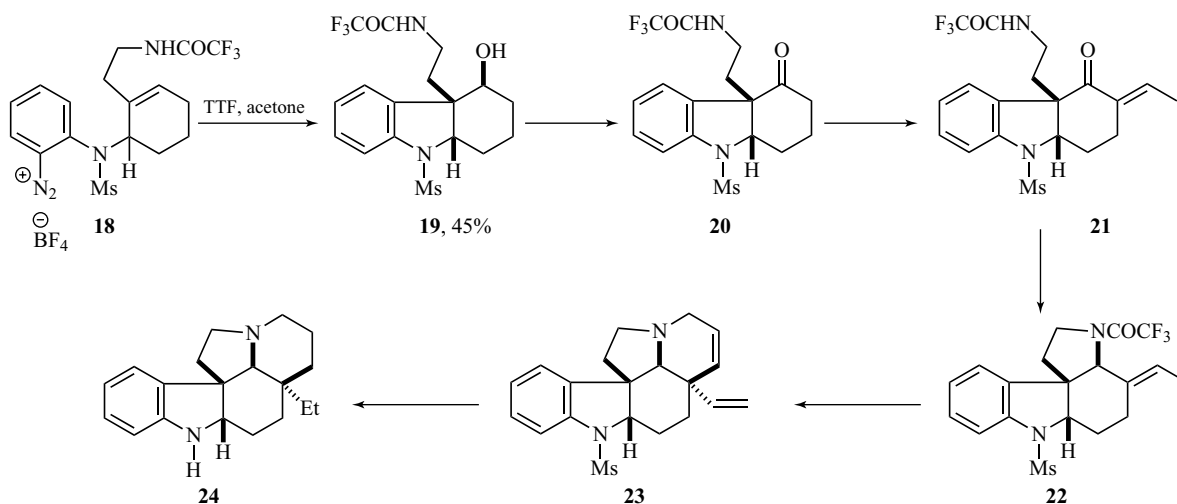
TTF forms complexes with electron-poor organic molecules such as 7,7,8,8-tetracyanoquinodimethane (TCNQ),¹¹ but as these have been used primarily in materials chemistry and as they have become so extensive, they are beyond the scope of this article and the reader is referred to an excellent review.¹²



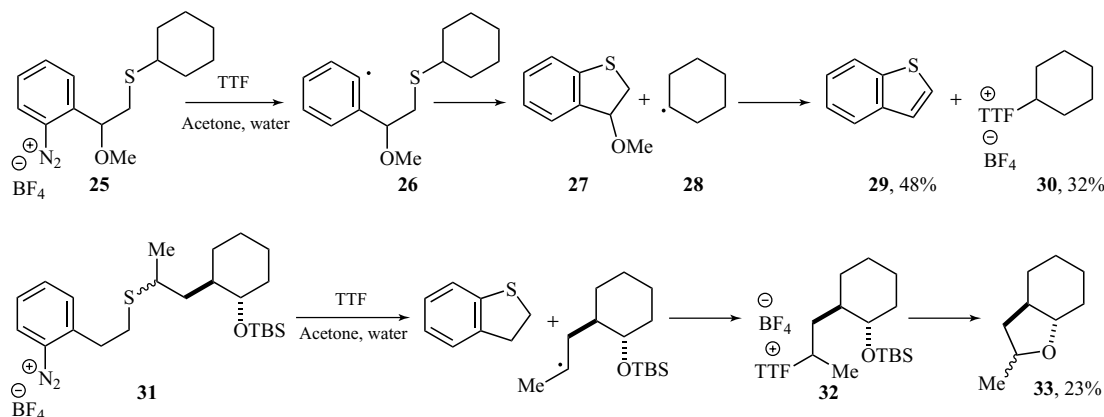
Scheme 4

Reaction of TTF with diazonium salts as organic oxidants was first mentioned in the Russian literature; these papers focused on the formation of the TTF radical cation **9** rather than on the fate of the arenediazonium entity^{13,14} and this was followed some years later by oxidation of TTF by hypervalent iodine compounds.^{15,16}

Murphy *et al.* reported that reaction of appropriately substituted arenediazonium salts **11** (Scheme 4) led to spontaneous evolution of nitrogen and formation of the aryl radical **12**.^{17,18} Cyclizations of aryl radicals afforded **13**, which trapped the TTF radical cation, **9**, derived from TTF, to afford **14**. For substrate **11a** (i.e.,



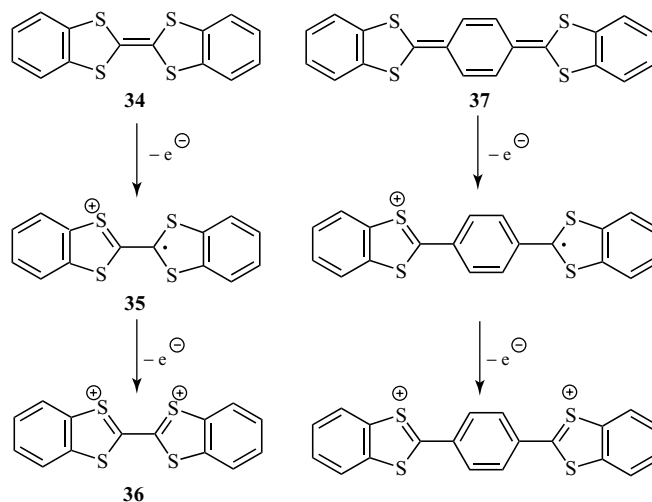
Scheme 5



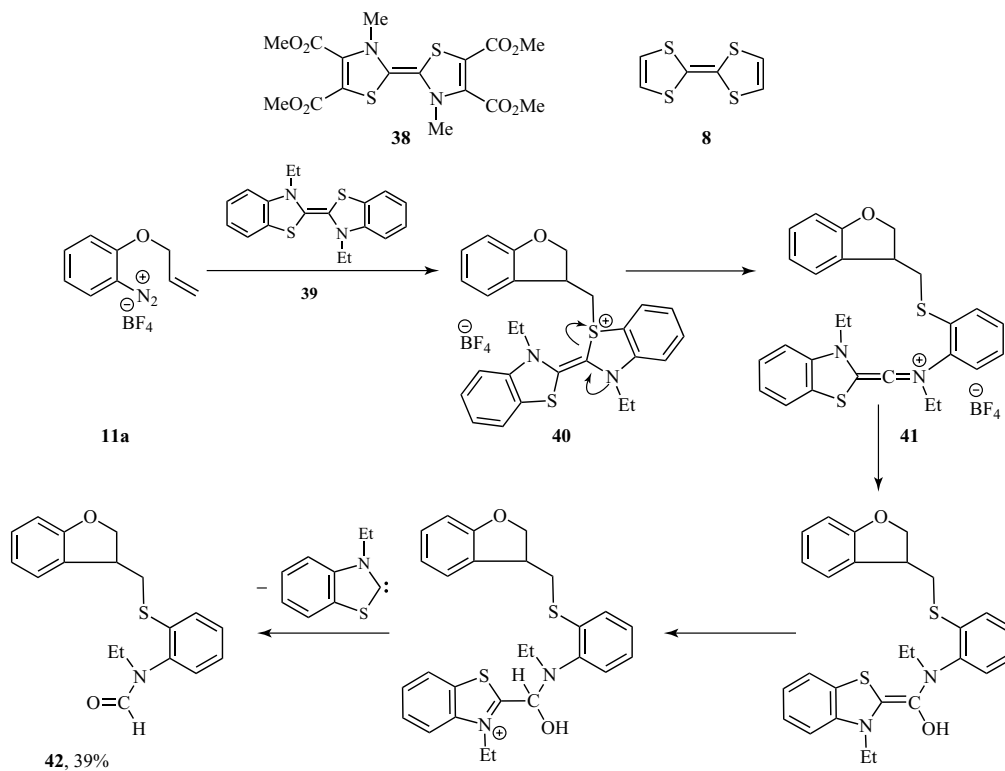
Scheme 6

R = R' = H), this product, **14a**, was quite stable, while for **11b** and **11c** the final product was the corresponding alcohol **16** when moist acetone was used as solvent. The nonsubstitution at a primary carbon in **14a** and the ready substitution at the secondary and tertiary carbons revealed this substitution as an S_N1 reaction, and evidence emerged later (see below) that the Ar–O grouping is required to trigger the displacement of the TTF from **14b**.¹⁹ In the formation of **15**, TTF is displaced and so, in principle, the compound can behave as a catalyst,²⁰ but its turnover number was not high, and investigations unearthed a number of possible novel side-reactions of TTF sulfonium salts.²¹

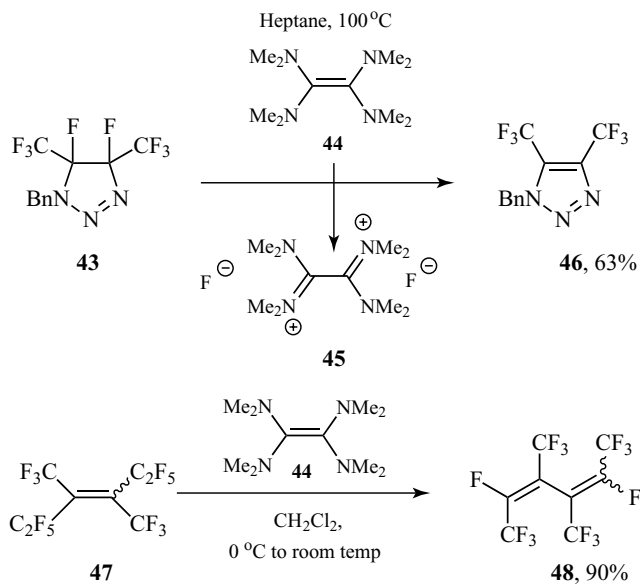
In principle, sequential C–C and C–S bond formation reactions might occur via an intermediate aryl cation rather than an aryl radical, but several factors disprove this. The regiochemistry of ring formation in **13** (five-ring rather than six-ring) is consistent with the kinetic properties of radical cyclizations. Also, arenediazonium salts can be converted into aryl cations on heating but are usually stable at ambient temperatures in solution (no spontaneous loss of N_2 occurs from most diazonium salts); furthermore, if aryl cations were intermediates arising from the decomposition of arenediazonium salts in this reaction, then the role of the sulfide would be as a cation trap,



Scheme 7



Scheme 8

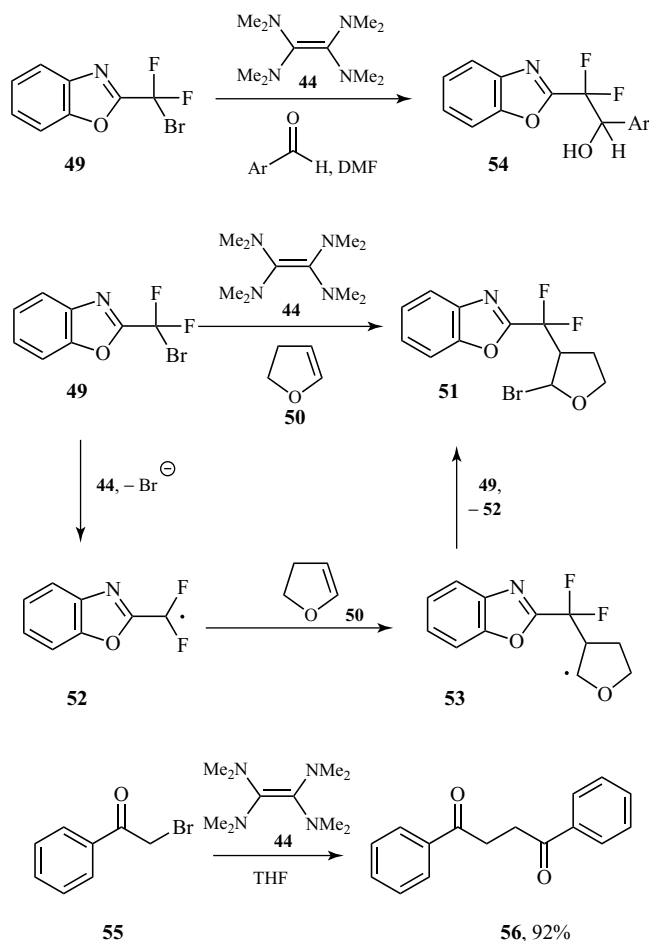


Scheme 9

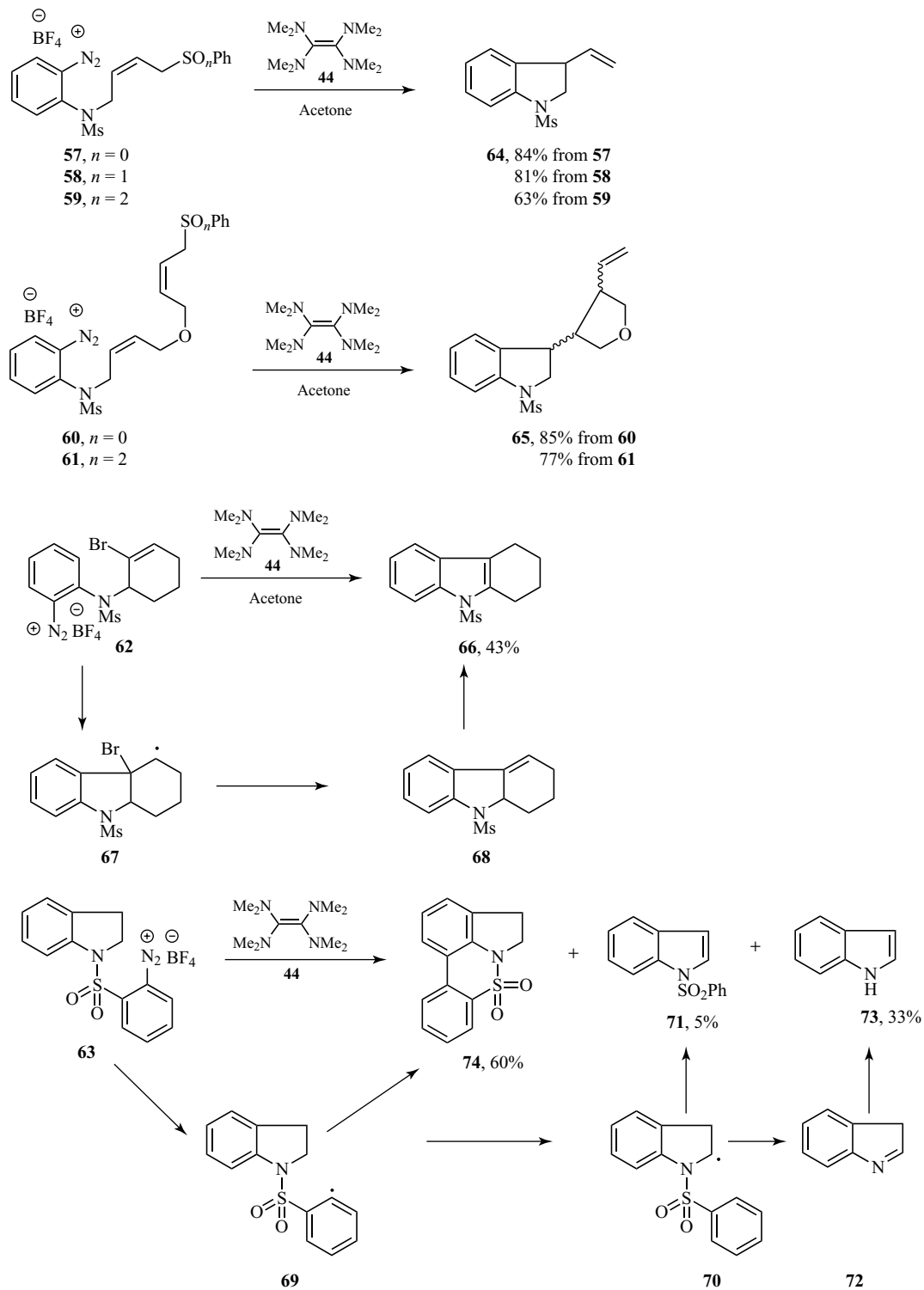
and this role could be fulfilled by sulfides other than TTF. However, trials showed that dimethyl sulfide did not trigger such reactions and did not form similar sulfonium salts, and hence the reaction is caused by the easily oxidized TTF undergoing electron transfer to the easily reduced arenediazonium salts.²² Because the overall reaction sequence featured a radical C–C bond formation and a nonradical C–O bond formation occurring by S_N1 chemistry, it was called the “radical-polar crossover” reaction, and afforded a new type of termination for aryl radicals. This traverse from radical to nonradical pathways has now been seen in a range of different types of reaction, and the term “radical-polar crossover” describes more than this TTF reaction in the literature. The reaction was extended to formation of amides instead of alcohols,

when dry acetonitrile was the solvent. Here, the intermediate cationic intermediates **15** are trapped in a Ritter-type reaction and the resulting nitrilium salts afford acetamides **17** on hydration.¹⁷

The reaction worked well in the synthesis of dihydrobenzofurans and indolines, and this led to its being harnessed as the key step in the synthesis of (±)-aspidospermidine **24** (Scheme 5).^{23,24} The conversion of diazonium salt **18** to alcohol **19** follows the path laid out for the formation of **16**. Inherent in this synthesis is the control of relative stereochemistry. The initial indoline formation occurs with cis ring-junction stereochemistry as is well preceded in radical cyclization reactions, leading the interception of carbocation intermediate by water to take place on the less crowded exo or β-face to afford **19**. Following oxidation



Scheme 10



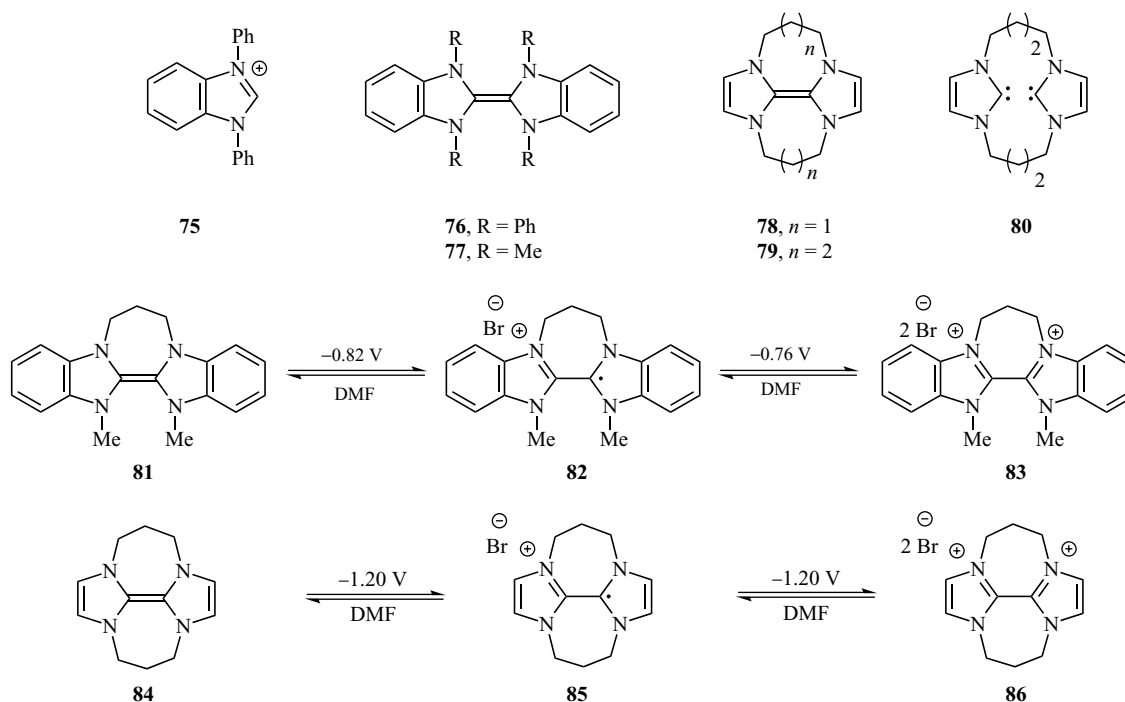
Scheme 11

to the ketone **20** and introduction of the ethylidene side-chain in **21**, the ketone was reduced to give an alcohol (α -stereochemistry) that was then displaced in an intramolecular Mitsunobu reaction to yield tertiary amide **22**. Further functionalization led to the formation of the final six-membered ring in **23**, and then hydrogenation and deprotection afforded ($\pm$)-aspidospermidine **24**.

As mentioned above, and as represented by structure **15**, the participation of the Ar–X heteroatom in displacing the TTF-derived sulfonium group was of key importance. A number of studies established that the absence of such a group prevented displacement of the sulfonium salt. Substrate **25** illustrates this point: reaction with TTF afforded the aryl radical **26** that displaced the cyclohexyl radical **28** in forming the methoxy dihydrobenzothiophene **27** (Scheme 6). The latter compound was converted into benzothiophene **29** under the conditions of the reaction, but the sulfonium salt **30** was not hydrolyzed, since in contrast to the analogous TTF salt **14**, no neighboring group was present to facilitate this. Diazonium salt **31** shows that the neighboring group does not need to be an aryl ether;

here, the silyl ether group effects the displacement within TTF salt **32**¹⁹ to afford **33**.

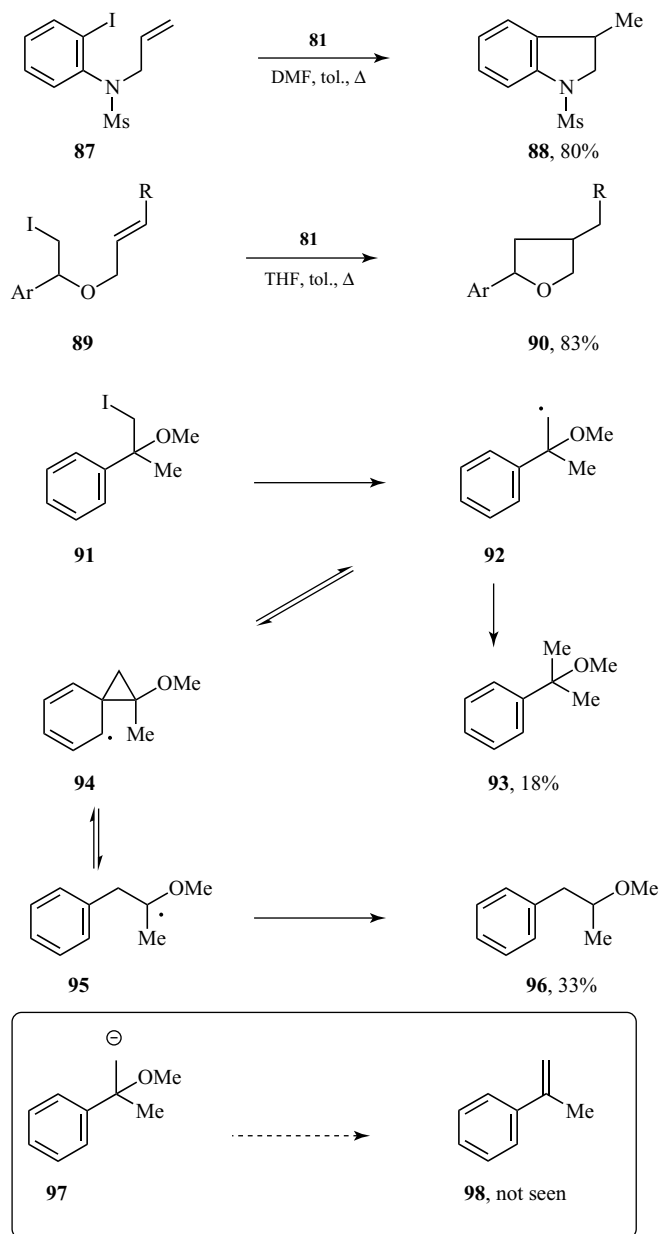
The conversion of arenediazonium salts to aryl radicals was accomplished efficiently at room temperature by an SET from TTF. Although TTF can lose a second electron in being oxidized to disalt **10**, this is relatively more difficult, and no evidence of aryl anion formation was seen with this system in reactions with diazonium salts. Comparison of the redox potentials is instructive: for TTF, $1 E^0_1 = +0.32$ V; $E^0_2 = +0.71$ V versus SCE in MeCN,¹⁰ while for an arenediazonium salt, the first electron transfer occurs at about -0.2 V versus SCE in DMF²⁵ or in MeCN.¹⁰ Even though the process appears energetically uphill, the formation of an aryl radical is accompanied by irreversible loss of dinitrogen, driving the reaction to completion. On the other hand, although the *standard* potential for reduction of an aryl radical to an aryl anion was later determined by Andrieux and Pinson²⁶ at 0.05 V versus SCE, a second electron was not transferred. (In practice, we find that the donor must have a potential circa -1 V to afford aryl anions by a second electron transfer.)



Scheme 12

The importance of aromatic stabilization energy in the oxidation of TTF had been apparent since its first synthesis. Under the same conditions in which TTF **8** had been instantaneously reactive, the dibenzoTTF **34** compound was not able to liberate N₂ from arenediazonium salts. Here, the aromatic stabilization associated with oxidation to

radical cation **35** or the dication **36** would be less than for TTF. The newly created aromatic five-membered rings in **35** and **36** were already partly aromatic due to the benzo fusion in **34**. In the search for stronger donors, Cava, Garito, and coworkers²⁷ had shown that the difficult-to-prepare sulfide **37** was a stronger donor than TTF, due to



Scheme 13

the aromatic stabilization energy associated with its oxidation, but characterization of this molecule was a challenge because of its sensitivity to oxidation. This compound shows only an irreversible oxidation in acetonitrile quoted at $E_p = -0.14$ V (if this is relative to standard hydrogen electrode (SHE), this would equate to -0.38 V vs SCE) (Scheme 7).

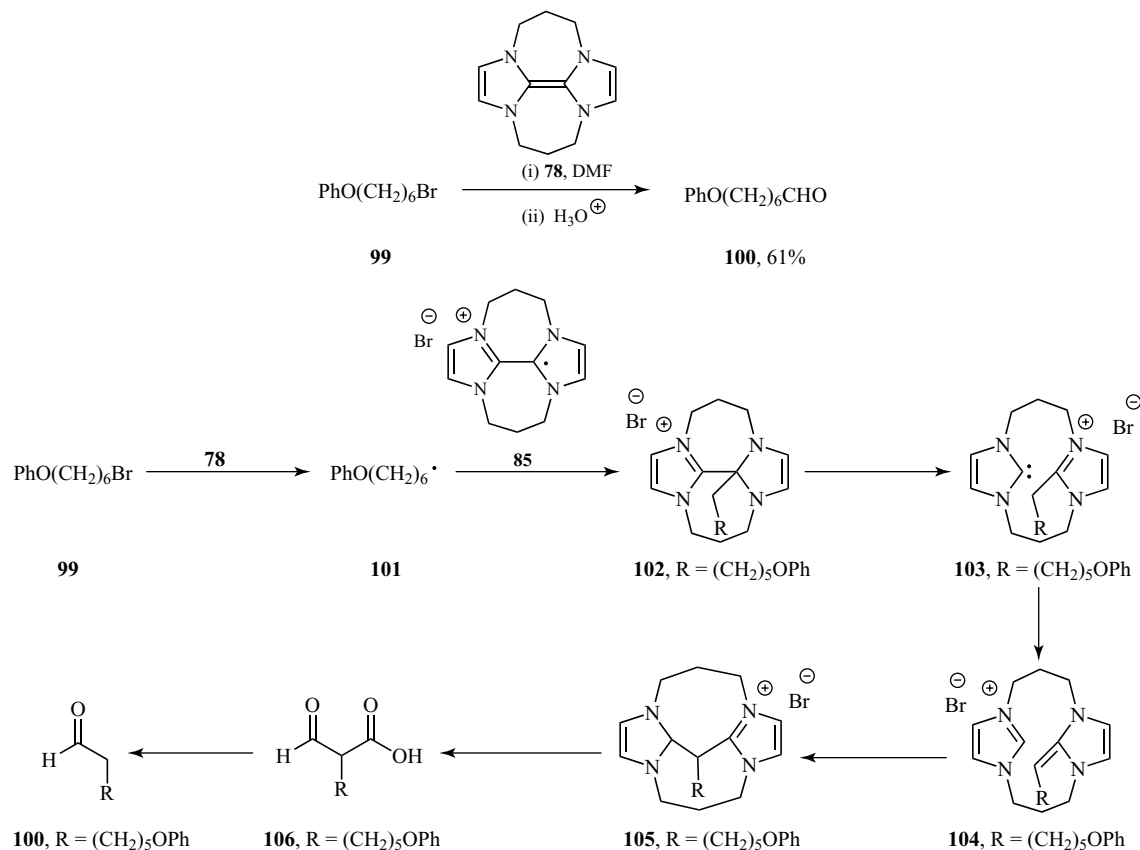
2.2 Polyaza-Substituted Ethenes

Dithiadiazafulvalenes (DADTFs) had been well investigated,^{28–30} and their oxidation had been studied. It was clear that replacing some of the sulfur atoms within TTF by nitrogen atoms afforded much more powerful donors. For example Bakker *et al.* showed that the tetraester **38** (Scheme 8) is a better reducing agent than TTF, despite the presence of the electron-withdrawing ester groups.³¹ This is due in

large measure to the stabilizing effect of the nitrogen atoms on the cationic system following oxidation, compared to sulfur.

The dibenzodiazadithiafulvalenes, being stronger donors than TTF **8**, were also able to reduce arene-diazonium salts. Murphy *et al.* treated diazonium salt **11a** with DADTF **39**.^{32,33} The contrast between sulfur and nitrogen atoms became immediately apparent, as the same products were not afforded from this reaction as from the TTF reactions. Instead, fragmentation of the intermediate **40** occurs, because of the great reactivity of the nitrogen lone-pair, leading to the ketiminium salt **41**, thereby deviating from the radical-polar pathway of TTF and affording amide product **42**.

TTF may be the most cited of the tetra-heterosubstituted alkenes, but its discovery was predated by another important molecule, namely, tetrakisdimethylaminoethene (TDAE), **44**, discovered in the industry laboratories of DuPont in



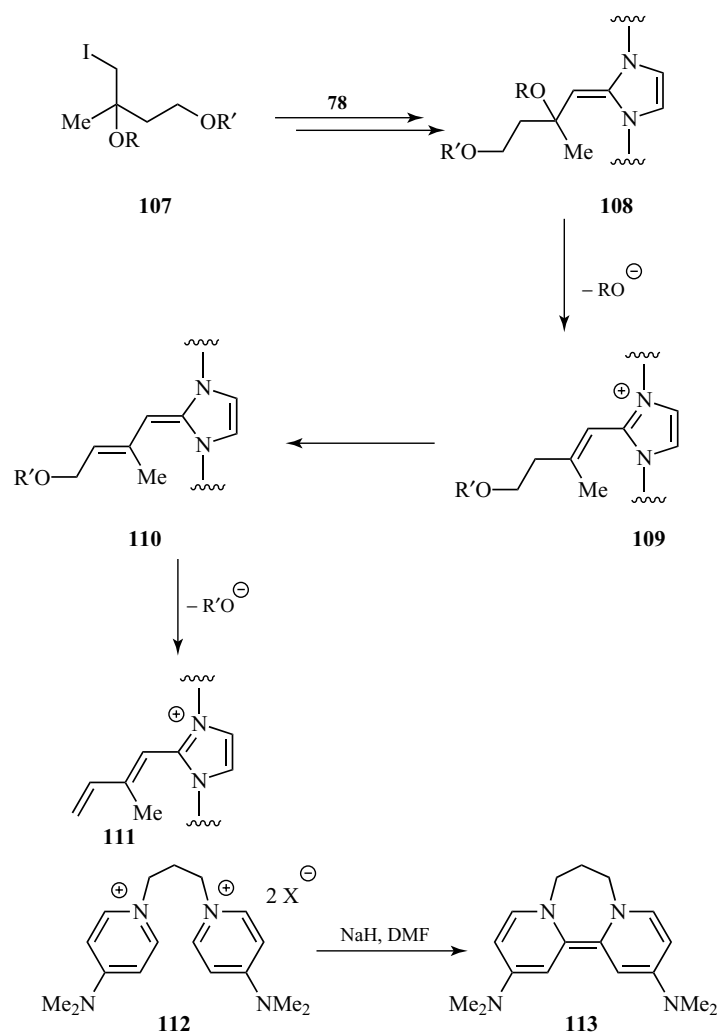
Scheme 14

1950.^{34,35} This molecule has been examined by cyclic voltammetry and provides reversible oxidation at more negative potentials than the molecules discussed so far above. The oxidation potentials for this molecule had been determined as $E^0 = -0.78$ and -0.61 V versus SCE in MeCN.³⁶ This compound has found widespread use as an electron donor since its discovery. Its oxidation potential shows as two separate peaks in acetonitrile, but as a single peak in DMF. Crystal structures of its dication salts have been determined, and show rotation of about 70° between the N–C–N planes.³⁷

Defluorination occurred when triazoline **43** was treated with TDAE **44** to afford triazole **46**.^{38,39}

(Scheme 9). The byproduct was the difluoride salt **45**. Chambers *et al.* converted fluoroalkenes, for example, **47** to fluorodienes **48** with TDAE.⁴⁰ These reactions were proposed to occur by electron transfer to the electron-deficient alkene **47** and expulsion of fluoride ion followed by another electron transfer and another loss of fluoride ion to afford **48**. More recently, formation of *o*-quinomethanes by dehalogenation of 1,2-bishalomethyl arenes by TDAE has been explored.^{41,42}

It is clear that this donor is sufficiently strong to donate two electrons to highly electron-poor halides where the resulting carbanions are well stabilized. This molecule has principally been used to transfer



Scheme 15

two electrons to electron-deficient substrates such as CF_3I and $\text{ArC}(\text{Br})\text{F}_2$ to form the corresponding trifluoromethyl anions or difluorobenzyl anions⁴³ that react with aldehydes^{43,44} (Scheme 10) and with acid chlorides.⁴⁵ These substrates appear to receive two electrons, presumably sequentially rather than simultaneously, and evidence of radical intermediates has been reported with substrate **49**. Here, the addition of the electron donor TDAE **44** is performed slowly and reaction of the benzyl radical **52** with dihydrofuran **50** affords intermediate radical **53**, followed by bromine atom-transfer from the substrate to give good yields of bromide **51**.

TDAE has been used to couple α -bromoketones, for example, **55** $\rightarrow$ **56** (Scheme 10). It is unclear whether one electron is transferred to form the radical followed by a coupling of radicals to form the product or whether two electrons are transferred to one molecule of bromoketone to form the enolate anion that then displaces bromide from another molecule in an $\text{S}_{\text{N}}2$ reaction.⁴⁶

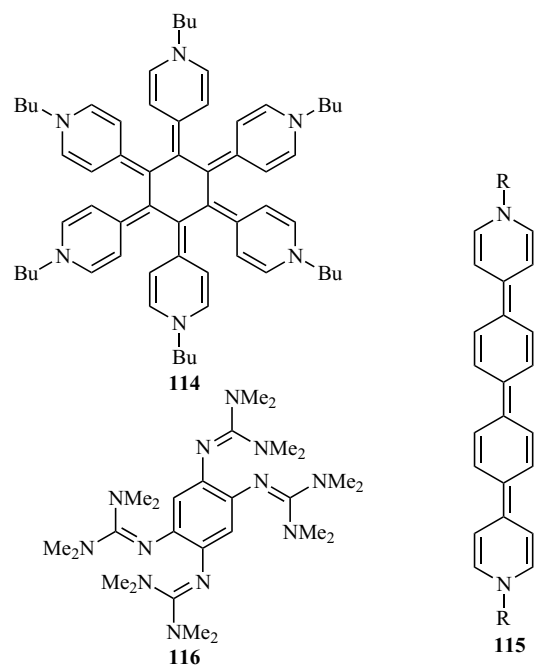
TDAE has also been used to reduce a range of arenediazonium salts, including **57–63** (Scheme 11), via aryl radicals to cyclized products.⁴⁷ For **57–61**, radical cyclizations are followed by loss of the PhSO_n radical to afford the alkene products **64** and **65**. The reaction of substrate **62** likely involves aryl radical cyclization onto the vinyl bromide to afford an intermediate cyclohexyl radical **67** that can expel the neighboring bromine to form an indolenine **68**, which on work-up tautomerizes to the indole **66**.

Reaction of diazonium salt **63** affords three products **71**, **73** and **74**. The intermediate aryl radical **69** either undergoes cyclisation to afford ultimately the isolated tetracycle **74** (60%), or abstracts a hydrogen atom to afford radical **70**. This radical principally afford indoles **71** (5%) and **73** (33%). It is possible that indole **73** arises from the indolenine **72**.

TDAE has even played a role in metal-catalyzed reactions. Here, it has been used in conjunction with chromium/nickel species for allylation of aldehydes and ketones⁴⁸ and for vinylation of aldehydes⁴⁹ using allyl and vinyl bromides, respectively, as well as with palladium^{50–52} in the homocoupling of aryl halides.

Combining the two factors above that produce strong donor characteristics, that is, (i) gain in aromatic stabilization energy on oxidation and (ii) the presence of nitrogen atoms to stabilize

the radical-cation and dication products of oxidation, leads to stronger donors than TDAE. Bourson first described⁵³ the deprotonation of a 1,3-diphenylbenzimidazolium salt **75** to form the tetraazaalkene **76** in 1971 (Scheme 12), followed by Hünig's synthesis of **77** and a study of the redox properties in 1972.^{54,55} Benzimidazole-derived compounds were also the focus of two papers from Thummel in 1995.^{56,57} In 1996, Taton and Chen reported⁵⁸ the preparation of a stable tetraazafulvalene **78** derived from imidazole and also reported on the stability of this and related compounds. The bis-tetramethylene-bridged compound **79**, on warming to room temperature, changed from the vibrant yellow crystals to a white solid, which turned out to be the dissociated bis-carbene **80**, attesting to the reactivity of the bridged compound. The bis-trimethylene bridged compound **78** was more stable and in the absence of air and moisture showed no signs of decomposition, allowing an X-ray crystal structure to be obtained on **78**. All of these compounds are extremely reactive to oxygen. In 1997, Ames *et al.* made a thorough overview of the oxidation potentials of these molecules as seen in cyclic voltammetry.⁵⁹ From all these studies,



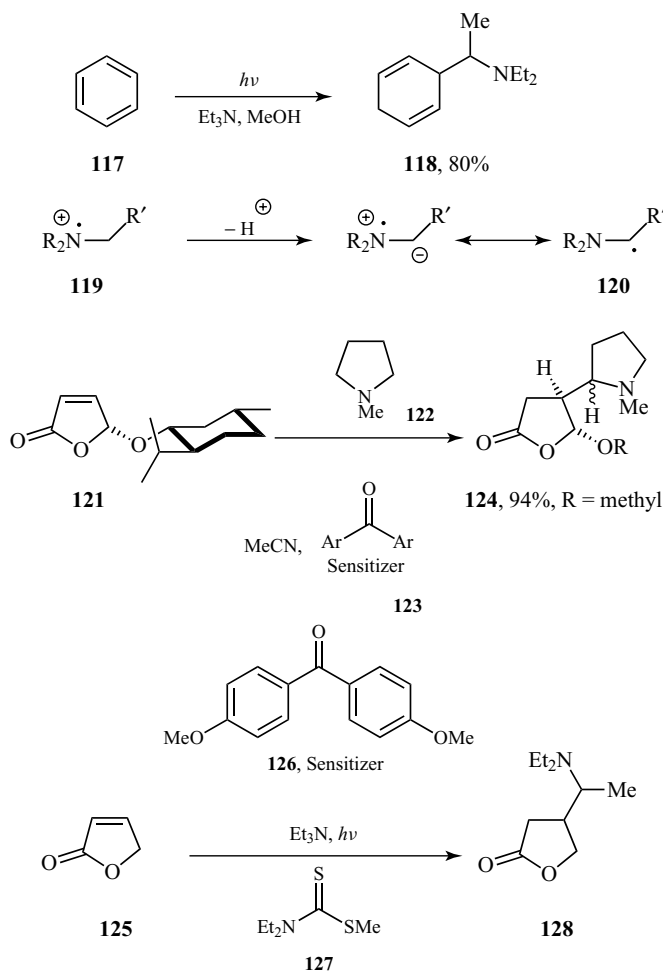
Scheme 16

it was clear that the oxidation potentials of the imidazole donors were more negative than those of the benzimidazole derivatives. This is in line with greater aromatic stabilization energy arising from the oxidation of the imidazolylenes.

Murphy *et al.* applied donor **81** to the reduction of aryl iodides and alkyl iodides.⁶⁰ This afforded aryl radicals, as seen in the cyclization of **87** to indoline **88** (Scheme 13). Although the oxidation potential was significantly less negative than the aryl iodides (−1.8 V), efficient reaction took place (assisted by the irreversible loss of iodide), while although the oxidation potential was significantly negative of the reduction potential of the aryl radicals (+0.05 V),²⁶ no reduction to aryl anions took place!

The involvement of alkyl radicals in the reactions of alkyl iodides was seen not only in cyclizations, for example, **89** → **90** but also in the neophyl rearrangements (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations and Intramolecular Homolytic Substitutions in Synthesis**) of radical **92** derived from iodide **91**, leading to isolation of the products **93** and **96**. If alkyl anion had formed in this reaction (or if a two-electron reaction were present, to be more precise) elimination to α -methylstyrene **98** would have been a likely product, but none was seen.

The cyclization of aryl iodide substrates like **87** with donor **81** was in contrast to the outcome with donor **78**; this more powerful donor leads to



Scheme 17

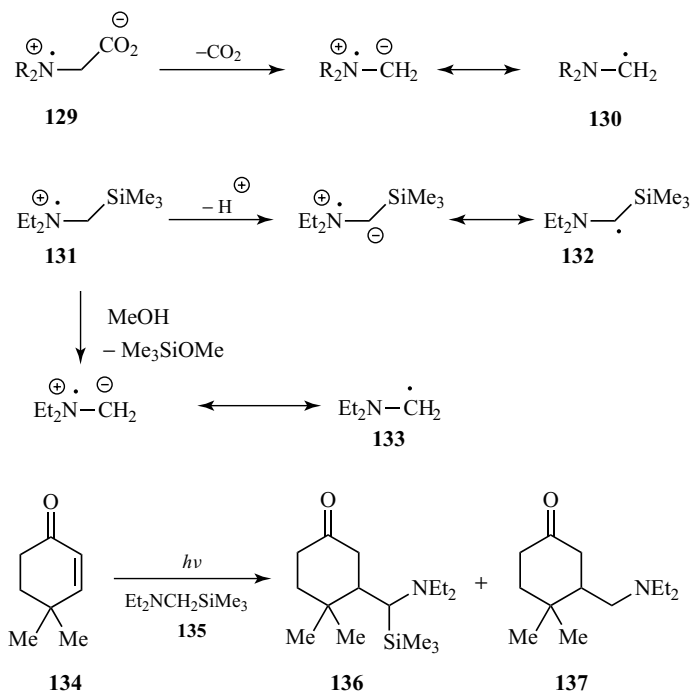
the formation of aryl anions by transfer of two electrons.⁶¹

While reduction of aryl radicals to aryl anions is relatively easy, as determined by Andrieux and Pinson,²⁶ reduction of alkyl radicals to alkyl anions is much more difficult. Hence, it was of great interest when treatment of alkyl iodides and bromides, for example, **99**, afforded homologated aldehydes (**100** in this case) on reaction in DMF with donor **78** (Scheme 14).⁶² However, the origin of the aldehyde carbon was not the DMF but rather the donor, and it appears that this reaction results from trapping of alkyl radicals **101** by the radical cation of the donor **86** to form key intermediates **102**, followed by a fragmentation process, leading to the formation of the aldehyde (**100**). Related experiments supported the intermediacy of iminium salts **103** and enamines **104**; thus, reaction of substrates **107** led, via trapping of alkyl radicals, to liberation of the alcohols ROH and R'OH in good yields, with the proposed mechanism as shown in Scheme 15. Here, enediamine **108** and

dienediamine **110** expel alkoxide leaving groups as they form salts **109** and **111**. More recently, similar chemistry has been reported for the donors **81** and **113**.⁶³ (Donor **113** is easily prepared from 4-dimethylaminopyridine (DMAP) by deprotonation of the intermediate disalt **112**.)

Sulfonamides, *gem*-disulfones,^{64,65} acyloin derivatives,⁶⁶ and Weinreb amides⁶⁷ all undergo cleavage with these strong donors, presumably via sequential SET steps.

The range of recently prepared neutral ground-state organic molecules being studied for their electron transfer properties includes the intriguing structures **114–116** (Scheme 16). Compounds **114** and **115** have been studied by Vaid.^{68,69} In both cases, oxidation can result in extensive aromaticity arising in a number of linked rings. Cyclic voltammetry of compound **114**⁶⁸ shows that only two oxidative peaks appear (−1.33 and −1.14 V vs Fc/Fc⁺, corresponding to −0.88 and −0.69 V vs SCE), one relating to the transfer of four electrons and the other to the transfer of

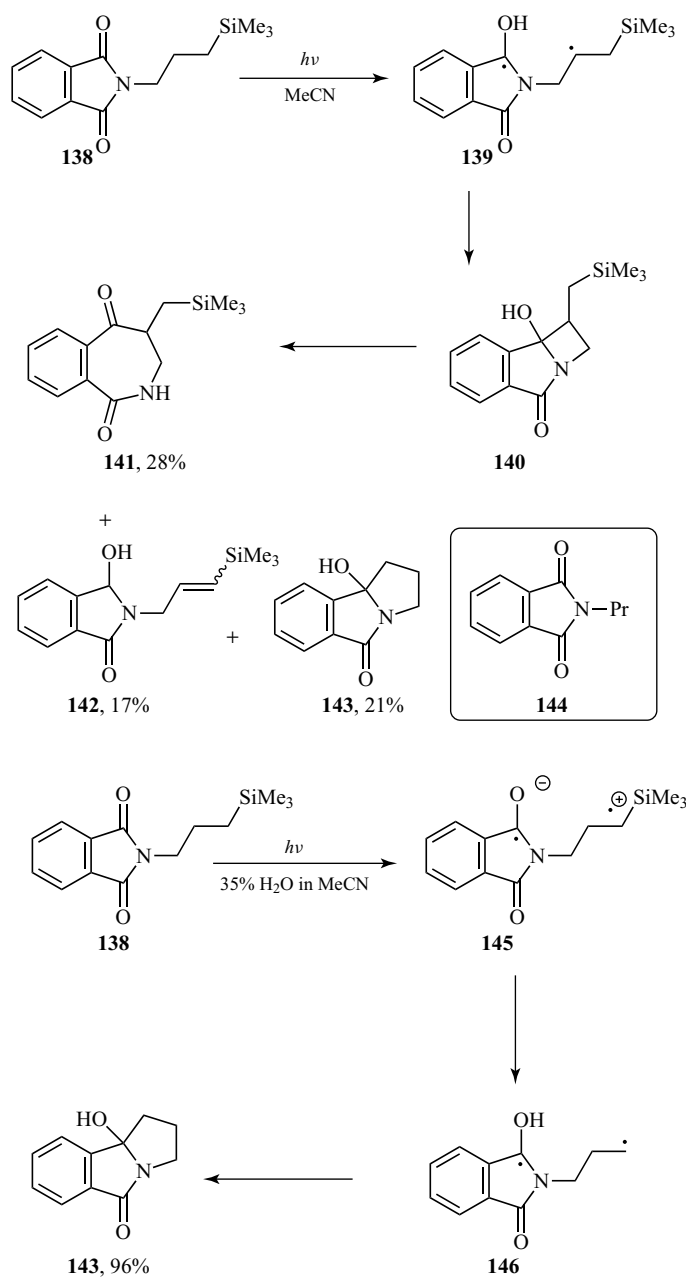


In MeCN, 70% **136**, 5% **137**
In MeOH, 30% **136**, 60% **137**

Scheme 18

two electrons. Redox chemistry of **115**⁶⁹ occurs at -1.48 V versus Fc/Fc^+ , corresponding to -1.03 V versus SCE; investigations into the nature of ground-state **115** were ambiguous about whether the molecule exists as a diradical or as a closed-shell species.

Himmel^{70,71} prepared **116** and tested its redox properties by cyclic voltammetry; this molecule showed a two-electron wave at $E_{1/2}(\text{MeCN}) = -0.32$ V, but computational studies suggested that in nonpolar solvents **116** could be a stronger donor even than **78**.



Scheme 19

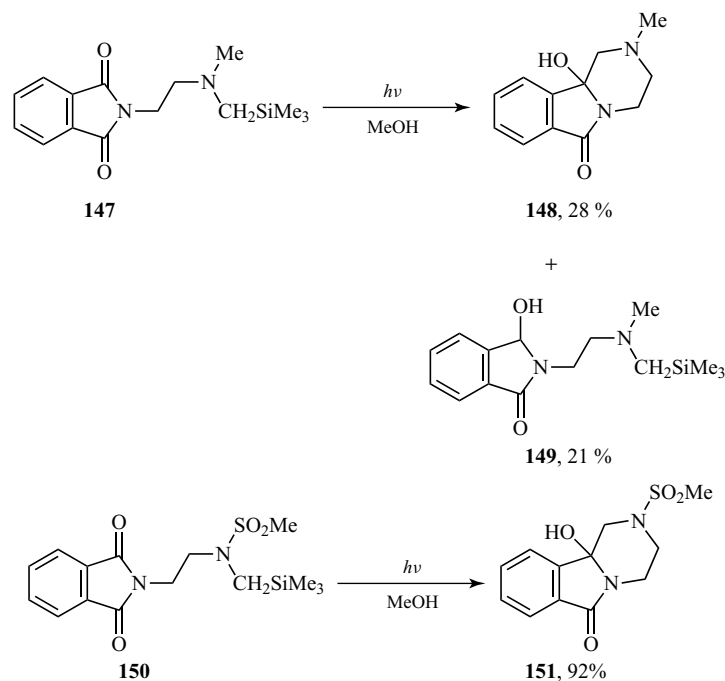
3 PHOTOELECTRON TRANSFER

One of the most intriguing ways of generating radicals in synthetic chemistry is by photoactivation (see **Synthetic Radical Photochemistry**). The ability of simple aliphatic amines and their derivatives to transfer an available electron into a hole created by photoexcitation of a partner reagent has produced some beautiful chemistry over the past few decades. Addition of triethylamine to benzene **117**, in the presence of methanol as a proton source, affording dihydrobenzene **118** was accomplished⁷² as early as 1971 (Scheme 17), but addition to alkenes and, in particular, to α,β -unsaturated carbonyl systems is more prevalent in the literature.⁷³ In these cases, electron transfer from the amine to a photoexcited acceptor affords the amine radical cation **119**. Deprotonation, for example, by the radical anion of the electron acceptor then gives radical **120**. Efficient and highly stereoselective examples of this reaction type are seen in Hoffmann's work of irradiation of substituted benzophenone sensitizers at 350 nm.⁷⁴ Here, the use of such sensitizers that feature electron-donating groups in the aryl rings, for example, **123**, **126** was found to be

important.⁷⁵ An example is the formation of **124**, using *N*-methylpyrrolidine **122**. In this case, the chiral auxiliary is present as an acetal on substrate **121**, and later removal is easy. For some amines, such as triethylamine, thiocarbonyl compounds, such as **127**, assist the efficiency of the addition as seen in the formation of **128**.⁷⁶

Amines that are α -substituted by metals or by carboxylate groups have special properties. On electron transfer, the amine radical cation **129**, undergoes decarboxylation to afford radical **130** (Scheme 18). In contrast to conversion of **119** to **120**, where deprotonation can occur at any C–H adjacent to the nitrogen, the carboxylate substitution here places the radical selectively at one specific carbon and, with speedy decarboxylation, this can simplify the subsequent radical chemistry.^{77–82} Synthetic applications of the carboxy-substituted cases have been substantially developed by Griesbeck^{79–82} and are elaborated in the article **Synthetic Radical Photochemistry**.

On the metals side, Mariano has engaged in a long-term study⁸³ of photoinduced electron transfer of α -trimethylsilylmethylamines, such as **135**. The reactions of the amine radical cation **131** that is



Scheme 20

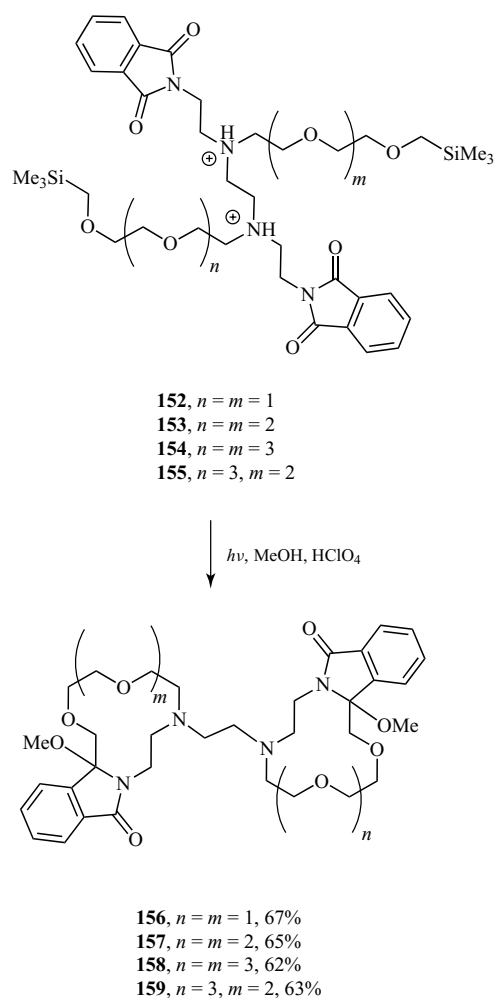
formed by electron transfer to an acceptor, can be determined by the nature of the solvent and by ionic additives such as lithium salts. Thus, the aminyl radical cation **131** is more likely to be deprotonated by an acceptor radical anion to form radical **132**, if that radical anion is basic. This basicity can be decreased by addition of lithium salts and by adding a hydrogen-bonding solvent that breaks up the radical cation (derived from donor)–radical anion (derived from acceptor) contact ion-pair. Slowing down the deprotonation gives a chance for the alternative reaction, desilylation, to occur, and with a silophilic solvent, for example, MeOH desilylation of **131** is encouraged, thereby forming radical **133**. As with the decarboxylation, this desilylation leads to regioselective radical formation, and the speedy desilylation adds to the efficiency of the reaction. This change of solvent and salt additives can lead to the preferential formation of different products, as seen above in the reactions of silylamine **135** with cyclohexenone **134** affording predominantly the silylated product **136** in acetonitrile and the desilylated compound **137** in methanol.^{84,85}

More recently, Mariano has focused on phthalimides as the electron acceptors for silylamines and for other silyl compounds. An example that reflects the relative efficiencies of the desilylation versus nondesilylation pathways is shown in Scheme 19.⁸⁶ When acetonitrile is the solvent, the excited state singlet phthalimide in **138** can abstract a hydrogen atom via a six-centered transition state; the resulting radical pair **139** then leads to a mixture of products **141** (via **140**) and **142** (28%, 18%, respectively), with **143** (21%) also produced. (A similar outcome arises for the nonsilylated analog **144**.⁸⁷) However, irradiation of **138** in 35% H₂O in MeCN results in 96% of the benzopyrrolizidinone **143**. This results from direct electron transfer from the C–Si σ -bond to the excited state phthalimide and affords a radical-cation–radical-anion pair. Desilylation leads to specific formation of the radical pair **146** that then couples efficiently to form **143**.⁸⁶

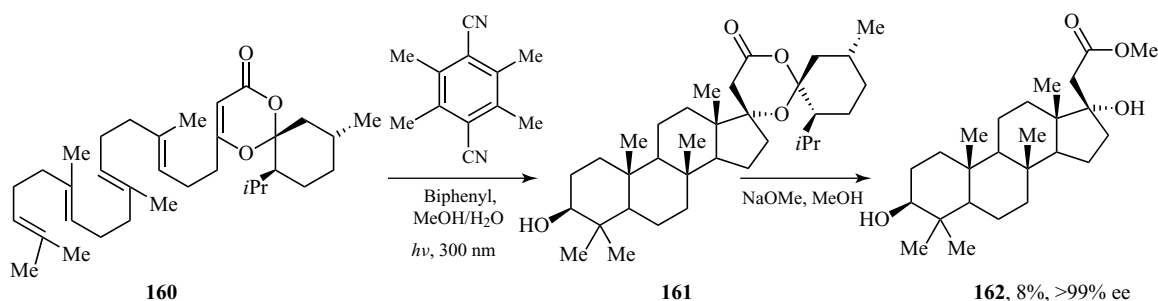
The singlet excited states of phthalimides can receive an electron from different groups including an α -silylamine or an α -silylamide.⁸⁶ However, desilylation of the radical cation of the amides to afford a radical occurs much more rapidly than for the amine, and this means that there is decreased time for back-transfer of the electron. In turn, this results in more selective and quantum-efficient processes. Thus amine **147** affords **148** (28%) and

149 (21%), while sulfonamide **150** affords **151** in 92% yield (Scheme 20).

An attractive application of this knowledge is featured in a study of acceptor phthalimides, in molecules that have more than one potential donor group.^{88,89} In the cases of **152**–**155**, protonation of the amines prevents them from taking part in the reaction and allows the ether oxygen lone pairs to be involved in the electron transfer (Scheme 21). It appears that equilibrium is set up between the possible oxygen radical cations, but that the oxygen radical cation adjacent to silicon undergoes rapid desilylation to afford the α -alkoxyalkyl radical at that site; this radical then couples with the phthalimide ketyl radical. The notable points about



Scheme 21



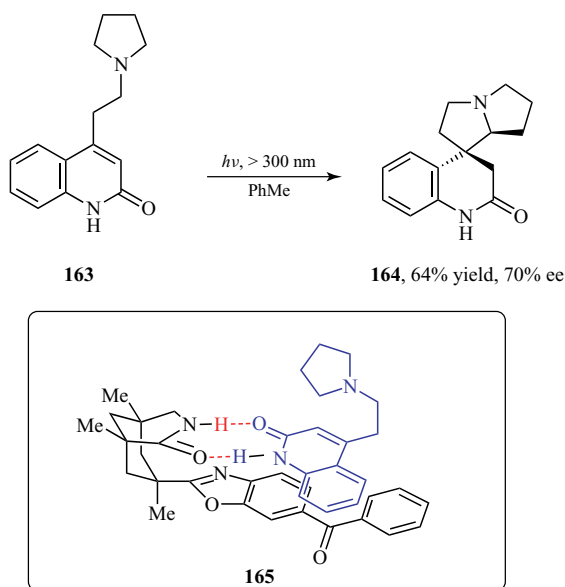
Scheme 22

these reactions are that the ring size is controlled by the site of the silicon, and that the yields of the products **156–159** appear to vary little for the different ring sizes formed. This strategy has also been used to make macrocyclic amides.⁹⁰

Demuth's work on photoelectron transfer produced some intriguing biomimetic cyclizations of isoprenoid precursors.⁹¹ For example, the pentalkene **160** underwent photoexcitation to afford an alkene radical cation, which then triggered a consecutive radical cyclization to afford the steroidal product **161** as the major product, with complete control of the stereochemistry (Scheme 22). This selectivity is thought to be due to the preorganization of the isoprenoid chain in the transition state for

cyclization, which was conducted at -25°C . The absolute stereochemistry in this example is controlled by the menthol acetal auxiliary that can be easily removed following the reaction to afford **162**.

The aim of inducing stereochemical control in complex radical processes in a catalytic sense has been addressed both by the singly occupied molecular orbital (SOMO) catalysis of MacMillan (see **Synthetic Radical Photochemistry**) and also by Bach's electron transfer (PET)-activated cyclization of the pyrrolidino-pyridone **163** to afford tetracycle **164**. A special sensitizer was used for this reaction with the aim of organizing the conformation of the precursor–acceptor complex through π stacking and H bonding (shown in red) in **165** (Scheme 23). The detailed mechanism of the reaction has not been reported.



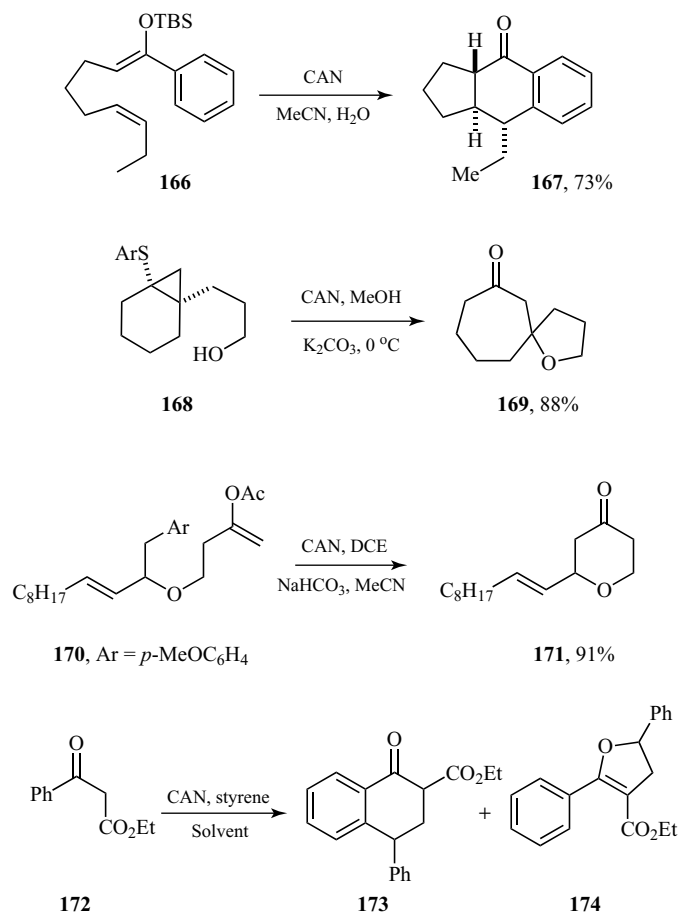
Scheme 23

4 REAGENT-INDUCED ACTIVATION

Ground-state molecules can also be electron donors to reagents of growing popularity; some of the reagents that trigger this process will now be discussed in brief.

4.1 Ceric Ammonium Nitrate (Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry)

The chemistry of this reagent has recently been reviewed.⁹³ This strong oxidant converts alkenes, and particularly electron-rich alkenes to radical cations. Thus, the oxidation of the silylenol ether



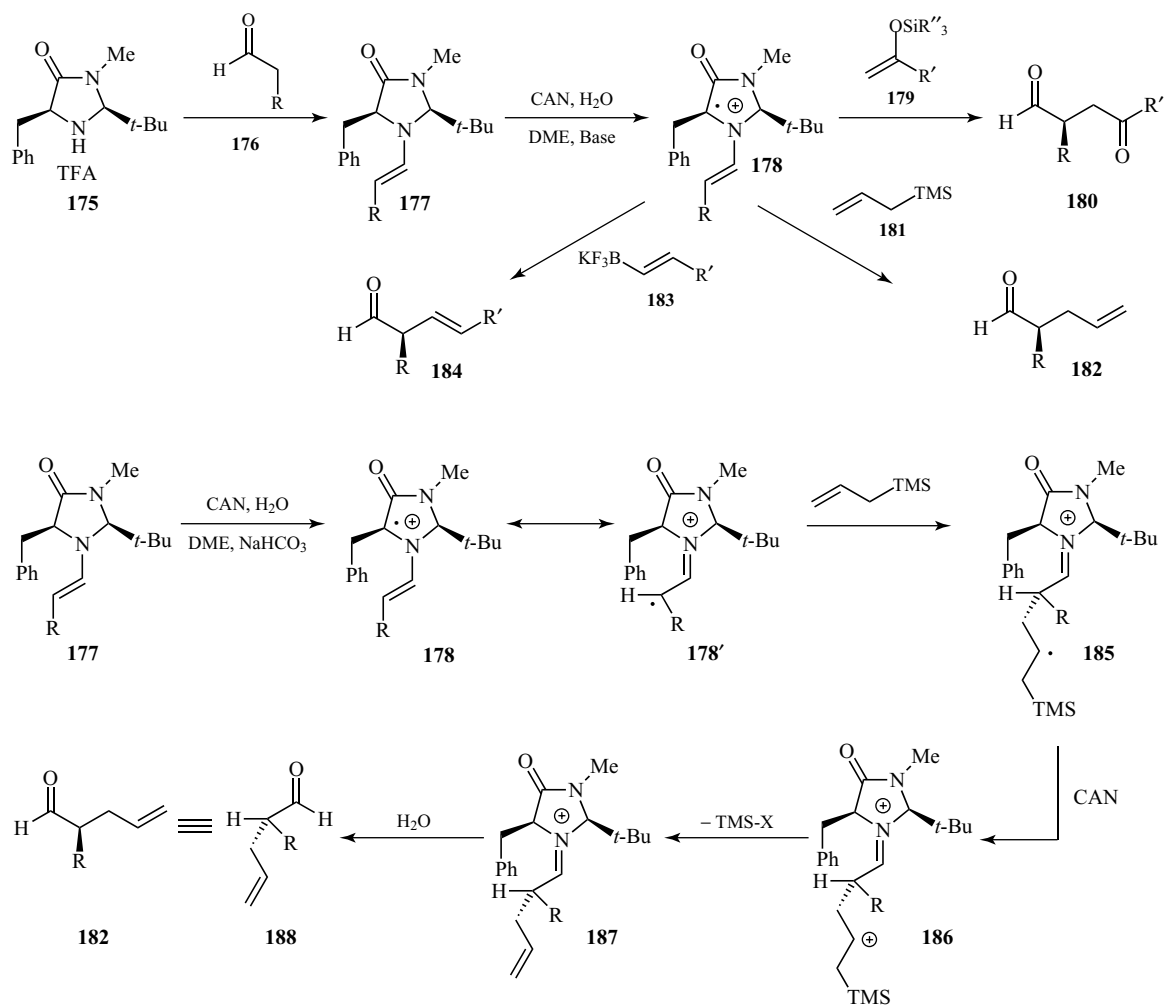
Scheme 24

166 (Scheme 24) leads to radical cyclization and oxidative rearomatization to **167**.⁹⁴ Oxidation of the cyclopropyl sulfide **168** to its radical cation leads to cleavage of the three-membered ring;⁹⁵ the resulting distal radical cation can be oxidized and trapped by the intramolecular alcohol and by water present in the solvent methanol as nucleophiles to afford **169**. Oxidation of the ether **170** to its radical cation can trigger loss of the ArCH_2 group; interception by the vinyl acetate would then lead to tetrahydropyranone **171**. The substitution on the aryl ring is crucial, and in this case, *p*-methoxyphenyl is used.⁹⁶ Oxidation of β -dicarbonyl compounds as **172** leads to the preferential formation of tetralones **173** or dihydrofurans **174**, depending on the solvent.⁹⁷

Very recently, ceric ammonium nitrate (CAN) has been employed by MacMillan in the oxidation

of enamines as a key part of his organocatalysis with SOMO activation. In general, CAN is the strongest of the oxidizing reagents used for enamine oxidation in his work. More selective oxidants that are required for certain reaction types are referred to later in the review.

In these reactions, aldehyde **176** combines with amine **175** to form the enamine **177** *in situ* (Scheme 25). The stereoselectivity of the ensuing process relies on the fact that the enamine adopts the *E* configuration lying away from the bulky *t*-butyl group. With the top face shielded by the benzyl group, the radical (most easily represented as **178'**) attacks the alkene of the allylsilane to afford radical **185**.^{98,99} (Only this SOMO-catalyzed reaction leading to the allylated aldehyde **188** is discussed here in mechanistic detail in this article,



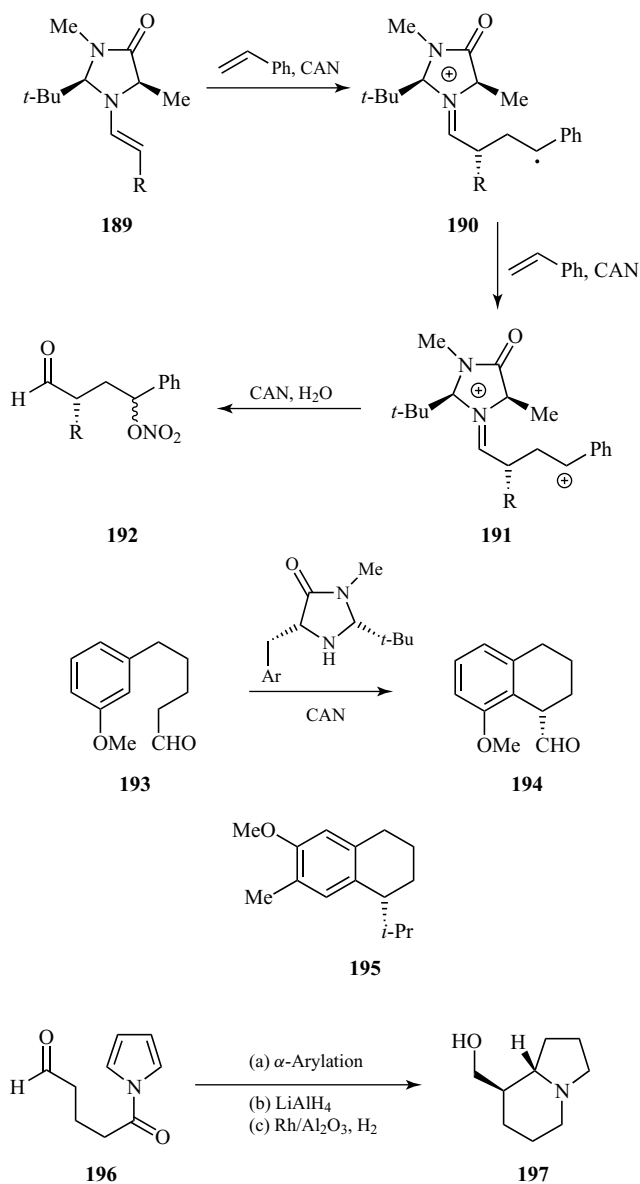
Scheme 25

but analogous pathways lead to **180**¹⁰⁰ and **184**.¹⁰¹) Oxidation of this radical affords the stabilized cation **186**, which undergoes nucleophile-assisted loss of the silyl group giving alkene **187**. Hydrolysis *in situ* then liberates the substituted aldehyde and the catalyst can trigger further enamine formation as it continues the catalytic cycle. It is noteworthy that the enamine undergoes oxidation by CAN far faster than the amine **175**.

With styrenes as radical acceptors, MacMillan illustrated that aldehydes could be converted to benzylic nitrates. An example is shown in Scheme 26 where the aldehyde-derived enamine **189** is oxidized to its radical cation, which

undergoes radical addition to styrene to afford adduct radical **190**. In turn, this radical is oxidized by CAN to a benzylic cation **191** that is trapped by nitrate ion derived from CAN¹⁰² to afford product **192**.

With the same type of reactivity and catalyst, Nicolaou reported an α -arylation of aldehydes by arenes bearing electron-donating groups. In this case also, the oxidant was CAN.^{103,104} Thus, aldehyde **193** was converted to its enamine and oxidized to a radical cation; addition to the aryl ring, oxidation, and deprotonation restored the aromaticity and enamine hydrolysis provided product **194**. This



Scheme 26

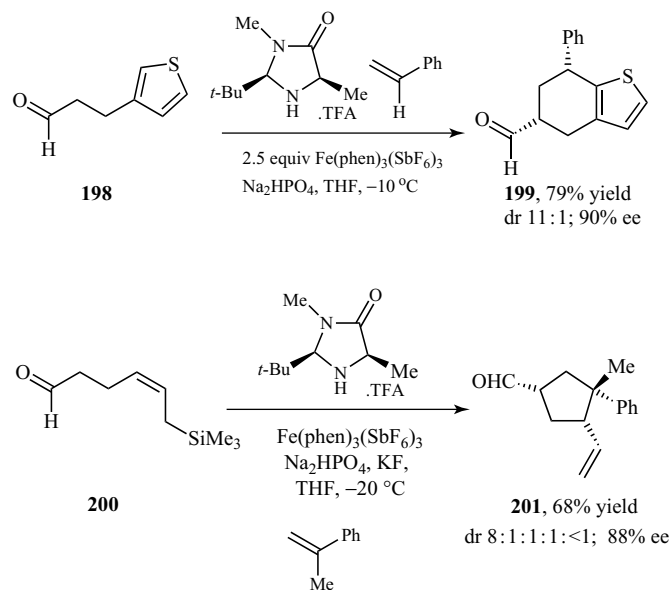
approach was used in a short synthesis of demethyl calamenene **195**.

4.2 Iron Reagents

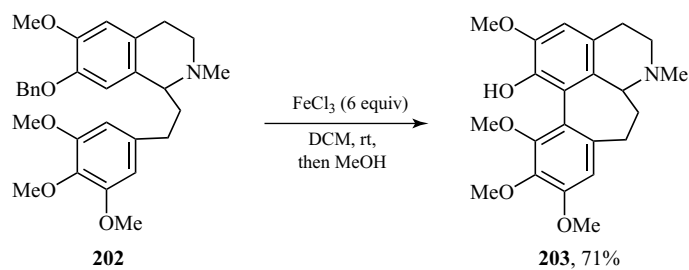
In a very similar approach, MacMillan reported that $\text{Fe}(\text{phen})_3 \cdot (\text{PF}_6)_3$ provided the best levels of yield

and ee, and used the arylation of aldehyde **196** as the key step (72% yield and 93% ee) in a synthesis of (–)-tashiromine **197**.¹⁰⁵ In the arylation of the radical cation intermediates, the question arises as to whether this is a radical-type cyclization or a cationic Friedel–Crafts type cyclization, and this has been analyzed.¹⁰⁶

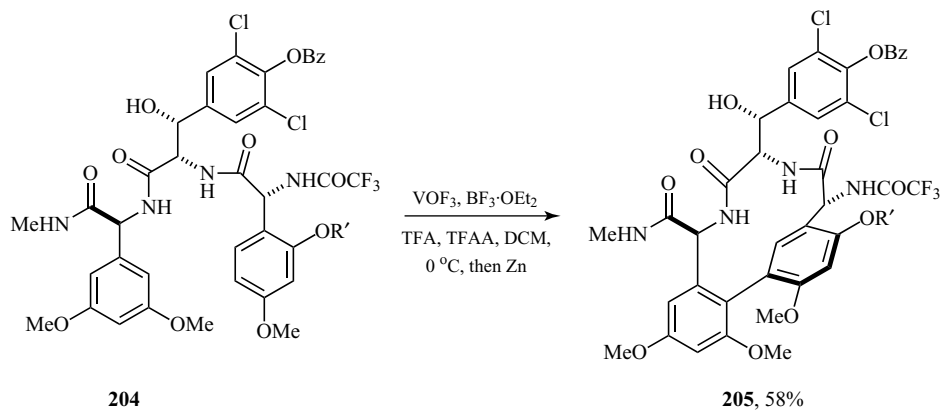
The tris-phenanthroline iron(III) complexes were also the oxidants of choice for reaction of



Scheme 27



Scheme 28



Scheme 29

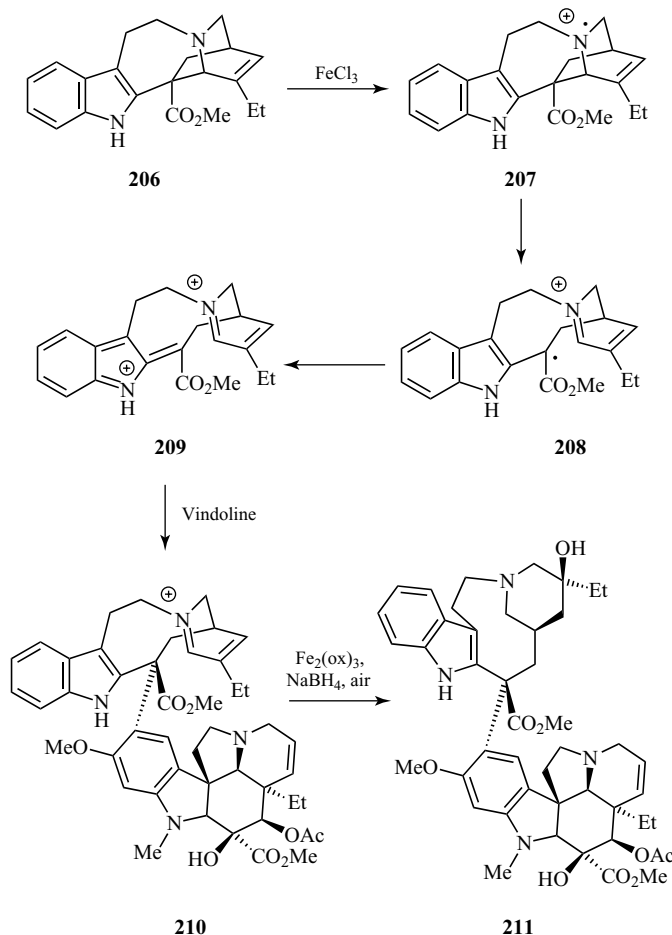
3-arylpropionaldehydes with styrenes, conjugate dienes, and allylsilanes (Scheme 27). A thiophene example, **198**, is shown that was converted with considerable selectivity into **199**, but other electron-rich arenes can also undergo this reaction (anisoles, indoles, benzofurans). The formation of the cyclopentane **201** from allylsilane **200** shows that the range of terminating nucleophiles can be extended further, and that the good selectivities are not confined to the preparation of six-membered rings.¹⁰⁷

Enamines are not the only compounds oxidized by iron complexes. Historically, phenol oxidative coupling has been triggered by iron(III) compounds. This will not be dealt with at length here and the reader is referred to an excellent recent review.¹⁰⁸ An example of such an oxidative coupling is shown

with the conversion of substrate **202** to alkaloid kresigine **203** (Scheme 28).¹⁰⁹ The exact nature of the intermediates of many of these reactions has not been determined, but the fact that iron(III) is a one-electron oxidant and that electron paramagnetic resonance (EPR) signals have sometimes been reported suggests that radical cation intermediates play a crucial role.

Alternative reagents are of course capable of performing these reactions and, among these, thallium(III) salts¹¹⁰ and vanadium(V) predominate. An impressive example, using VOF_3 is shown in the conversion of **204** to **205** in approaches to the vancomycin antibiotics (Scheme 29).¹¹¹

Amines can also be oxidized by iron salts, and this was important in the synthesis of vinblastine **211** accomplished by Kutney.¹¹² Thus, treatment



Scheme 30

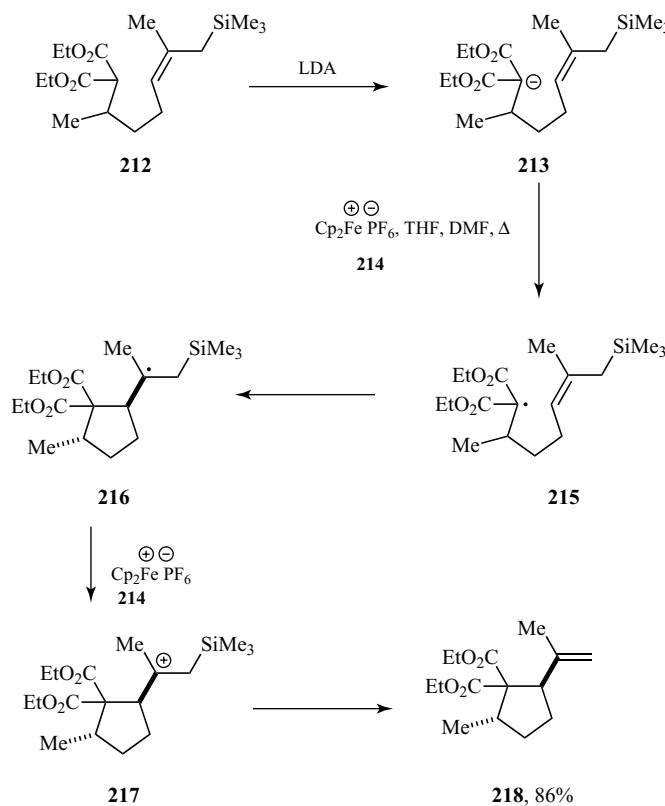
of catharanthine **206** with ferric chloride formed the radical cation **207** that underwent fragmentation; further oxidation likely led to **209**, which was intercepted by vindoline, acting as a nucleophile, to afford **210** (Scheme 30). In the original Kutney paper, this intermediate was reduced and later transformed further to vinblastine **211**, but Boger has recently found a one-pot route with ferric oxalate, $[\text{Fe}_2(\text{ox})_3]$, sodium borohydride, and air to afford the alcohol **211** directly and quite efficiently (41% of **211** together with 20% of its hydroxy-epimer).¹¹³ This should provide easier access to analogs of the important anti-cancer agent, vinblastine.

An alternative iron-based reagent is the ferrocenium hexafluorophosphate **214**. This oxidizes the ester enolate **213**, derived from malonate **212**, to the radical **215**. Cyclization, and further oxidation, affords cation **217**, which then undergoes desilylation to yield **218** (Scheme 31). Jahn has used this methodology for the synthesis of a range of cyclic products.^{114,115}

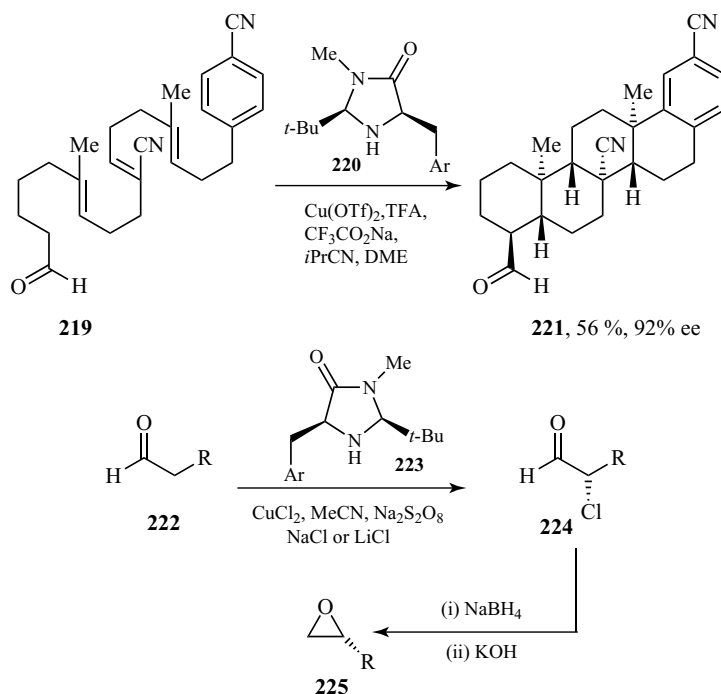
4.3 Copper Reagents

While CAN is used for the most robust of the SOMO-catalyzed processes, milder oxidants provide enamine radical cations for other processes. MacMillan has seen enantioselective polyene cyclization based on radical cations (cf. the work of Demuth⁹¹ discussed above) using $\text{Cu}(\text{OTf})_2$ as the oxidant and sodium trifluoroacetate as the mild base. The efficacy of the approach is seen in the preparation of **221** from trienal **219** using catalyst **220** (Scheme 32). Even more adventurous examples are also successful with a 63% yield of a heptacyclic analog of **221** that includes formation of six new C–C bonds in the cyclization, with control of 11 contiguous stereocentres, of which five are all-carbon quaternary stereocenters.¹¹⁶

A further and important example of SOMO catalysis was reported in the interception of enamine radical cations derived from oxidation of enamines formed from aldehydes **222** with amine **223**. The



Scheme 31



Scheme 32

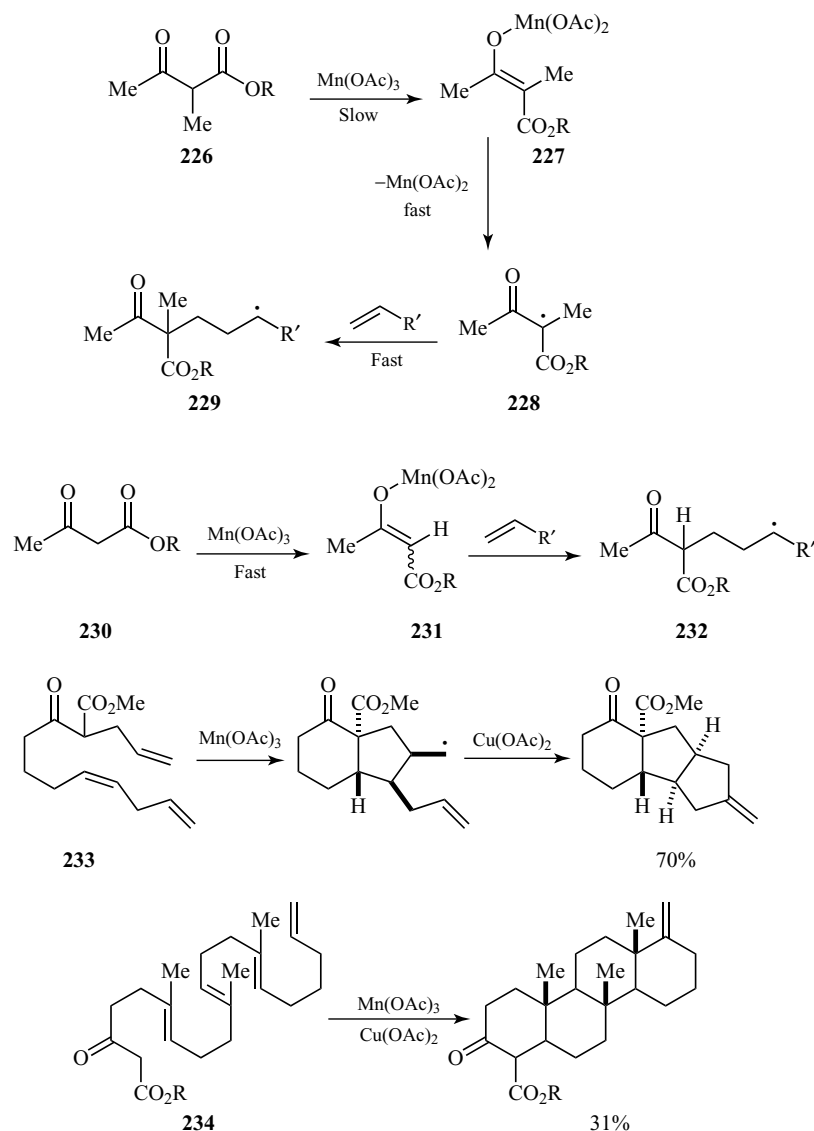
simple chloride sources NaCl or LiCl performed the interceptions with excellent stereocontrol. The produced α -chloroaldehydes **224** were converted, with full maintenance of enantiomeric excess, into the terminal epoxides **225**. As with all of these transformations, this conversion is compatible with a wide range of functional groups in R (Scheme 32).¹¹⁷

4.4 Manganese Reagents

The addition of acetic acid to alkenes mediated by manganese triacetate was first described in 1968.^{118,119} This reaction expanded in synthetic utility when β -dicarbonyl compounds were studied. A great deal of information has been gleaned through careful mechanistic and synthetic studies, and the reader is referred to reviews.^{120,121} The α -alkyl substituted β -ketoesters **226** and the α -unsubstituted β -ketoesters **230** react in surprisingly different ways (Scheme 33). The substituted esters lead to slow formation of a Mn(III) enolate **227**, followed by rapid homolysis of the Mn–O

bond to form a free radical **228** that adds rapidly to alkenes to form radical **229**. The intermediate radical **228** appears unbound since it behaves identically to a radical generated by other methods. On the other hand, the α -unsubstituted β -ketoesters **230** form a manganese(III)-enolate **231** rapidly, and this is followed by a slow addition to an alkene to form a radical product **232**. In this case, it is not thought that a free radical forms prior to the addition to the alkene, although radical **232** results from the addition.

Regardless of source, once the radical resulting from addition to an alkene has formed, its fate depends on its substitution pattern. Tertiary radicals can be oxidized to carbocations by $\text{Mn}(\text{OAc})_3$, while secondary and primary radicals cannot be. Primary radicals can abstract hydrogen atoms, but they are frequently oxidized by the additive $\text{Cu}(\text{OAc})_2$ to give reactive Cu(III) intermediates that can undergo reductive elimination to form Cu(I) byproducts and alkenes. Secondary radicals can also follow this pathway or can be oxidized to carbocations by Cu(II).^{122,123} Representative cyclizations of substrates **233** and **234** featuring Cu(II)-based terminations are shown.



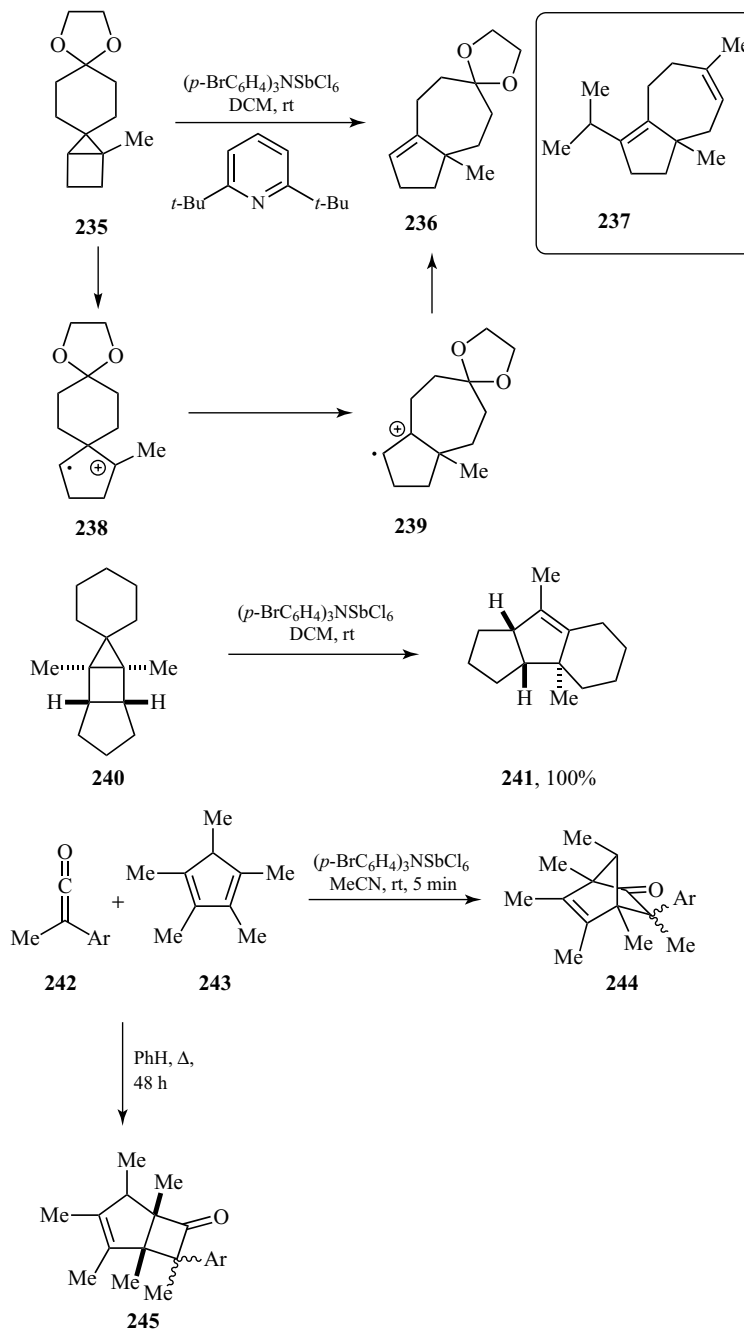
Scheme 33

4.5 Aminium Cation-Radical Salts

It is not only metal compounds that can receive electrons from organic substrates. Among organic compounds, the triarylaminium radical cations feature widely.¹²⁴ The cyclopropane **235** has been oxidatively rearranged to the alkene **236** (Scheme 34) by Little, by means of mediated electron transfer.¹²⁴

The tris(4-bromophenyl)aminium cation is generated *in situ* electrochemically; this then

mediates the oxidation of the cyclopropane to form the radical cation **238**. This undergoes cationic migration to afford the seven-membered ring intermediate **239** and the resulting radical is thought to oxidize the triarylamine to continue the cycle and afford the product **236** (85%). This product was then transformed into Daucene **237**.¹²⁵ In another excellent and earlier example, a very efficient ring expansion from **240** to diquinane **241** was observed by Adam, Heidenfelder, and Sahin.¹²⁶ In this case,

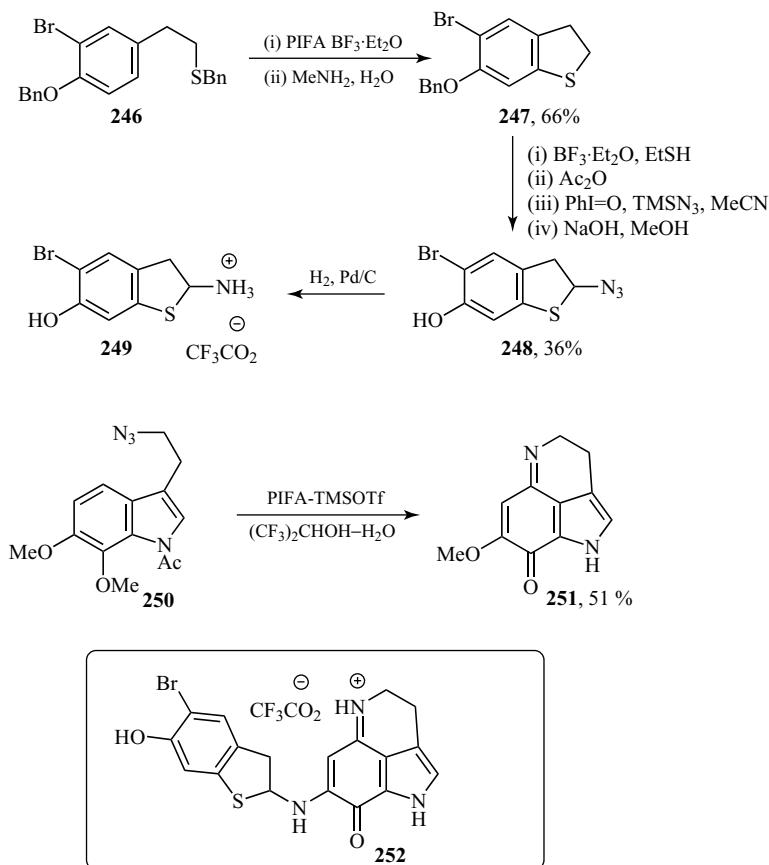


Scheme 34

catalytic quantities of the aminium radical cation were used without electrochemical activation.

One of the principal reaction types that are triggered by aminium cationic radicals is the

oxidation of conjugated dienes to their radical cations. Schmitt and von Segern have explored¹²⁷ the mechanistic details of the cycloadditions of ketenes to cyclopentadienes, as well as other



Scheme 35

cycloadditions. An example is the cycloaddition of **242** and **243**. The thermal reaction leads to the formation of cyclobutanone **245**, while the aminium-catalyzed process affords the “Diels–Alder” products **244**.

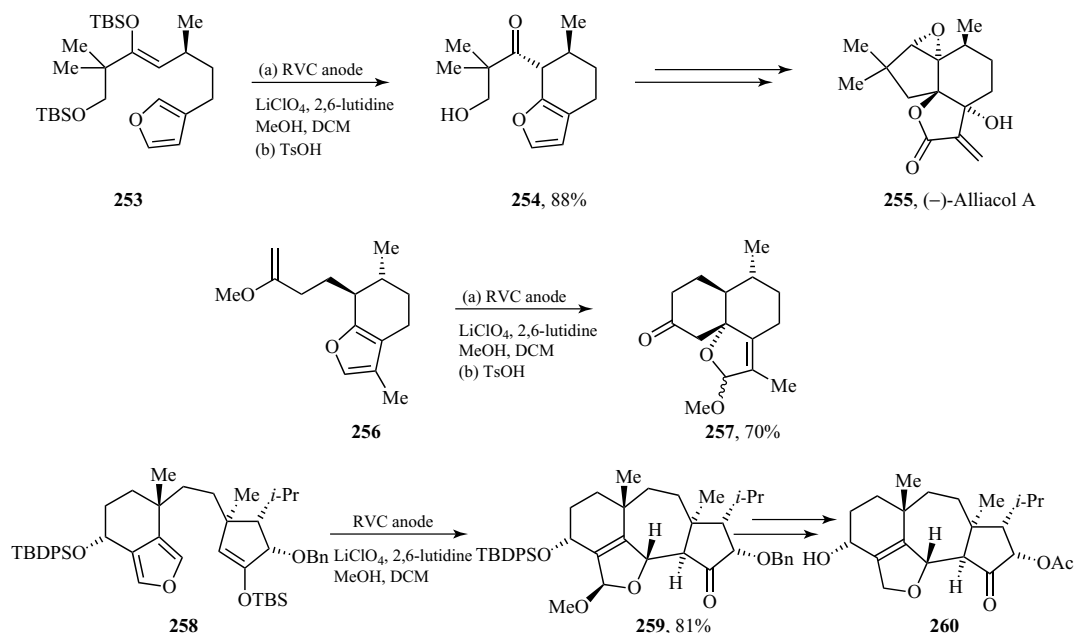
4.6 Hypervalent Iodine Reagents

Hypervalent iodine compounds¹²⁸ can oxidize a number of functional groups to their radical cations. In an elegant synthesis that employs such compounds in three separate steps, Kita *et al.* announced the synthesis of (±)-Makaluvamine F, whose trifluoroacetate salt is shown as **252**,¹²⁸ by coupling components **249** and **251**, in 86% yield (Scheme 35). Radical cations arising from oxidations of the substrates with hypervalent iodine reagents were the proposed intermediates for each

of the transformations of **246** → **247**, **247** → **248**, and **250** → **251**.

5 ELECTROCHEMICAL INDUCTION

High-yielding oxidative electrochemical transformations involve the reaction of the cation radical of an enol ether derivative with a furan in substrates **253** en route to Alliacol A **255**,^{129,130} and **256**—a precursor to the arteannuin ring skeleton in **257**^{131,132} (Scheme 36). Trauner has also elegantly demonstrated the power of anodic oxidation using reticulated vitreous carbon (RVC) electrode twice in the syntheses of (–)-Heptemerone B and (–)-Gaunacastepene E **260**.¹³³ For deeper insights into electrochemical oxidations, the reader is referred to article **Electrochemically Initiated Radical Reactions** of this encyclopedia.



Scheme 36

6 CONCLUSION

In summary, electron-donating properties of organic molecules exhibit a wide range of reactions for use in synthesis. The diversity of the chemistry and the rapid developments that are seen currently testify to the wide usefulness of this route for the generation of radicals and radical cations in preparative chemistry. This article showcases the recent use of radical cations in organocatalysis as one of the fastest moving areas that has applications to diverse reactions. We can expect that this will continue to develop rapidly in the near future. At the same time, the flexibility of synthesis of highly reducing organic structures suggests that the current impressive frontiers of neutral organic compounds as super-electron-donors may soon again be breached, and that these molecules may soon challenge the most powerful reducing metals in achieving difficult reductions. The development of elegant electrochemistry is also an area of great promise, particularly at a time when “reagentless” chemistry has environmental attractions, and recent demonstrations of the power of photoelectron transfer in synthesis, as represented in this article, also herald an impressive future.

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Organic Synthesis Using Samarium Diiodide

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1 INTRODUCTION

Samarium diiodide (SmI_2) was first prepared at the turn of the twentieth century,¹ but it was not used as a reagent in organic synthesis until it was introduced to organic chemists by Kagan in 1977.² It has since attained an importance reserved for few reagents and is now a standard reductant in most synthetic laboratories. The unique place held by SmI_2 in the arsenal of synthetic chemists is a result of its versatility in mediating numerous important organic reactions that proceed through free-radical intermediates. These selective reactions include functional group reductions, reductive couplings, and cascade reactions. The use of SmI_2 often allows alternative routes to multifunctional targets to be considered. Although numerous SmI_2 -mediated reactions have been developed, its scope in synthesis is far from exhausted and new applications for this reagent continue to be discovered. This article provides a “snapshot” of the organic chemistry mediated by SmI_2 . The importance of additives and the mechanism of reactions is also discussed.

Samarium, like other lanthanides, has a shell core configuration of $[\text{Xe}] 4f^n 6s^2$. The loss of the three outermost electrons, namely, the $5d^1$, $6s^2$ electrons, results in enhanced thermodynamic

stability in which a closed-shell Xe-like electronic configuration is adopted resulting in a thermodynamically stable +3 oxidation state across the lanthanide series. The +2 oxidation state is most relevant for samarium (f^6 , near half-filled), europium (f_7 , half-filled), thulium (f^{13} , nearly filled), and ytterbium (f^{14} , filled). To attain the more stable +3 oxidation state, SmI_2 readily gives up its final outer-shell electron, in a thermodynamically driven process, making it a very powerful and synthetically useful single-electron-transfer reagent.

The reducing power (reduction potential) of SmI_2 has been established through the use of linear sweep and cyclic voltammetry and was found to be approximately -1.41 V, determined for a solution of SmI_2 in tetrahydrofuran (THF).^{3,4} Although the preparation of SmI_2 in a variety of different solvents is known, THF is the most common solvent associated with its use because of the high solubility of the reagent. It is possible to alter the reduction potential of SmI_2 through the use of various additives, most commonly neutral or Lewis basic oxygen functionalities. The most common example of this is the use of hexamethylphosphoramide (HMPA) as an additive, for which it was determined that, upon incorporation of 4 equiv, the reduction potential of SmI_2 in THF is increased to approximately -1.79 V, thereby significantly increasing its potency as an

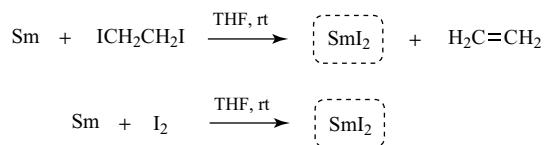
electron-transfer reagent.^{4–6} Similar effects are also observed in the presence of alcohols and even water, for which it has been reported that, upon the addition of 500 equiv, the reduction potential can be increased as far as -1.9 V.⁷

The solvent milieu and the additives employed in reactions of SmI_2 have a significant impact on the coordination sphere and the reactivity of the reagent. Samarium, like other lanthanides, is oxophilic so a great deal of the coordination chemistry of SmI_2 is dominated by oxygen-containing solvents and ligands. In a THF solution, SmI_2 exists in a hepta-coordinate geometry in which five THF molecules are equatorially bound to the central Sm(II) ion through their oxygen lone pairs, with iodine ligands bound axially.⁸ The coordination number and geometry of SmI_2 is variable depending on the nature of the ligands involved. For example, in the $[\text{SmI}_2(\text{HMPA})_4]$ complex, the more sterically demanding HMPA ligands are positioned equatorially around the Sm(II) ion resulting in an octahedral (hexacoordinate) geometry.^{9,10} Other common additives such as glycols and glymes produce coordination numbers as high as eight ($[\text{SmI}_2\{\text{O}(\text{CH}_2\text{CH}_2\text{OMe})_2\}_2]$) and nine ($[\text{Sm}\{\text{O}(\text{CH}_2\text{CH}_2\text{OH})_2\}_3\text{I}_2]$).^{11,12} The high coordination number coupled with the oxophilic nature of SmI_2 is beneficial for stereoselective reactions. The coordination of Sm(II) and Sm(III) to oxygen donors on substrate, solvent, or cosolvent provides a means for achieving a high level of selectivity in reactions.

2 THE REAGENT AND THE EFFECT OF ADDITIVES

Although SmI_2 is commercially available as a 0.1 M solution in THF from a range of suppliers, it is straightforward to prepare. The two most convenient procedures involve addition of either 1,2-diiodoethane or iodine to a slight excess of samarium metal in THF.^{13,14} After stirring the mixture for several hours, the characteristic dark blue solution of SmI_2 is formed in concentrations up to 0.1 M (Scheme 1).

The solution is stable for extended periods as long as it is stored in an inert atmosphere. Several other approaches for the rapid synthesis of SmI_2 have been developed. Concellón has shown that sonication of a solution of samarium metal



Scheme 1 Convenient preparation of SmI_2 .

with iodoform, 1,2-diiodoethane, diiodomethane, or iodine in THF provides SmI_2 within 5 minutes.¹⁵ Similar results can be achieved by microwave heating.¹⁶

When necessary, SmI_2 can be prepared in solvents other than THF. Kagan has reported formation of the reagent in tetrahydropyran (THP),¹⁷ and Ruder reported the use of acetonitrile.¹⁸ Interestingly, Tani has shown that SmI_2 can be prepared in a solution in benzene and HMPA.¹⁹ More recently, Flowers showed that high-intensity ultrasound could be used to facilitate the preparation of SmI_2 in low concentrations (0.02–0.05 M) in acetonitrile, dimethoxyethane (DME), 2-propanol, 2-methyl-2-propanol, and 2-heptanol.²⁰ Attempts to prepare SmI_2 in ethereal solutions other than THF, including diethyl ether, *tert*-butylmethyl ether, and dioxane have been reported to be unsuccessful.¹⁷ One of the unique features of SmI_2 is the use of cosolvents or additives to control reactions. For example, cosolvents and additives can be used to control the rate of reduction or chemo- and stereoselectivity of reactions. Additives commonly utilized to alter reactions of SmI_2 can be classified into three major classes:

1. Lewis bases—HMPA and other electron donor ligands, chelating ethers, and so on;
2. Proton donors—predominantly alcohols, glycols, and water;
3. Transition-metal salts— NiI_2 , FeCl_3 , and so on.

Lewis bases containing basic oxygen or nitrogen are important promoters of reactions initiated by SmI_2 . Among these additives, HMPA has played an important role in the development of the chemistry of SmI_2 . The unique potential of the SmI_2 –HMPA combination was first recognized by Inanaga who discovered that the use of this additive significantly increased the rate of reduction of alkyl and aryl halides.²¹ Since Inanaga's initial studies, HMPA has been employed in a wide range of functional group conversions and bond-forming reactions, which

are discussed in subsequent sections of this article. Several research groups have studied reactions initiated by SmI_2 –HMPA and have uncovered a complex role for the additive. Coordination of HMPA to SmI_2 not only produces a more powerful reductant but also displaces iodide ligands to the outer sphere of samarium, creating open coordination sites for substrates while concomitantly producing a sterically encumbered reductant.^{3,4,6,22,23} HMPA also plays a critical mechanistic role in post-electron-transfer events in SmI_2 -mediated reactions. Addition of HMPA retards the rate of bimolecular coupling of biaryl ketyl radicals through complexation of Sm(III) that bridges colligating radical anions.²⁴ Conversely, HMPA accelerates SmI_2 -initiated 5-*exo*-trig ketyl–olefin cyclizations through conversion of the intermediate Sm(III) -ketyl radical contact ion pair to a solvent-separated ion pair.²⁵ More recently, Flowers has shown that HMPA activates alkyl halide bonds, providing the basis for selectivity in samarium Barbier reactions.²⁶

While the behavior of HMPA is unique and there are many synthetic advantages to its addition to reactions involving SmI_2 , safety hazards make its use undesirable. Other Lewis basic cosolvents have been utilized successfully in reactions with SmI_2 ; these include 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU),^{27–29} 1,1,3,3-tetramethylurea (TMU),³⁰ and nitrogen donor solvents.³¹ More recently, tripyrrolidinophosphoric acid triamide (TPPA) has been employed as an additive in SmI_2 -mediated reactions, and it is reported that the complex formed between SmI_2 and 4 equiv of TPPA possesses greater reactivity than the corresponding complex containing HMPA.³² In many of these reactions, a relatively large excess of additive is required. Although all of the aforementioned Lewis bases have found uses in specific reactions, none has yet been shown to provide the general utility of HMPA.

Many reactions of SmI_2 require the presence of a proton donor to quench the carbanion and alkoxide intermediates formed during the course of a reaction. The most common proton donors are water, alcohols, and glycols. Proton donors often have a considerable impact on the regiochemical and stereochemical outcome of SmI_2 -mediated reactions. For example, Keck has shown that the efficiency and stereoselectivity of the reduction of β -hydroxy ketones by SmI_2 in THF is dependent upon the proton donor employed and

its concentration.³³ In another important example, Procter showed that γ,δ -unsaturated ketones undergo two very different stereoselective cyclization reactions mediated by SmI_2 depending upon the alcohol cosolvent used in the reaction.³⁴

Several studies have shown that the basis for selectivity in many reactions is related to the affinity of the proton donor for SmI_2 .^{28,35,36} In particular, water was found to have a higher affinity for SmI_2 compared to alcohols and generated a more powerful reductant.⁷ The activation of SmI_2 by H_2O is best illustrated by Procter's recent findings that simple lactones can be reduced using SmI_2 – H_2O .^{37,38} These studies led to the proposal that glycols capable of chelating through multiple interactions should enhance rates of reduction by SmI_2 , and there are a number of examples where glycols have been used to accelerate SmI_2 -initiated reductions.^{39–42} Care should be taken when using chelating alcohols since it has been shown that low concentrations of glycols enhance the reactivity of SmI_2 whereas high concentrations lead to coordinative saturation of samarium resulting in a less reactive reductant.¹²

In some cases, proton donors can be used in concert with Lewis bases to provide unique methods for increasing the reactivity of SmI_2 . This is best exemplified by the work of Hilmersson, who has shown that the appropriate stoichiometry of water and amine with SmI_2 can be used to reduce a range of functional groups or carry out selective deprotections.^{43–46} This method not only provides an alternative to HMPA, but also has several advantages including fast reaction times and precipitation of inorganic by-products, making workup straightforward.

Inorganic salts are another important additive used to enhance the rate and selectivity of SmI_2 -mediated reactions. The use of inorganic additives can be traced to the seminal studies of Kagan during which he used catalytic amounts of ferric chloride to accelerate the coupling reactions of alkyl iodides and ketones.¹³ The most commonly utilized salts are based on Fe(III) or Ni(II) , and Kagan has shown that NiI_2 was superior to other transition-metal salts in many of these reactions.⁴⁷ As a result, NiI_2 has become the additive of choice in reactions requiring a transition-metal-based catalyst. NiI_2 has been used in a range of important reactions including the conjugate addition of alkyl iodides to α,β -unsaturated esters, amides, and lactones,^{48,49} the coupling of acid chlorides

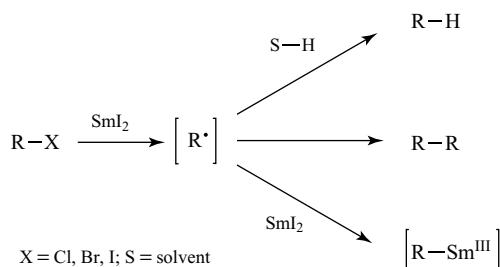
and esters,⁵⁰ intramolecular cyclizations and Grob fragmentations,⁵¹ and the coupling of alkyl halides with nitriles.⁵²

3 THE MECHANISMS OF REACTIONS USING SAMARIUM DIIODIDE

Most bond-forming reactions using SmI₂ produce radicals and subsequently anions by the reduction of alkyl halides, or ketyl radical anions by the reduction of carbonyl groups.

3.1 Reduction of Organohalides

The reduction of aryl or alkyl halides by SmI₂ provides access to radicals that can undergo a range of follow-up reactions including hydrogen atom abstraction from solvent, dimerization, or reduction to an anion as shown in Scheme 2. The mechanism for reduction of alkyl and aryl halides to form



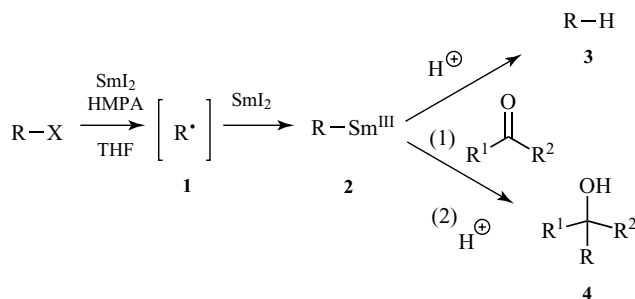
Scheme 2 Fate of radicals formed by reduction of organohalides with SmI₂.

an initial radical is recognized to proceed through dissociative electron transfer.

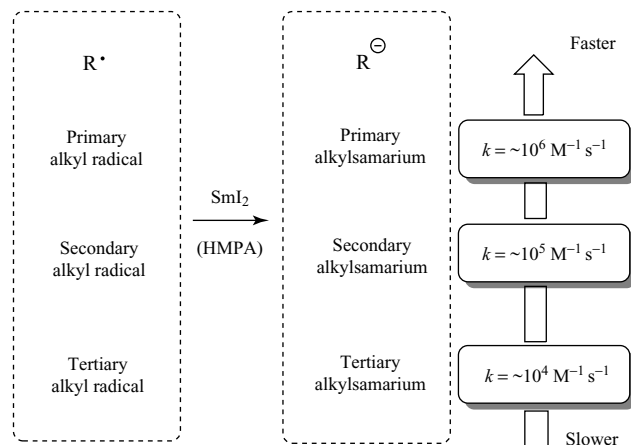
The presence of additives alters the reduction significantly. The addition of HMPA to reactions of SmI₂ and primary or secondary alkyl halides in THF leads to a radical **1** that is rapidly reduced to an organosamarium intermediate **2**. In the presence of a proton donor (alcohol, water, glycol, etc.), the organosamarium intermediate is protonated to form **3**. If an electrophilic carbonyl is present, it can capture the intermediate organosamarium to form a new C–C bond **4** (Scheme 3).⁵³

Reduction of tertiary alkyl halides by SmI₂–HMPA produces organosamarium species of limited stability.⁵⁴ The reduction of aryl and vinyl halides depends on the solvent milieu and the presence of additives. For example, vinyl and aryl halides are reduced to radicals by SmI₂ and subsequently abstract a hydrogen atom from THF. To circumvent this process, Tani utilized SmI₂–HMPA in benzene to prepare aryl organosamarium intermediates.⁵⁵

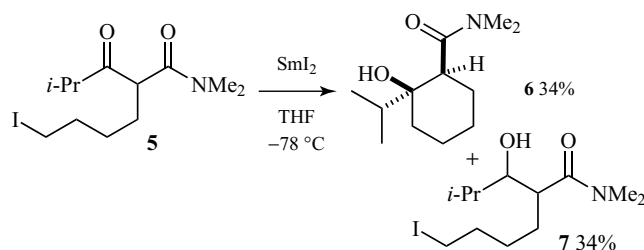
An understanding of the impact of solvent and substrate structure as well as the role of additives is crucial in the design of new reactions mediated by SmI₂. Additionally, a knowledge of reaction rates is indispensable for planning new processes. Curran's work on hexenyl radical clocks determined the rate of reduction of primary, secondary, and tertiary radicals by SmI₂–HMPA.⁵⁶ This data is important when any proposed radical reaction using SmI₂ is considered. For example, radical-based reactions must be faster than the rate of reduction of the radical, and, similarly, any proposed anionic process must take into account competition from fast radical reactions. The data provided from this work is shown in Scheme 4. It is important to note that the efficiency of radical reduction is dependent



Scheme 3 Effect of HMPA on the reduction of organohalides with SmI₂.



Scheme 4 Rates of reduction of alkyl radicals with SmI_2 -HMPA.



Scheme 5 Issues of regioselectivity in an attempted Barbier reaction.

upon the amount of HMPA present in the reaction medium.

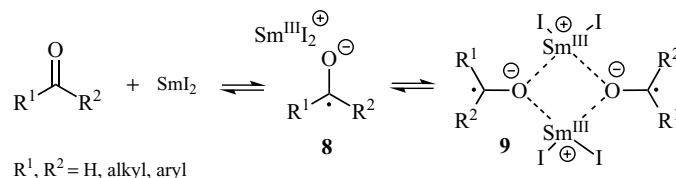
Radical reduction is inefficient when HMPA is absent, and typically 4–5 equiv [based on (SmI_2)] is necessary in most alkyl halide and radical reductions. Rate data for the reduction of radicals to organosamarium intermediates allows an element of predictability but problems can arise when multifunctional substrates are involved. For example, in the attempted intramolecular Barbier reaction of alkyl iodide **5**, treatment with SmI_2 results in the formation of side product **7** in addition to the expected product cyclohexanol **6** (Scheme 5).

In this case, the β -keto amide motif in **5** is reduced at a rate competitive with alkyl iodide reduction, indicating that there are likely two mechanistic pathways through which the reaction proceeds: a thermodynamic pathway initiated by reduction of the R–I bond providing the cyclohexanol **6**, and a kinetic pathway involving chelation of SmI_2 to the β -keto amide and reduction of the ketone carbonyl group to give **7**.⁵⁷

3.2 Reduction of Carbonyls

The reduction of a carbonyl by SmI_2 is the first step in a number of bond-forming reactions and reductions of synthetic importance. These reactions include reduction to alcohols, pinacol coupling, and carbonyl–alkene couplings. In many of these reactions, the use of additives including HMPA and proton donors is critical for their success. The initial electron transfer from SmI_2 to a carbonyl results in an intermediate ketyl radical anion **8** that can form dimeric **9** or higher order ion pairs (Scheme 6).⁵⁸

The equilibrium in the initial reduction is dependent on the identity of substituents and the presence of additives. In dialkyl ketones and alkyl aldehydes, the equilibrium lies to the side of the starting substrate. The presence of aryl groups stabilizes the ketyl radical anion, and in benzophenone derivatives the equilibrium lies toward the ketyl radical intermediate and reductions are fast. Addition of HMPA



Scheme 6 Monomeric and dimeric ketyl radical anions.

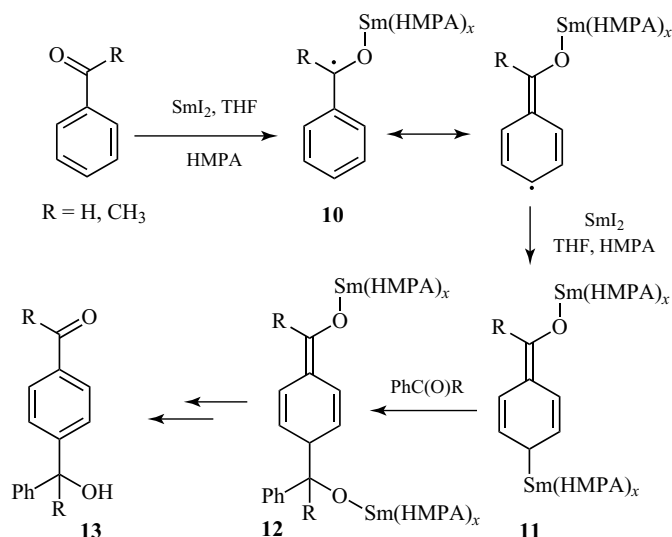
or proton donors, or the presence of a neighboring functional group, also drives the equilibrium toward the ketyl intermediate. Although the reaction shown in Scheme 5 provides an example in which a neighboring functional group leads to an unproductive pathway, proximal functional groups can be useful for enhancing the rate of carbonyl reduction and enhancing the stereoselectivity of reductions. This is best exemplified by the work of Keck who showed that β -hydroxy ketones are stereoselectively reduced by SmI_2 using methanol as a proton donor source (Section 4.2).³³ While the identity of the proton donor source has an impact on the reaction outcome, the key feature of this reaction is the intermediacy of a chelated intermediate. Kinetic studies by Flowers have shown that the presence of a chelation pathway dramatically increases the rate of reduction of carbonyls by SmI_2 .⁵⁹

It is important to recognize that more distant Lewis basic functional groups can also coordinate to SmI_2 , altering reactivity and stereoselectivity. For example, eight- and nine-membered chelates have been invoked to rationalize the stereoselectivity observed in a number of reactions.^{60,61} This facet of SmI_2 -mediated chemistry should be kept in mind when employing the reagent in reactions involving highly functionalized substrates.

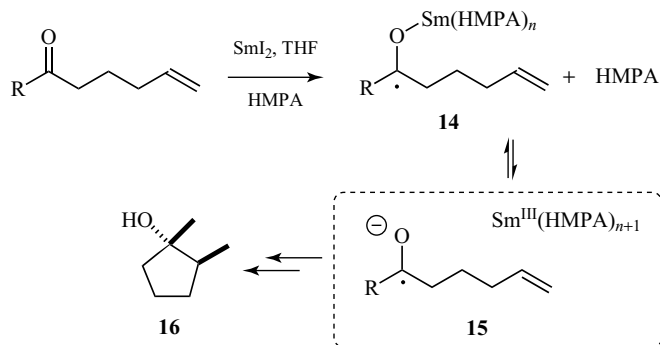
HMPA also has a marked impact on carbonyl reduction using SmI_2 . Elegant studies by Daasbjerg and Skrydstrup have shown that addition of 4–10 equiv of HMPA produces $[\text{Sm}(\text{THF})_2(\text{HMPA})_4]\text{I}_2$ and further addition beyond 10 equiv likely produces $[\text{Sm}(\text{HMPA})_6]\text{I}_2$.⁶ Additionally, coordination of HMPA to SmI_2 provides a more powerful reductant and carbonyl groups are reduced at a faster rate. Mechanistic work by Flowers has shown that the rate of reduction of dialkyl ketones increases by 1–2 orders of magnitude upon the addition of 4–10 equiv of HMPA.²² The results of these studies are consistent with coordination of ketyl radical anion to $\text{Sm}(\text{III})$ even in the presence of 10 equiv

of HMPA. While addition of HMPA increases the rate of reduction of dialkyl ketones by SmI_2 , aryl aldehydes and acetophenones provide “head to tail” coupling products. Fang proposed that, after initial reduction of aryl aldehyde, the $\text{Sm}(\text{HMPA})$ coordinated ketyl radical anion **10** is too sterically encumbered to dimerize through pinacol coupling.⁶² As a consequence, a second reduction occurs to produce dianion **11**, which reacts with substrate to provide **13** after workup. In this example, HMPA plays an important mechanistic role in post-electron-transfer events by altering the reactivity of the ketyl radical anion formed from the carbonyl (Scheme 7).

Recent mechanistic work has revealed several examples of the importance of HMPA after the initial electron transfer. Hoz has studied the mechanistic role of HMPA in reactions involving the ketyl radical formed from 4,4'-dichlorobenzophenone.²⁴ This study showed that increasing the amount of HMPA led to a decrease in the rate of coupling to give the pinacol product. $\text{Sm}(\text{III})$ is required for the bridging in **9**, which is a prelude to dimerization. Hoz proposed that increasing the amount of HMPA reduces the concentration of $\text{Sm}(\text{III})$ available for bridging through competitive coordination with the metal, thus decreasing the rate of coupling. HMPA has also been shown to play an important role in post-electron-transfer steps in carbonyl–alkene coupling reactions. This carbon–carbon bond-forming reaction provides an important route to cyclic alcohols, and the presence of HMPA is often important for obtaining high yields and diastereoselectivities in the transformation. A recent mechanistic study has shown that HMPA plays a further mechanistic role after the initial electron transfer (Scheme 8). Not only does coordination of HMPA to $\text{Sm}(\text{III})$ stabilize the intermediate ketyl **14**, but this coordination also inhibits cyclization. An additional molecule of HMPA liberates the contact ion pair to produce solvent-separated ion



Scheme 7 “Head to tail” coupling of benzaldehydes and acetophenones.



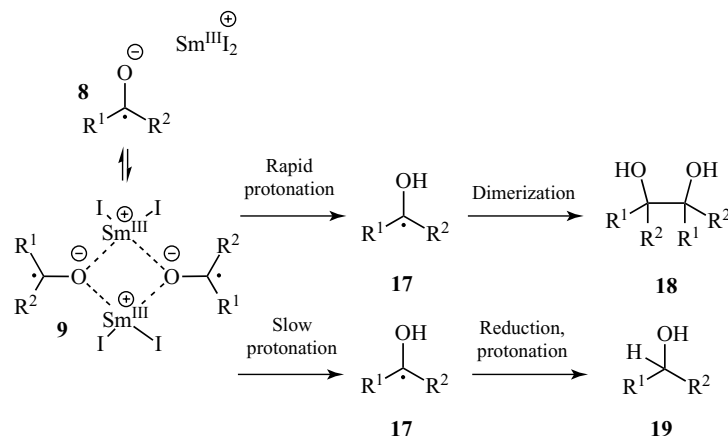
Scheme 8 Role of HMPA in post-electron-transfer steps.

pair **15**, thus relieving the steric constraints that inhibit cyclization.²⁵

Addition of proton donors including alcohols, glycols, and water to SmI_2 also have a profound impact on the rate and mechanism of carbonyl reduction. Kinetic studies by Flowers have shown that the rate of ketone reduction is directly related to the $\text{p}K_{\text{a}}$ of the alcohol proton source used in the reaction and that the proton source must be sufficiently acidic to protonate the ketyl radical anion intermediate produced after the initial electron transfer.³⁶ Hoz has studied the role of 2,2,2-trifluoroethanol as a proton donor in the reduction of benzophenones by SmI_2 .⁵⁸ This study

showed that protonation of dimer **9** (Scheme 6) is an order of magnitude faster than protonation of monomeric ketyl **8**. This allows one to control the follow-up reactions of ketyl radicals generated using SmI_2 (Scheme 9). For example, the use of trifluoroethanol leads to fast protonation of **8** or **9** and formation of intermediate radical **17** and pinacol **18**. If protonation of the ketyl is slow, reduction of **17** provides alcohol **19** through a traditional House mechanism (Scheme 9).

The ability of proton donors to coordinate to SmI_2 also has an important impact on carbonyl reduction. The presence of a coordinated alcohol during reduction of a carbonyl by SmI_2 places



Scheme 9 Importance of protonation on the fate of ketyl radical anions.

the proton in close proximity to the developing negative charge on the ketyl radical anion, facilitating rapid proton transfer. As a consequence, the reduction of less reactive carbonyl substrates is accelerated by high-affinity proton donors such as water. The enhanced reactivity is best exemplified by Procter's work using the $\text{SmI}_2\text{-H}_2\text{O}$ in the reduction of lactones and cyclic diesters, substrates that are highly resistant to carbonyl reduction by electron transfer.^{37,38,63,64} Under certain circumstances, glycols significantly accelerate the rate of carbonyl reduction by SmI_2 . The seminal work of Hilmerisson showed that coordinating alcohols enhance the rate of ketone reduction substantially and that the rate increase is proportional to the number of ethereal oxygens in the proton donor source.⁴² The mechanistic basis for this acceleration is also likely to be related to the proximity of the proton donor to the carbonyl being reduced. Interestingly, a large excess of glycol leads to a decrease in the rate of some reactions. For example, Flowers has shown that addition of glycol sufficient to fill the coordination sphere of SmI_2 decreases the rate of substrate reduction through the production of a sterically encumbered complex that is unable to coordinate to the ketone substrate.¹² Follow-up studies by Procter and Flowers have shown that high-affinity proton donors including water and glycols displace iodide ligands to the outer sphere of $\text{Sm}(\text{II})$ while leaving open coordination sites for carbonyl coordination.⁶⁵ As a consequence, these additives can be used to carry out

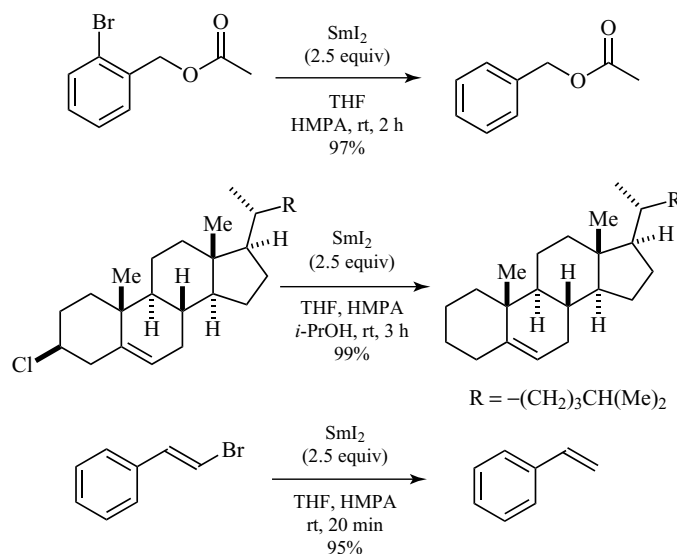
a range of bond-forming reactions and reductions usually reserved for $\text{SmI}_2\text{-HMPA}$.

4 FUNCTIONAL GROUP TRANSFORMATIONS MEDIATED BY SAMARIUM DIIODIDE

Reductants are one of the fundamental classes of reagent used to carry out functional group transformations and SmI_2 is one of the most versatile members of this class. The SmI_2 -mediated reduction of a number of functional groups, often in the presence of other groups, underpins the reagent's ability to mediate carbon–carbon bond-forming reactions, where reactive intermediates are formed, from functional groups, and trapped. The Lewis acidic nature of SmI_2 means that coordination to functional groups facilitates electron transfer. In addition, the $\text{Sm}(\text{III})$ salts that are produced as by-products can enhance the leaving ability of those groups to which it can complex, thereby facilitating their loss. As discussed in Section 2, additives and cosolvents can be used to fine-tune the reactivity of the reagent according to the functional group to be reduced.

4.1 Reduction of Alkyl Halides Using SmI_2

SmI_2 reduces alkyl halides with the following order of reactivity: iodides > bromides > chlorides. In the



Scheme 10 Alkyl halide reduction.

absence of activating additives, the SmI_2 -mediated reduction of primary alkyl iodides and bromides (but not chlorides) to the corresponding alkanes can be achieved under reflux in THF.¹³ Inanaga found that the more powerful reductant obtained by the addition of HMPA to SmI_2 allowed the reduction of alkyl halides to be carried out under milder conditions (Scheme 10).²¹ A detailed discussion of the mechanism of alkyl halide reduction can be found in Section 3.1.

The ability of SmI_2 to reduce alkyl halides is routinely exploited in a number of carbon–carbon bond-forming reactions. Radicals generated from the reduction of alkyl halides can be trapped by alkenes in cyclization reactions (see Section 7), while the alkylsamarium intermediates can be used in intermolecular and intramolecular Barbier and Grignard reactions (see Section 8). The reduction of α -halocarbonyl compounds generates $\text{Sm}(\text{III})$ enolates that undergo Reformatsky reactions (Section 9). The reduction of α -halocarbonyl compounds is discussed in Section 4.4.

In the presence of HMPA, SmI_2 is a useful reagent for the reduction of alkyl halides. Primary, secondary, and tertiary alkyl halides as well as alkenyl and aryl halides are reduced rapidly under these conditions, often in the presence of other functional groups (Scheme 10).^{21,56,66,67}

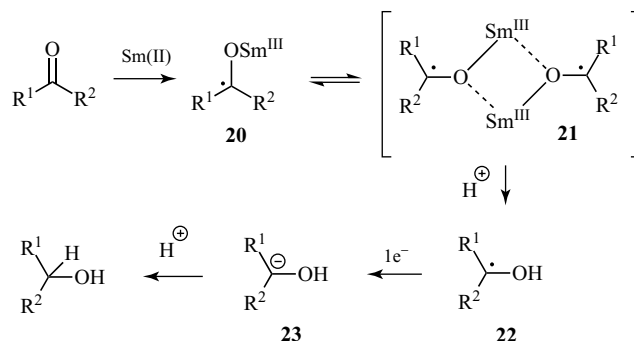
The reduction of alkyl halides with SmI_2 has been used to trigger β -elimination and the formation of alkenes.⁶⁸

4.2 Reduction of Ketones and Aldehydes Using SmI_2

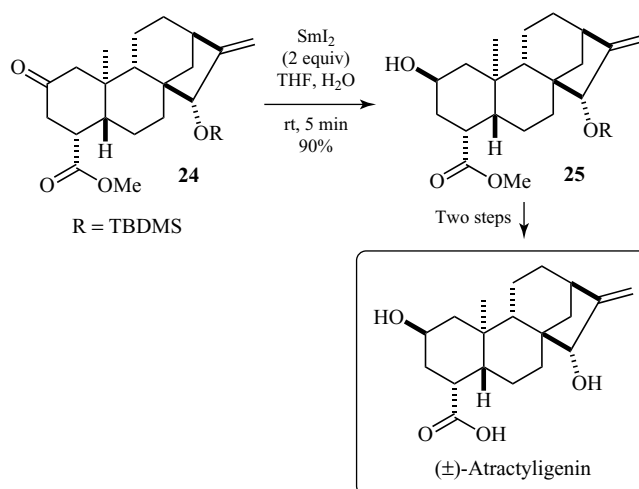
SmI_2 reduces aldehydes and ketones to the corresponding alcohols. In some cases, SmI_2 can display useful reactivity, stereoselectivity, and chemoselectivity that conventional hydride reagents cannot achieve.

The reduction of aldehydes and ketones using SmI_2 (and other low-valent metallic reagents) generates a metal ketyl radical anion **20** that can form dimeric or polymeric ion pairs **21**.^{69,70} In the presence of a proton source, the O–M bond of the metal ketyl radical anion is protonated to form a carbinol radical **22**. Further reduction then forms a hydroxyalkyl carbanion **23**, and protonation gives an alcohol product (Scheme 11).^{69,70}

Further discussion of the mechanistic details of carbonyl reduction and the impact of additives can be found in Sections 2 and 3.2. Ketone reduction using SmI_2 can be highly diastereoselective. For example, in Corey's synthesis of the diterpenoid natural product atractyligenin,



Scheme 11 Reduction of aldehydes and ketones.



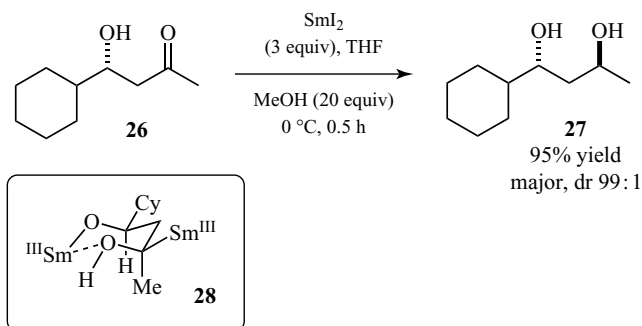
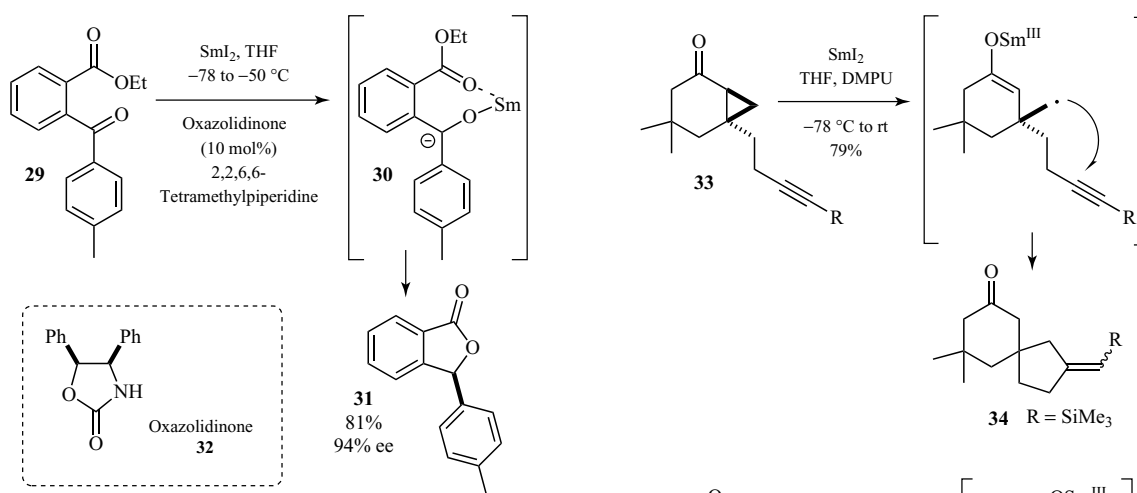
Scheme 12 Ketone reduction in natural-product synthesis.

SmI₂-mediated reduction of ketone **24** proceeded with complete diastereocontrol to give secondary alcohol **25** in 90% yield (Scheme 12).⁷¹

Keck has reported the diastereoselective reduction of β -hydroxy ketones with SmI₂ to give 1,3-*anti* diols.³³ For example, reduction of **26** with SmI₂ in THF with MeOH gave 1,3-*anti* diol **27** in 95% yield and 98% de. The reaction proceeds by initial coordination of Sm(II) to the free hydroxyl, followed by intramolecular electron transfer to the ketone carbonyl to form a ketyl radical anion. A second electron transfer gives alkyl-samarium **28**, in which the C–Sm bond adopts a pseudoequatorial position owing to the steric demand of samarium and its associated ligands, before being protonated by MeOH to give **27** (Scheme 13).³³

Keck showed that protection of the β -hydroxyl group in β -hydroxyketones as *t*-butyldimethylsilyl and benzyl ethers shuts off reduction, underlining the importance of pre-coordination of Sm(II) to the β -oxygen.³³ However, small ether-protecting groups are tolerated as they still allow coordination to Sm(II).⁷² Keck has also reported the diastereoselective reduction of β -amino ketones using SmI₂ in THF, with MeOH as the proton source.⁷³

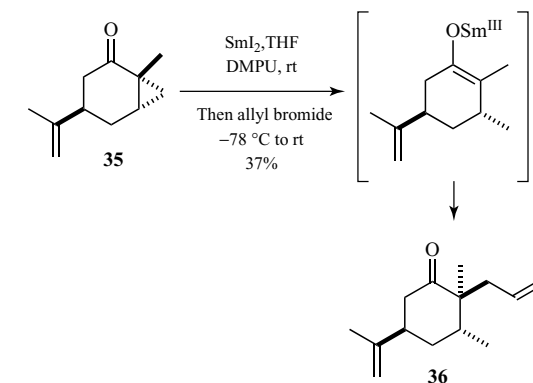
In 2006, Xu and Lin reported a rare example of asymmetric reduction using SmI₂. For example, reduction of 2-acylarylcarboxylate **29** using SmI₂ and a catalytic amount of a chiral proton source gave chelated anion **30** that was protonated by enantiomerically pure oxazolidinone **32**. A stoichiometric achiral proton source 2,2,6,6-tetramethylpiperidine then regenerated the

Scheme 13 Directed reduction of β -hydroxyketones.

Scheme 14 Asymmetric ketone reduction.

chiral proton source. Lactone **31** was obtained in excellent yield and high enantiomeric excess (Scheme 14).⁷⁴

The SmI_2 -mediated reduction of ketones to give ketyl radical anions can result in the cleavage of a carbon–carbon bond α to the carbonyl group. This is a particularly efficient process when the carbon–carbon bond is part of a cyclopropane ring system. In fact, a cyclopropane group attached to a carbonyl group is often used to probe the mechanism of SmI_2 -mediated reactions: if a ketyl radical anion is formed during the reaction, fragmentation of the three-membered ring occurs rapidly.^{75,76} These fragmentation processes proceed via Sm(III) enolate/radical intermediates that can be trapped. For example, Motherwell has shown that the Sm(III) enolates/radicals resulting from ketone reduction



Scheme 15 Ketone reduction and fragmentation.

and cyclopropane fragmentation can be quenched by radicophiles or electrophiles.⁷⁷ Treatment of cyclopropyl ketone **33** with SmI_2 gave bicyclic ketone **34** from interception of an intermediate radical, while exposure of cyclopropylketone **35**

to the reagent gave **36** after quenching of the Sm(III)-enolate intermediate with allyl bromide (Scheme 15).⁷⁷

4.3 Reduction of Carboxylic Acids, Esters, and Amides Using SmI₂

While SmI₂ has been used to partially reduce α -heteroatom-substituted esters, lactones, and amides (see Section 4.4), the reduction of simple unfunctionalized substrates is not usually possible. It is now clear that in certain cases reduction using SmI₂ is possible provided an activating additive is used. For example, Kudo reported the reduction of carboxylic acids with SmI₂, H₂O, and NaOH,⁷⁸ and the reduction of aryl acids, esters, and amides using SmI₂ and H₂O.⁷⁹ The H₂O cosolvent is known to activate SmI₂ (Section 2) and its inclusion is crucial to the success of these reductions.

More recently, Procter has shown that unfunctionalized lactones can be reduced using SmI₂-H₂O.^{37,38,64} The reagent system is selective for the reduction of lactones over esters; furthermore, it displays ring-size selectivity in that six-membered lactones are most readily converted

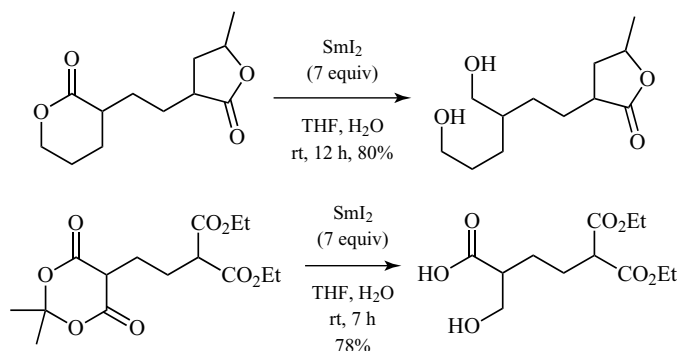
to the corresponding diols (Scheme 16). Procter has also shown that SmI₂-H₂O can be used for the selective monoreduction of cyclic 1,3-diester (Scheme 16).^{63,80}

Recently, Markó used the SmI₂-mediated reduction of aryl esters in a new deoxygenation protocol.⁸¹ Reduction of primary, secondary, and tertiary toluates using SmI₂-HMPA at reflux in THF (or THP) gave the corresponding deoxygenated products via ketyl radical anions **37** (Scheme 17).⁸¹

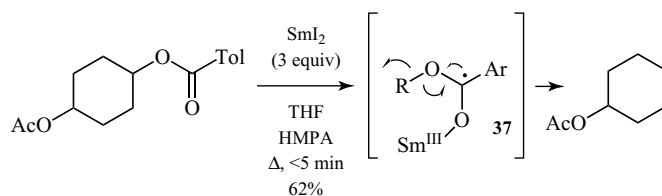
4.4 Reduction of α -Heteroatom-Substituted Carbonyl Groups Using SmI₂

The reduction of α -heteroatom-substituted carbonyl compounds to the parent carbonyl compound is a common use for SmI₂. A range of heteroatom substituents can be removed efficiently in the presence of a range of other functional groups, and the Sm(III) enolates generated can be used in C-C bond-forming reactions (Section 9).

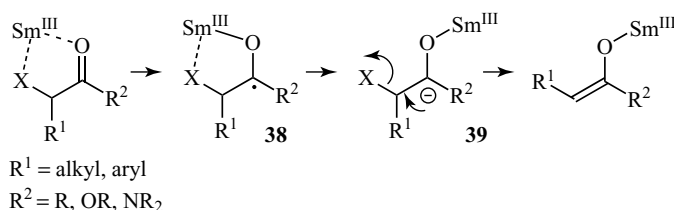
The mechanism of reduction is thought to proceed via ketyl radicals **38** and carbanions **39**, which undergo β -elimination to produce Sm(III) enolates that are then protonated (Scheme 18).⁸² In some



Scheme 16 Lactone and cyclic 1,3-diester reduction.



Scheme 17 Aryl ester reduction and fragmentation.

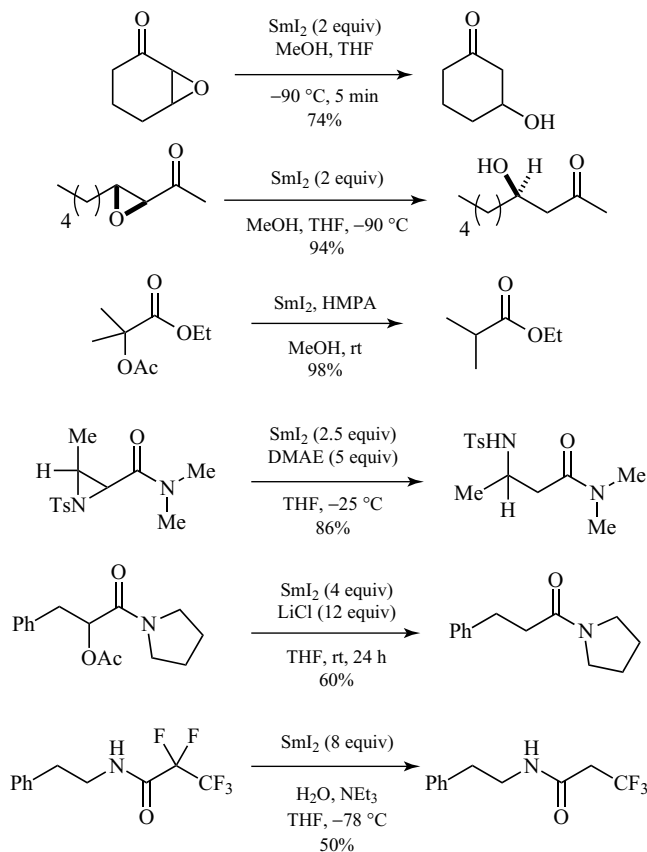


Scheme 18 Reduction of α -heteroatom substituted carbonyl compounds.

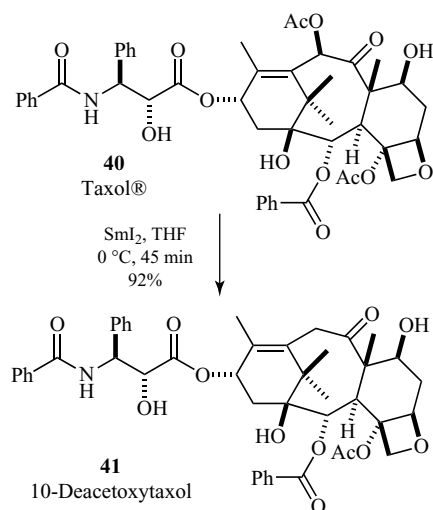
cases, electron transfer to the α -substituent generating a radical anion intermediate and fragmentation may provide an alternative mechanism not involving carbonyl reduction (Scheme 18).⁸³

Molander has shown that a range of α -oxy, α -halo, and α -sulfanyl ketones undergo efficient conversion to the parent ketones with no over-reduction of the ketone carbonyl.⁸³ α,β -Epoxy ketones and 2-acylaziridines are also

reduced to give β -hydroxy and β -amino ketones, respectively.^{84,85} α -Heteroatom-substituted esters, lactones, and amides can also be partially reduced to the parent carbonyl compound using SmI_2 although activating additives are required.^{85–88} Recently, the defluorination of esters and amides using the $\text{SmI}_2\text{--Et}_3\text{N--H}_2\text{O}$ reagent system has been described (Scheme 19),⁸⁹ and the use of SmI_2 for the reductive carbon–nitrogen bond cleavage



Scheme 19 Partial reduction of α -heteroatom-substituted carbonyl compounds.



Scheme 20 Chemoselective reduction of an α -heteroatom-substituted ketone.

of α -amino carbonyl compounds has recently been reviewed.⁹⁰

The chemoselectivity of SmI_2 in this transformation is highlighted in Holton's one-step synthesis of 10-deacetytaxol **41** from Taxol® **40** (Scheme 20).⁹¹

Procter has applied the reduction of α -heteroatom-substituted amides in a linker strategy for solid-phase and fluorous synthesis (Scheme 21).⁷⁶

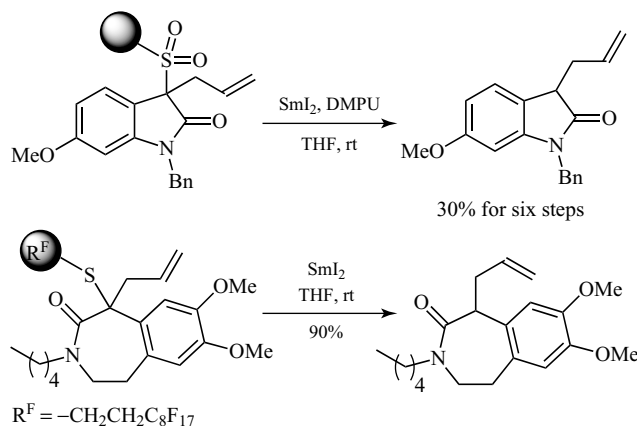
The reduction of α -heteroatom-substituted carbonyl compounds with SmI_2 has been used to

trigger elimination and the selective synthesis of α,β -unsaturated esters and amides.^{68,92,93}

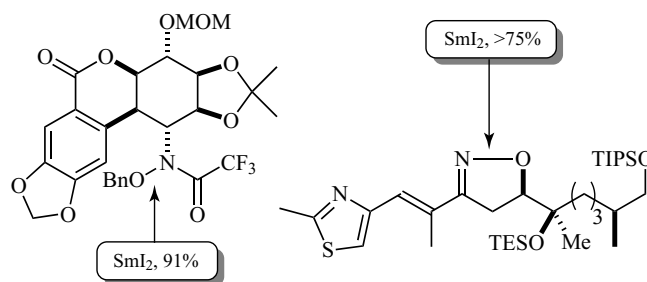
4.5 Reduction of Nitrogen-Containing Compounds

In Kagan's early investigations, it was shown that nitroarenes could be reduced to the corresponding anilines using SmI_2 .⁹⁴ Subsequently, Kende showed that primary, secondary, or tertiary nitroalkanes could also be reduced using SmI_2 to the corresponding hydroxylamines or amines, depending on the amount of reagent used.⁹⁵ SmI_2 can reduce N–O bonds in many other substrates including hydroxamic acid derivatives,⁹⁶ pyridine *N*-oxides,⁹⁷ isoxazoles,⁹⁸ and isoxazolines,^{99,100} often when the use of other reagents prove unsuccessful (Scheme 22).

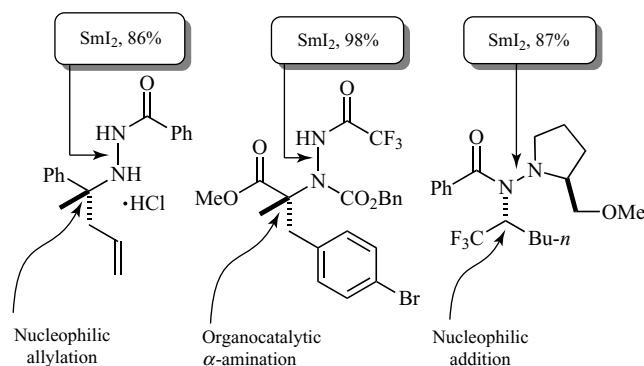
Since Kagan's first report of N–N bond reduction using SmI_2 ,⁹⁴ the reagent is now routinely used for the transformation. For example, the reaction has been used widely in asymmetric synthesis to reduce the products of asymmetric additions to, or reductions of,¹⁰¹ hydrazone derivatives. Selected examples include the reduction of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazones,¹⁰² and the reduction of activated N–N bonds in adducts resulting from asymmetric allylation¹⁰³ and organocatalytic α -amination¹⁰⁴ (Scheme 23).



Scheme 21 Linker strategy involving the reduction of α -heteroatom-substituted amides.



Scheme 22 Examples of N–O bond cleavage.



Scheme 23 Reduction of N–N bonds.

4.6 Reduction of Electron-Deficient Alkenes

In the early 1990s, Inanaga and Alper independently reported the conjugate reduction of α,β -unsaturated esters and amides with SmI_2 , activated by the additives *N,N*-dimethylacetamide (DMA) and HMPA, respectively.^{105,106} The reduction of electron-deficient alkenes in lactones and cyclic enones using SmI_2 is also possible.¹⁰⁷ More recently, the use of the SmI_2 – H_2O –amine system has been shown to be effective for the selective reduction of α,β -unsaturated esters and conjugated double and triple bonds.^{43,108} Keck utilized SmI_2 to reduce an electron-deficient alkene in an approach to the marine natural product dolabelide B.¹⁰⁹ Treatment of α,β -unsaturated ester **42** with SmI_2 in the presence of MeOH and DMA gave **43** in moderate yield (Scheme 24).

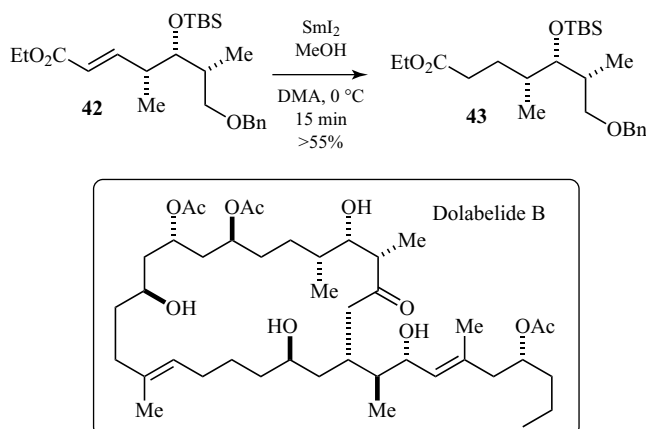
The reduction of electron-deficient alkenes is thought to proceed through radical enolate species **44**. Further reduction generates dianionic species **45**, which undergo stepwise protonation to give

the product of reduction via Sm(III) enolates (Scheme 25).

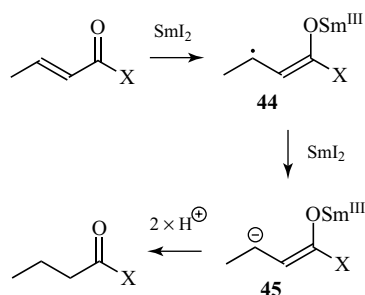
4.7 Reduction of Sulfur-Containing Compounds

Sulfoxides are reduced to sulfides by SmI_2 activated by HMPA.¹¹⁰ The reduction of sulfones with SmI_2 can result in deoxygenation, to give the parent sulfide,¹¹⁰ or carbon–sulfur bond cleavage, depending on the substrate and the reaction conditions employed.¹¹¹ Gin has utilized the reduction of an alkyl phenyl sulfone in a recent synthesis of the anti-leukemia natural product (–)-deoxyharringtonine.¹¹² Treatment of complex sulfone **46** with SmI_2 –HMPA gave **47** in 74% yield (Scheme 26).

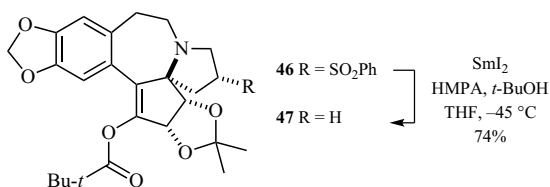
The most important application of sulfone reduction using SmI_2 is in the modified Julia–Lythgoe olefination.¹¹³ Fukumoto¹¹⁴ and Keck²⁹ independently reported the use of SmI_2 –HMPA and SmI_2 –DMPU, respectively, in olefination processes



Scheme 24 Conjugate reduction in natural product synthesis.



Scheme 25 Mechanism of conjugate reduction.



Scheme 26 Sulfone reduction in natural product synthesis.

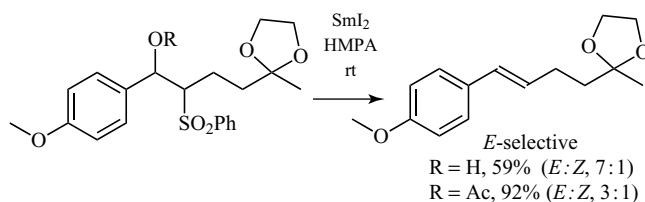
involving phenylsulfones. Both approaches are selective for the formation of *E*-alkenes. The use of SmI_2 shows considerable advantages over the use of Na-Hg in the classical olefination (Scheme 27). More recently, Markó has used SmI_2 to reduce β -benzoyloxy sulfones¹¹⁵ and sulfoxides¹¹⁶ in modified Julia–Lythgoe olefinations.

5 PINACOL COUPLINGS

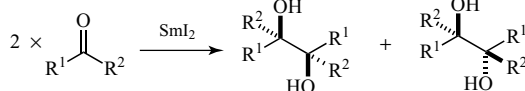
The reductive coupling reaction between two carbonyl compounds represents an important synthetic tool for the preparation of carbon–carbon bonds.^{117–121} Typically, low-valent metals or metal complexes promote these reactions and it is well accepted that metal ketyl radical anions are intermediates. Owing to the ease with which the reagent is prepared and used, and the high yields that are often obtained, SmI_2 has become one of the most popular reagents for mediating pinacol couplings (Scheme 28).

Although the precise mechanism for SmI_2 -mediated pinacol couplings is not fully known, there are three possible pathways depending on the character of the carbonyl functionality undergoing reductive coupling and whether the reaction is intra- or intermolecular (Scheme 29). An initial reduction step involving a rapid and reversible inner-sphere electron transfer from Sm(II) to the C=O bond resulting in the formation of the Sm(III) -bound ketyl radical anion is common to all three mechanisms. If the carbonyl group is easily reduced, then a high concentration of the ketyl is generated, leading to dimerization (Path A). This mechanism is believed to operate for the intermolecular coupling of aldehydes and activated ketones.

In Path B, a second electron transfer reduces the ketyl radical anion, generating a dianionic intermediate that adds to a second equivalent of carbonyl substrate. Finally, the ketyl radical anion may undergo radical addition to the carbonyl group of a



Scheme 27 Sulfone reduction in the Julia–Lythgoe olefination.



Scheme 28 Intermolecular pinacol coupling.

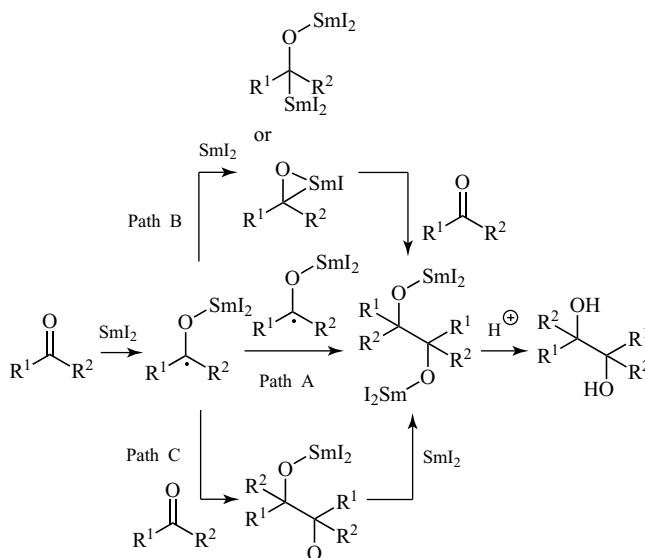
second equivalent of substrate, generating a highly reactive oxy radical species (Path C). Although this addition is typically unfavorable, activation of the carbonyl substrate by the Lewis acidic Sm(III) center of the ketyl radical anion and rapid reduction of the highly reactive oxy radical intermediate by SmI₂, resulting in the formation of a stable Sm(III) complex, would facilitate the addition.

Path C explains why α -heteroatom-substituted carbonyl compounds undergo intramolecular pinacol couplings without cleavage of the α -heteroatom substituent: Pinacol cyclization is faster than

the reduction of the ketyl radical anion to the corresponding anion. Furthermore, coordination of Sm to the second carbonyl group after the first electron-transfer step, explains the selectivity for *cis*-diol formation in five- and six-membered ring synthesis.

5.1 Intermolecular Pinacol Couplings

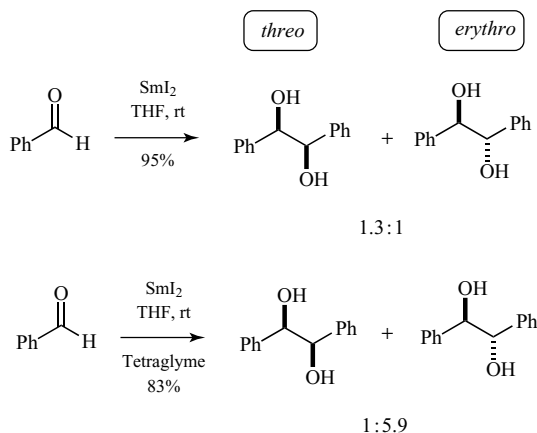
SmI₂ promotes the intermolecular reductive dimerization of aldehydes or ketones giving rise to diols.^{122–124} Although aryl aldehydes and ketones often react rapidly, aliphatic aldehydes and ketones can react more slowly and the addition of activating additives such as HMPA is required.²¹ In most cases, particularly with simple aldehydes, both the threo- and erythro-diols are



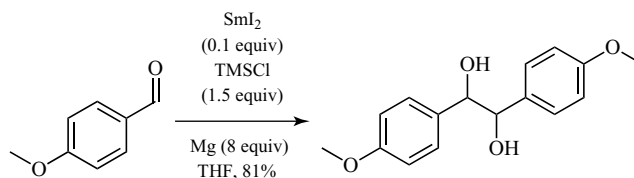
Scheme 29 Alternative mechanisms for pinacol coupling.

formed, with low stereocontrol.¹²⁵ However, strategies are available to improve the levels of stereoselectivity observed in SmI_2 -promoted pinacol couplings. For example, Skrydstrup has reported that the use of tetraglyme and its derivatives as additives can increase diastereoselectivities while maintaining good coupling yields (Scheme 30).^{125,126}

Uemura has demonstrated that enantiomerically pure (arylaldehyde)tricarboxylchromium complexes afford exclusively the threo-pinacols, providing an asymmetric synthesis of hydrobenzoin.¹²⁷ In 1996, Endo reported a protocol for pinacol coupling using catalytic amounts of SmI_2 with magnesium as the stoichiometric reductant and tetramethylsilyl chloride (TMSCl) to liberate Sm(III) from the pinacolate. The method provides good yields of the vicinal diol products and employs only 10 mol% of SmI_2 (Scheme 31).¹²⁸ Greeves and Aspinall later modified this protocol by using Me_2SiCl_2 as the chlorosilane and tetraglyme as an additive to improve the diastereoselectivity of the reductive couplings.¹²⁹



Scheme 30 Intermolecular pinacol couplings of aldehydes.

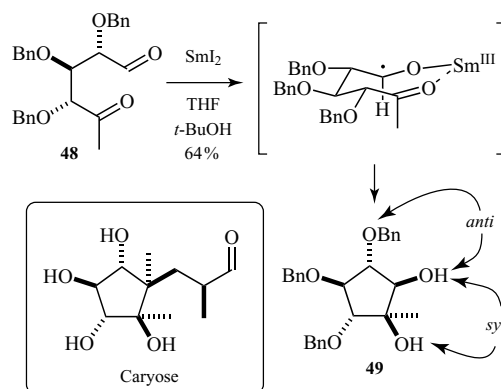


Scheme 31 Pinacol couplings using catalytic SmI_2 .

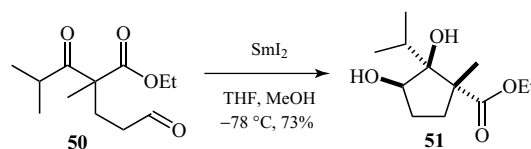
The use of this protocol provided good to excellent diastereoselectivities in a range of intermolecular and intramolecular pinacol coupling reactions. Coordination of glyme to both Sm(II) and Sm(III) is believed to be important in enhancing the diastereoselectivity of the pinacol couplings as well as facilitating the reduction of Sm(III) to Sm(II) .¹²⁹

5.2 Intramolecular Pinacol Couplings

In contrast to intermolecular couplings, high levels of diastereoselectivity can be attained in the cyclization of a variety of 1,5- and 1,6-dicarbonyl



Scheme 32 Diastereoselective, intramolecular pinacol coupling.

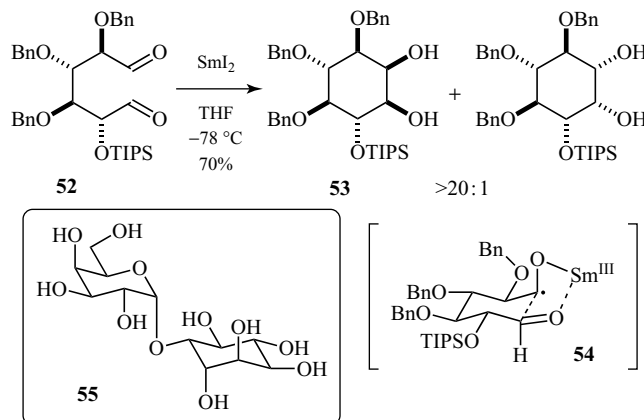


Scheme 33 Chelation control in diastereoselective intramolecular pinacol couplings.

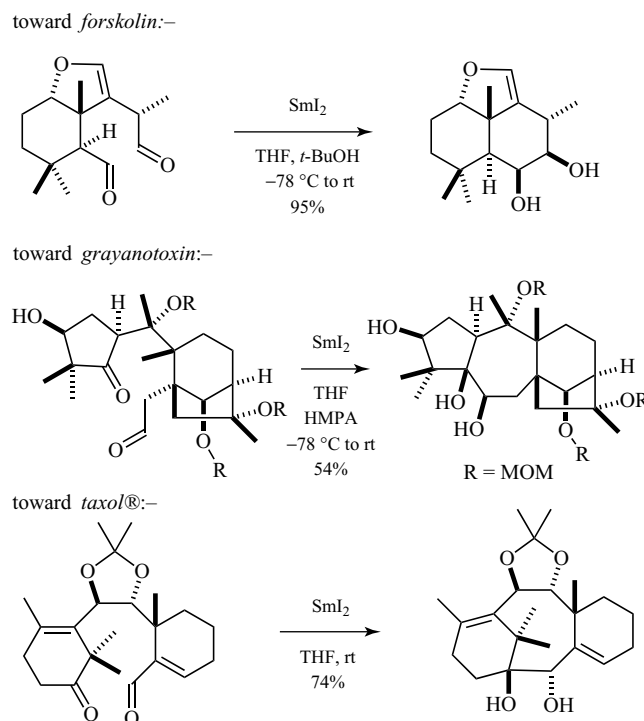
substrates, leading almost exclusively to the formation of *cis*-vicinal diols. Electron-withdrawing substituents α to the reacting carbonyl can act as controlling elements and the *cis*-1,2-diol forms anti to the substituent in the product. For example, Iadonisi reported an intramolecular SmI₂-promoted pinacol coupling of the keto-aldehyde **48** leading

to the *cis*-diol **49** with high diastereocontrol in the synthesis of caryose (Scheme 32).¹³⁰

Chelation to a neighboring Lewis basic carbonyl can also control the diastereoselectivity of pinacol cyclizations. For example, cyclization of ketoester **50** proceeds with high diastereocontrol to give *cis*-diol **51** (Scheme 33).^{131,132} The application of



Scheme 34 Effect of substituents on the diastereoselectivity of pinacol cyclization.



Scheme 35 Intramolecular pinacol couplings in natural-product synthesis.

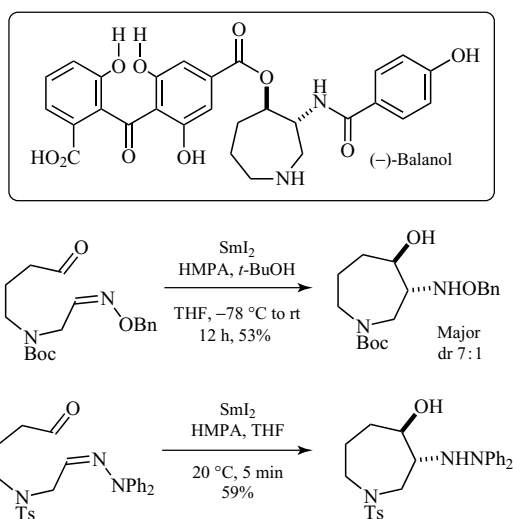
analogous chelation control in six-membered ring formation is less effective.

The stereochemical outcome of SmI_2 -mediated pinacol couplings to form six-membered rings is also dependent on neighboring substituents. For example, in d'Alarcao's studies on the synthesis of the myo-inositol derivative **55**, non- C_2 -symmetrical dialdehyde **52** underwent reductive cyclization on treatment with SmI_2 to give *cis*-diol **53** via transition state structure **54** (Scheme 34).¹³³

The intramolecular SmI_2 -mediated pinacol coupling has been exploited for the construction of different ring sizes in many natural product syntheses. A selection of applications is shown in Scheme 35.¹³⁴

5.3 Pinacol Couplings of Imines and Their Equivalents

Pinacol couplings in which one of the coupling partners is an imine derivative are useful for the construction of vicinal amino alcohols. Oximes and hydrazones undergo *heteropinacol* cyclizations resulting in five- to seven-membered carbo- and heterocycles. In contrast to analogous pinacol cyclizations of dicarbonyl compounds, trans products are often the major products formed from heteropinacol



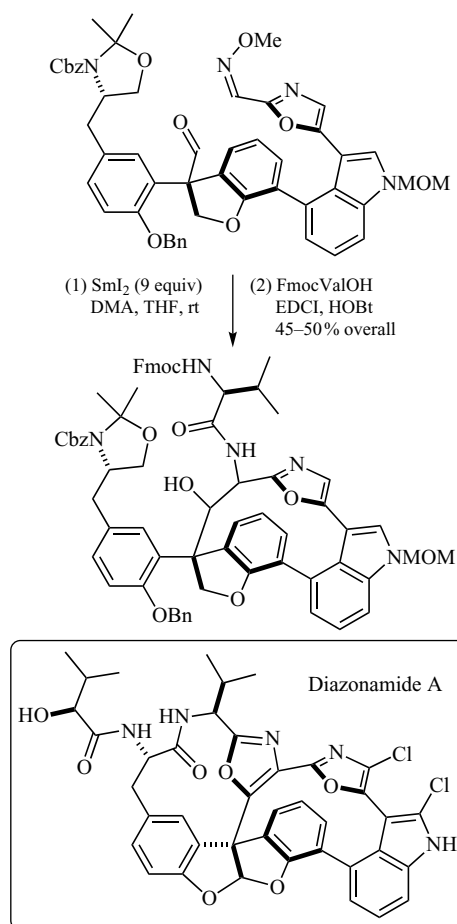
Scheme 36 Heteropinacol couplings in natural product synthesis.

cyclizations.^{135,136} As oximes and hydrazones are not easily reduced, the mechanism for these reactions most likely involves addition of a ketyl radical anion to the $\text{C}=\text{N}$ double bond.

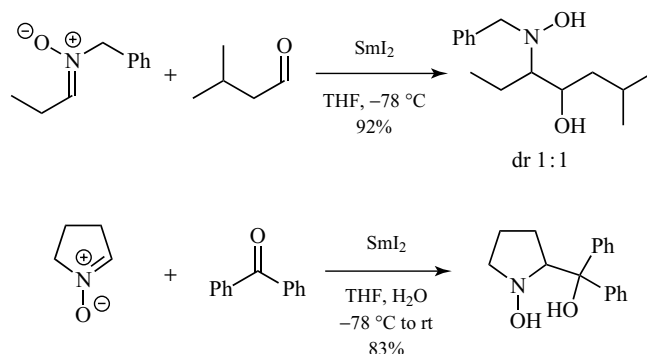
Naito¹³⁷ and Skrydstrup¹³⁸ have reported the stereoselective synthesis of the azepine ring of the protein kinase C (PKC) inhibitor balanol using a heteropinacol cyclization (Scheme 36).

Nicolaou used an aldehyde–oxime coupling to construct the 12-membered macrocyclic core of diazonamide A in an impressive total synthesis of the complex natural product (Scheme 37).^{139,140}

Analogous intermolecular couplings have only recently been shown to be a viable strategy for the preparation of vicinal amino alcohols. In 2002,



Scheme 37 Heteropinacol coupling in the synthesis of diazonamide A.



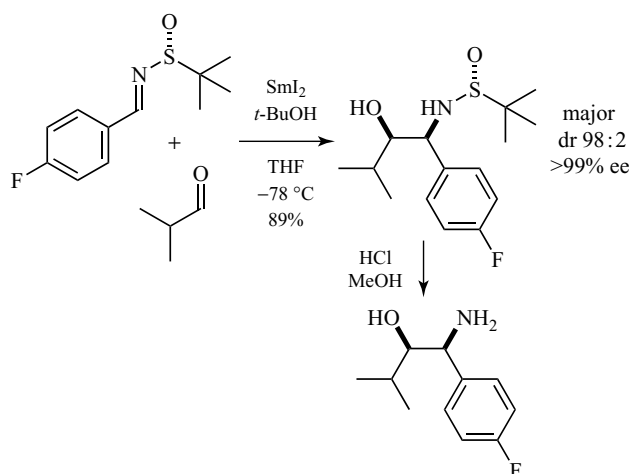
Scheme 38 Intermolecular heteropinacol couplings of nitrones.

Py and Vallée described the intermolecular heteropinacol couplings of nitrones with aldehydes and ketones, generating *N*-hydroxyamino alcohols (Scheme 38).^{141,142} More recently, Huang described the use of chiral nitrones in SmI_2 -mediated reductive couplings with aldehydes, ketones, and acyl chlorides.¹⁴³

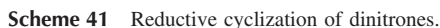
Intramolecular carbonyl–nitron couplings have been studied and, after concurrent N–O bond reduction with excess SmI_2 , provided *syn*-amino alcohols, thereby complementing analogous anti-selective cyclizations of oximes and hydrazones.¹⁴¹ In nitron–carbonyl couplings, a mechanism in which the nitron is preferentially reduced to a ketyl radical anion-like intermediate followed by addition to the carbonyl is likely to operate.

Although Uemura has reported the stereoselective heteropinacol coupling of planar chiral ferrocenecarboxaldehydes with imines,¹⁴⁴ stereoselective intermolecular heteropinacol couplings have only recently been developed.¹⁴⁵ Xu has shown that the SmI_2 -induced reductive coupling of *N*-*t*-butylsulfinyl imines with aliphatic aldehydes provides the pinacol products in high yield and with excellent diastereoselectivity (Scheme 39).

Xu has also developed asymmetric approaches to vicinal diamines via the homo- and cross-pinacol coupling of imine derivatives. Reductive homocoupling of aryl *N*-*t*-butylsulfinyl imines upon treatment with SmI_2 –HMPA gave C_2 -symmetrical vicinal diamines as single stereoisomers after removal of the sulfinyl groups from nitrogen



Scheme 39 Intermolecular heteropinacol couplings with *N*-*t*-butylsulfinyl imines.

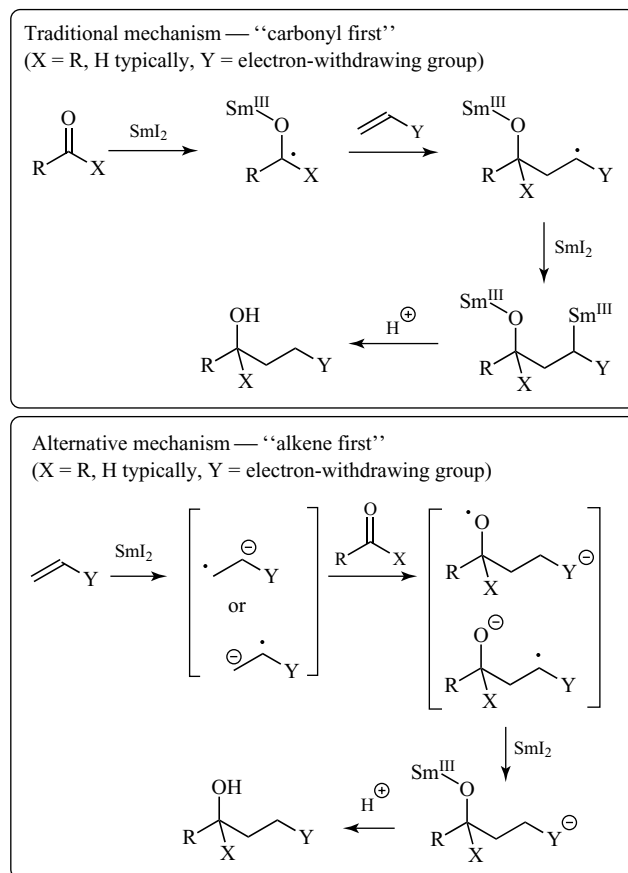


Finally, Skrydstrup has reported that five-membered ring systems containing *cis*-diamine motifs can be prepared using a SmI_2 -mediated reductive cyclization of dinitrones.¹⁴⁸ The couplings show similarities to intramolecular pinacol couplings in that syn-products predominate (Scheme 41).

6 CARBONYL-ALKENE COUPLINGS

Electron-deficient olefins represent the best coupling partners in intermolecular SmI₂-promoted carbonyl–alkene couplings. These reactions have been described as ketyl–olefin couplings in which a ketyl radical anion is generated from the carbonyl substituent followed by addition to the unsaturated C–C bond. Subsequent reduction of the new radical intermediate leads to a Sm(III) enolate or enolate-type species, which abstracts a proton from an acidic source (Scheme 42). An alternative mechanism involving conjugate reduction of the double bond followed by anionic (or possibly radical) addition to the carbonyl group may also operate when electron-deficient alkenes are involved (Scheme 42).

Procter has suggested that a study of the dependency of reaction outcome on the stereochemistry of the double bond in the alkene can be used to gain information on the mechanistic "direction" of reductive couplings.^{34,149} In cases where the alkene stereochemistry has a marked effect on the reaction outcome, a traditional "carbonyl first" mechanism may be in operation, whereas in reactions where alkene stereochemistry has little effect, an alternative mechanism in which the alkene is



Scheme 42 Mechanisms of carbonyl–alkene coupling.

reduced first and a common reactive intermediate is formed, regardless of the geometry of the starting alkene, may operate.^{34,149}

In contrast to *intermolecular* carbonyl–alkene couplings, *intramolecular* variants tolerate a wide range of radical acceptors including unactivated alkenes. In these cases, the reactions must proceed through the “traditional” pathway, as the alkene cannot be reduced under the reaction conditions.

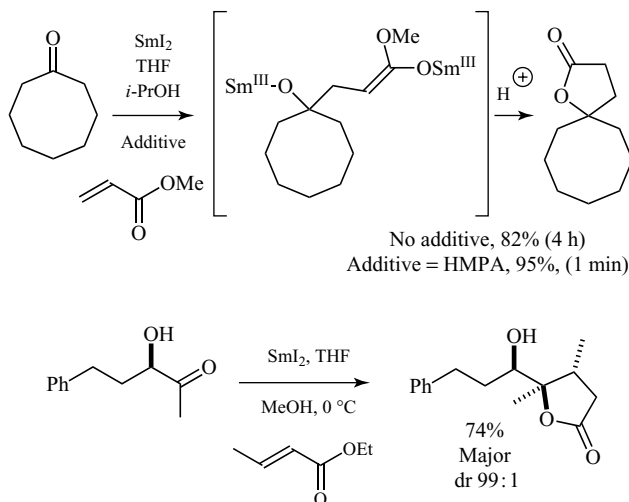
6.1 Intermolecular Carbonyl–Alkene Couplings

Essentially all carbonyl–alkene coupling reactions require the presence of an alcohol proton source for high yields to be obtained. Although the additive can perform different functions in these reactions (see

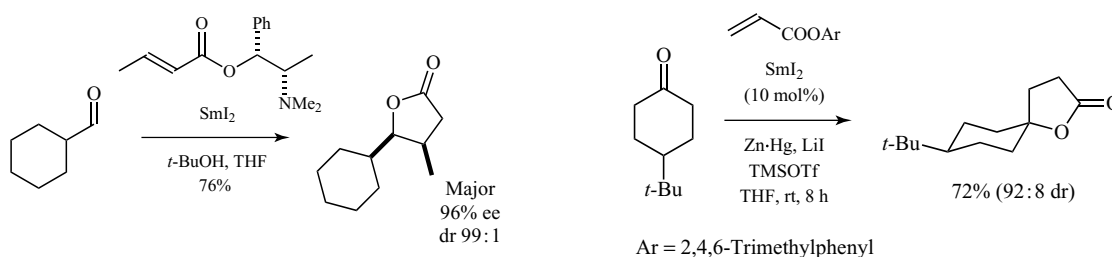
Section 2), one important role of the alcohol additive is to quench anionic intermediates. The addition of HMPA accelerates couplings by the generation of a more powerful reducing agent.¹⁵⁰

Fukuzawa and Inanaga showed that the coupling of ketones and aldehydes with acrylates mediated by SmI_2 often gives γ -lactones after cyclization of the intermediate alkoxide produced from the carbon–carbon bond-forming step (Scheme 43).^{150–152} The inclusion of a chelating α -substituent in the ketone component has been shown to induce high levels of asymmetric induction in the formation of adducts (Scheme 43).¹⁵³

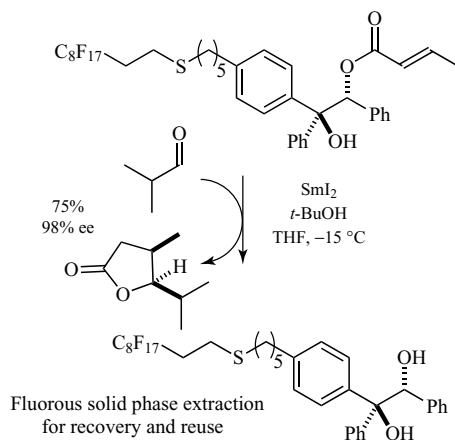
In 1997, Fukuzawa reported the asymmetric synthesis of γ -lactones by reductive coupling of aldehydes and ketones with acrylates and crotonates bearing the chiral auxiliary *N*-methylephedrine (Scheme 44).¹⁵⁴ This reaction has been used



Scheme 43 Intermolecular carbonyl–alkene couplings.



Scheme 45 Reductive coupling of ketones with acrylates.



Scheme 44 Asymmetric intermolecular carbonyl–alkene couplings.

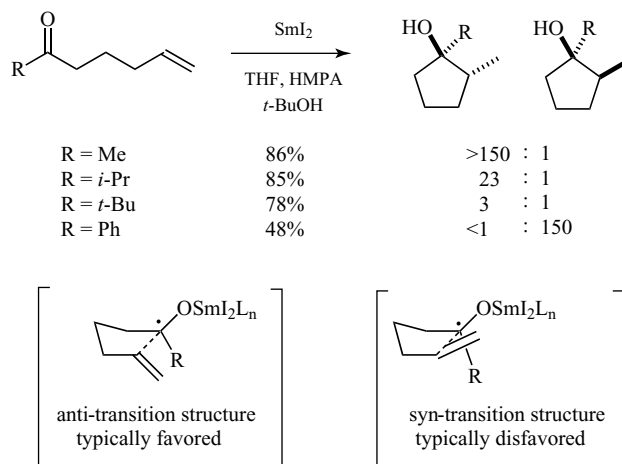
A range of alkenes bearing other chiral auxiliaries¹⁵⁸ and enantiomerically pure aryl aldehyde:Cr(CO)₃ complexes have been used in analogous asymmetric couplings.¹⁵⁹

In a seminal study on the development of a catalytic SmI₂ reagent system, Corey showed that the combination of SmI₂, LiI, and Me₃SiOSO₂CF₃ (TMSOTf) with Zn–Hg gave excellent results in the reductive coupling of ketones with acrylates to produce γ -butyrolactones (Scheme 45).¹⁶⁰

6.2 Intramolecular Carbonyl–Alkene Couplings

Intramolecular carbonyl–alkene couplings have been used to prepare a wide range of carbo- and heterocyclic systems of varying ring size and are tolerant of several types of acceptors, including

by Procter in solid-phase and fluororous asymmetric catch-and-release approaches to γ -lactones using acrylates and crotonates and a chiral linker (Scheme 44).^{155–157}



Scheme 46 Intramolecular carbonyl–alkene couplings.

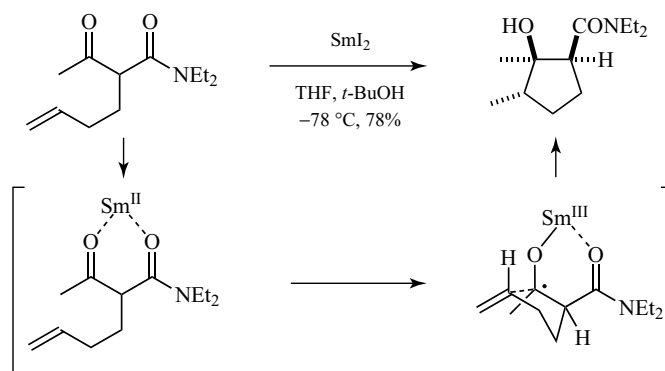
unactivated alkenes. Good levels of diastereocontrol are typically observed in these cyclizations.

The cyclization of isolated ketones onto unactivated alkenes represents the most straightforward carbonyl–alkene cyclization. In common 5-*exo*-cyclizations, stereoselectivities depend markedly on the substituent on the ketone (Scheme 46).¹⁶¹ HMPA is used to allow the ketyl additions to proceed at a satisfactory rate. The outcome of 5-*exo*-carbonyl–alkene cyclizations can be explained by invoking a chair-like anti-transition structure.¹⁶¹ Increasing the size of the ketone can lead to a reversal of diastereoselectivity.

High levels of diastereoselectivity are also commonly observed for 5-*exo*-cyclizations leading to both fused and bridged bicyclic ring systems.^{161,162}

Alkynes can also be used as radical acceptors for the generation of cyclopentanols bearing an exocyclic alkene, but yields are often lower than those obtained in the related cyclizations of alkenes. Activation of the alkynes by electron-withdrawing groups or silyl substituents leads to more efficient 5-*exo*-dig ring closure.¹⁶³ Molander has demonstrated that 5-*exo*-transannular reductive carbonyl addition to an endo- or exocyclic alkene can be highly effective for the formation of bicyclic ring systems.¹⁶⁴

The presence of a proximal carbonyl group that can coordinate to Sm(II) and Sm(III) is advantageous, as HMPA is not required to promote reduction (the electron-withdrawing nature of the substituent lowers the lowest unoccupied



Scheme 47 Chelation control in a carbonyl–alkene cyclization.

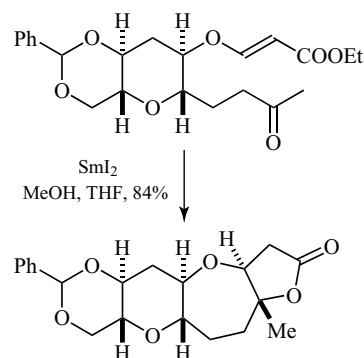
molecular orbital (LUMO) of the carbonyl) and chelation of the Sm(III) in the ketyl intermediate to the group leads to high diastereoselectivity (Scheme 47).¹³²

In addition to the popular five-membered ring-forming reactions with non-activated alkenes, the 6-*exo* variant has been used to generate cyclohexanols and bicyclic alcohols.^{161,162} Molander has also described unusual 8-*endo* cyclizations.¹⁶⁵ The ability of SmI₂ to promote the formation of medium-sized rings can be attributed to the high steric bulk of the alkoxy-samarium–HMPA substituent that protects the radical anion from alternative reaction pathways such as hydrogen abstraction. Molander has exploited an 8-*endo* cyclization in the synthesis of (+)-isochizandrin (Scheme 48).¹⁶⁶

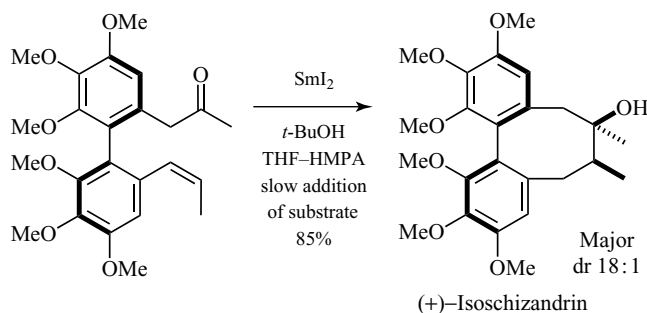
The use of electron-deficient olefins in these cyclization reactions has been widely studied and a variety of cyclic systems have been prepared. In most cases, the use of HMPA is not necessary for achieving high conversions, and chelation control can therefore lead to products with high diastereoselectivity. For example, Weinges and Procter have reported an efficient 4-*exo* cyclization of γ,δ -unsaturated aldehydes to give

anti-cyclobutanols in good yield (Scheme 49).^{167–169} The cyclization has been employed by Procter in an approach to the natural product pestalotiopsin A.¹⁷⁰

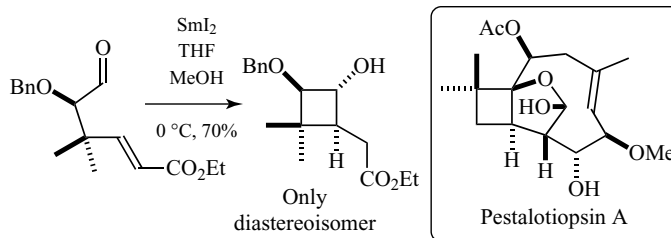
Carbonyl–alkene additions are also effective for the diastereoselective construction of oxacyclic ring systems. Nakata has shown that even the formation of seven-membered cyclic ethers using the transformation can be efficient and has



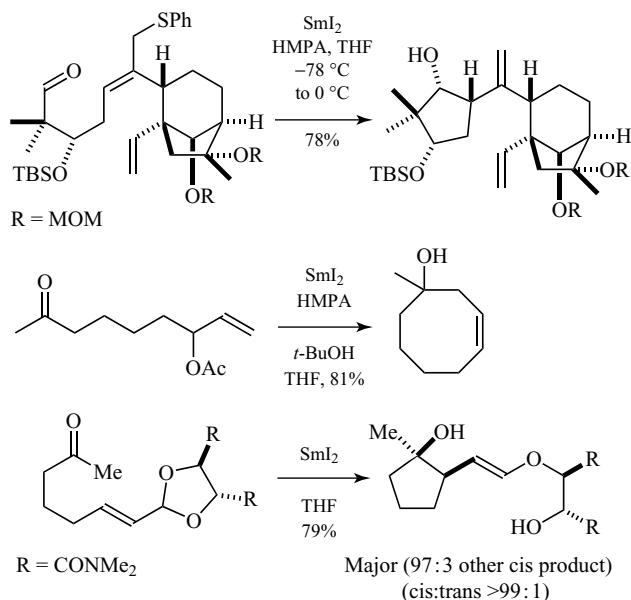
Scheme 50 Heterocycle formation using a carbonyl–alkene cyclization.



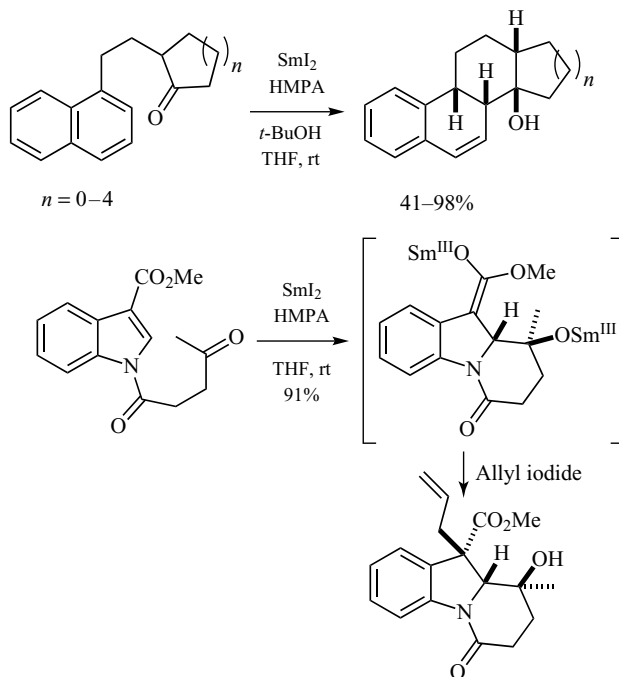
Scheme 48 8-*endo* Carbonyl–alkene cyclization in natural product synthesis.



Scheme 49 4-*exo*-Carbonyl–alkene cyclizations.



Scheme 51 Cyclizations involving alkenes with allylic leaving groups.



Scheme 52 Carbonyl–arene cyclizations.

utilized the strategy to form the E ring of the polycyclic ether marine natural product yessotoxin (Scheme 50).¹⁷¹

An alternative means of promoting carbonyl–alkene cyclizations is to use an alkene-activating

group that is removed spontaneously after cyclization by elimination from an organosamarium intermediate. Allylic sulfides,¹⁷² acetates,¹⁶⁵ and chiral acetals,¹⁷³ have been employed in carbonyl–alkene cyclizations (Scheme 51).

6.3 Carbonyl–Arene Couplings

In addition to alkenes, arenes can sometimes be used as radical acceptors in carbonyl–alkene couplings. Studies carried out by Reissig have demonstrated the utility of these reactions for the synthesis of polycyclic systems.¹⁷⁴ For example, cyclizations of naphthyl ketones,¹⁷⁴ indolo ketones,^{175,176} and pyrrolo ketones¹⁷⁶ proceed in good yield and often with high levels of diastereocontrol (Scheme 52).

6.4 Reductive Couplings of Imines and Their Equivalents

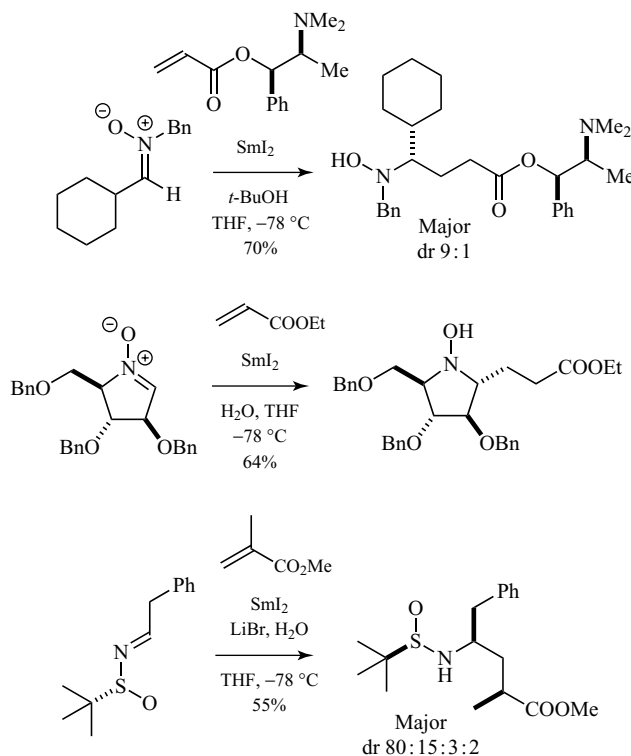
Imine equivalents have recently been used in place of the carbonyl component in reductive couplings with alkenes. In particular, Py and Skrydstrup have shown that nitrones are excellent coupling partners in intermolecular reactions. In their work on the asymmetric synthesis of γ -amino acids, Skrydstrup studied the reductive coupling

of nitrones and α,β -unsaturated esters bearing a chiral auxiliary (Scheme 53).¹⁷⁷ Py has used a nitron–alkene coupling in a short, asymmetric synthesis of (+)-hyacinthacine A₂ (Scheme 53).¹⁷⁸ Finally, Ellman has reported a sulfinimine–alkene coupling mediated by SmI₂ in the total synthesis of the anticancer agent tubulysin D (Scheme 53).¹⁷⁹

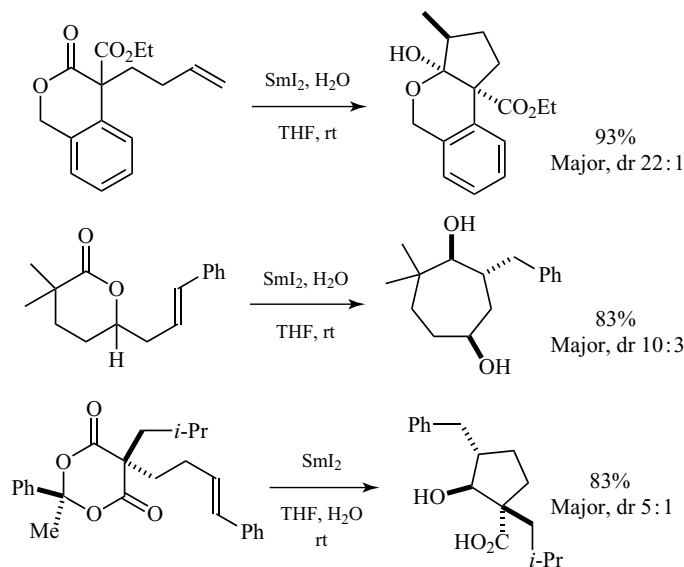
The use of a nitron in couplings with alkenes provides an alternative approach for asymmetric control through the attachment of a chiral auxiliary to the nitrogen of the nitron. Carbohydrate-based auxiliaries and the 1-(triisopropylphenyl)ethyl auxiliary group have been developed by Skrydstrup¹⁸⁰ and Py,^{181,182} respectively, for asymmetric reductive couplings.

6.5 Ester Carbonyl–Alkene Cyclizations

Procter has recently shown that the use of H₂O as an additive allows some ester carbonyls to be reduced by one electron and that the resultant radical anions



Scheme 53 Nitron and sulfinimine–alkene couplings.



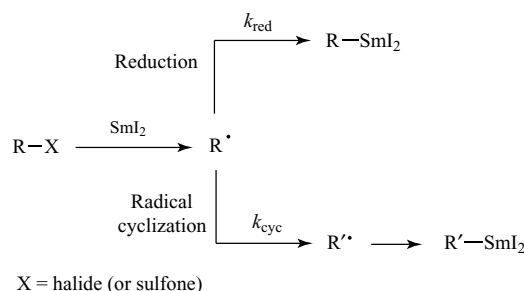
Scheme 54 Ester carbonyl–alkene couplings.

can undergo intramolecular coupling with pendent alkenes (Scheme 54).^{37,38,63,64,80}

7 RADICAL ALKENE–ALKYNE ADDITIONS

7.1 Introduction

SmI_2 also mediates the addition of sp^3 or sp^2 carbon-centered radicals, typically formed from halides or sulfones, to carbon–carbon multiple bonds. In the majority of these cyclizations, the radical acceptors are unactivated alkenes and alkynes, but activated radical acceptors including α,β -unsaturated amides, esters, nitriles, lactams, and lactones have also been employed. Although tributyltin hydride can be used to mediate such reactions, the use of SmI_2 requires lower reaction temperatures and the lanthanide salt by-products are less toxic and are easily separated from products. However, as the reducing conditions used to generate an alkyl radical will also reduce the radical to the corresponding organosamarium, for successful ring closure the unimolecular rate constant for cyclization (k_{cyc}) must be higher than the bimolecular rate constant for the second reduction step multiplied by the SmI_2 concentration ($k_{\text{red}} \cdot [\text{SmI}_2]$).⁵⁶ Performing the reactions at low substrate concentration is a common



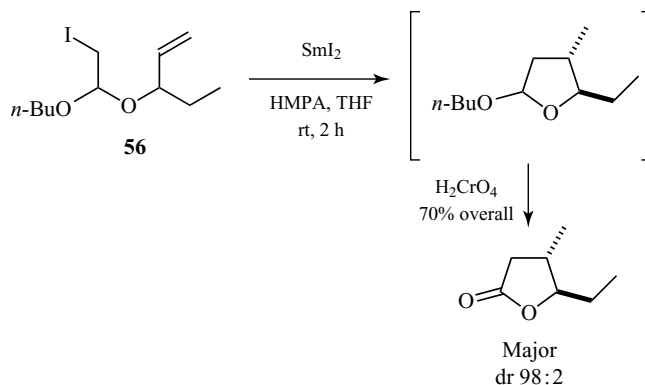
Scheme 55 Cyclization versus over-reduction of alkyl halides.

strategy to reduce the chance of organosamarium formation prior to cyclization (Scheme 55).

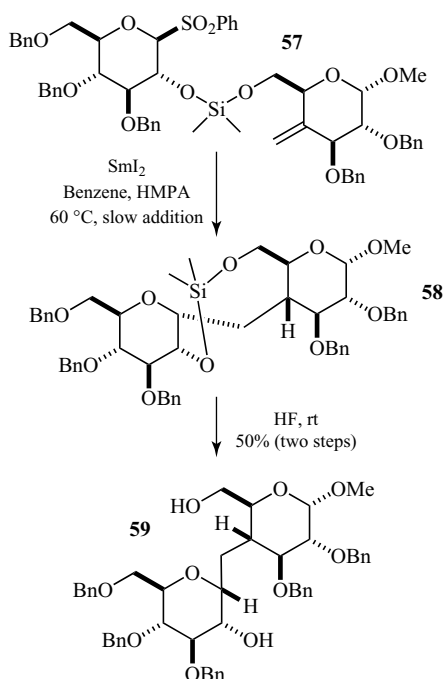
The 5-*exo*-trig and 5-*exo*-dig radical cyclizations represent the most successful classes of SmI_2 -mediated radical-alkene/alkyne cyclizations.

7.2 Radical Additions to Alkenes

Alkyl radicals generated from the reduction of halides or sulfones with SmI_2 have been successfully exploited in intramolecular additions to alkenes to form small carbocyclic and heterocyclic ring systems. Substrates containing an oxygen atom within

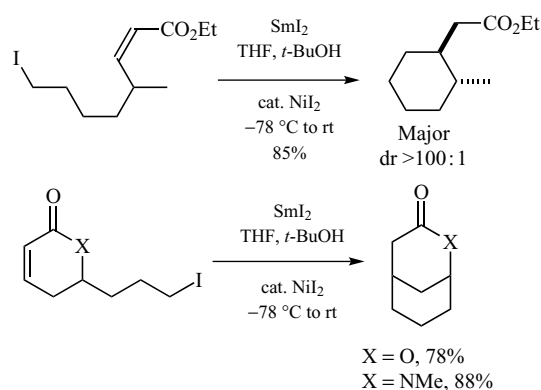


Scheme 56 Radical-alkene cyclizations to form heterocycles.



Scheme 57 Radical-alkene cyclization in the formation of a C-disaccharide.

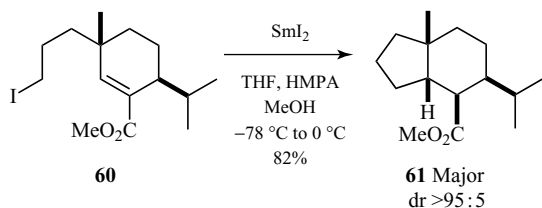
the tether linking the radical and the alkene undergo particularly successful 5-*exo*-trig cyclizations. For example, Fukuzawa has shown that unsaturated alkyl halides, such as **56**, undergo efficient cyclization in an efficient two-step synthesis of γ -lactones (Scheme 56).¹⁸³



Scheme 58 Radical-alkene cyclizations with electron-deficient alkenes.

Analogous cyclizations of glycosyl sulfones have been exploited in the stereoselective synthesis of C-glycosides. For example, Sinay reported that slow addition of SmI₂ in benzene and HMPA to glycosyl sulfone **57** bearing a tethered unsaturated sugar triggered a 9-*endo* radical cyclization to give **58**. Subsequent desilylation of the major C4-epimer **58** provided the disaccharide mimic **59** in an overall yield of 50% (Scheme 57).¹⁸⁴

Electron-deficient alkenes, such as α,β -unsaturated esters and amides (and alkynes), can also be exploited in SmI₂-mediated radical cyclizations. For example, Molander has shown that yields and selectivities often exceed those obtained in similar radical cyclizations using alternative reagents (Scheme 58).⁴⁸ These additions typically require an alcohol additive to quench the enolates



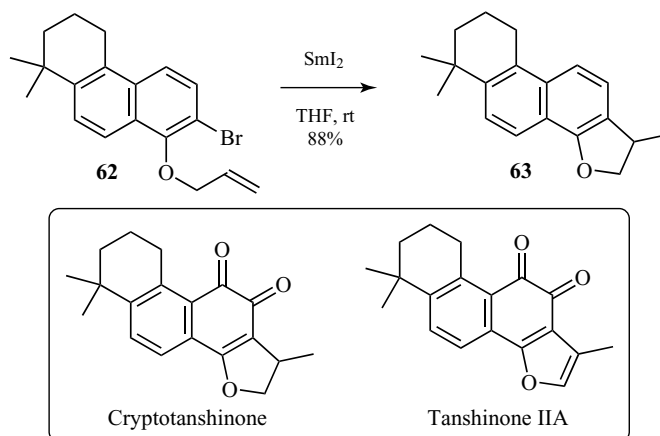
Scheme 59 sp^3 -Radical-alkene cyclization in natural-product synthesis.

that result from the addition and the use of NiI_2 as an additive has a beneficial effect.

Bennett has shown that sugar-derived substrates can also be used for the preparation of highly functionalized cyclopentanes.^{185,186} Procter has employed a highly diastereoselective SmI_2 -mediated intramolecular 1,4-addition during studies on the synthesis of faurinone: treatment of iodide **60** with SmI_2 in THF–HMPA gave *cis*-hydrindane **61** in good yield (Scheme 59).^{187,188}

N -[(N',N' -Dialkylamino)alkenyl]benzotriazoles have been shown to be useful precursors to α -amino radicals in 5-*exo*- and 6-*exo* ring closure onto α,β -unsaturated esters or nitriles.¹⁸⁹

Aryl halides have been widely exploited in 5-*exo*-trig and 6-*exo*-trig radical cyclizations. For example, Lu and Cai reported a synthesis of the natural products cryptotanshinone and tanshinone IIA, in which the dihydrofuran ring in the intermediate **63** was installed using a SmI_2 -mediated cyclization of the aryl bromide **62** (Scheme 60).¹⁹⁰



Scheme 60 sp^2 -Radical-alkene cyclization in natural-product synthesis.

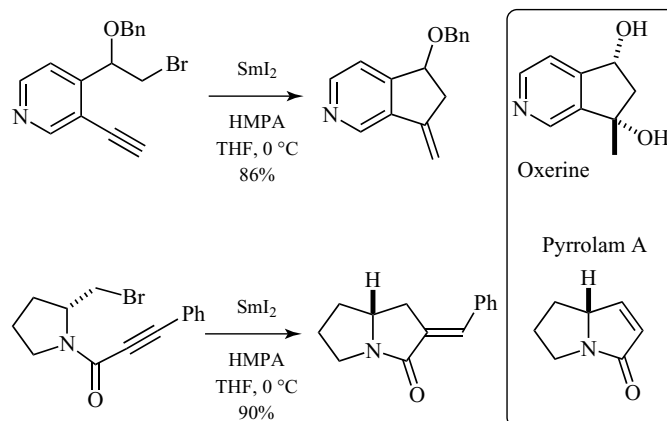
7.3 Radical Additions to Alkynes

Carbon-centered radicals formed from halides using SmI_2 undergo 5-*exo*-dig additions to alkynes to give cyclic systems bearing exomethylene substituents. The alkenyl radicals formed after ring closure can abstract a hydrogen atom from the solvent if they are unstable, or can be reduced to the corresponding anion if they are stabilized by neighboring groups.^{191–193} Ohta has exploited 5-*exo*-dig cyclizations in approaches to the natural products oxerine and pyrrolam A (Scheme 61).^{194,195}

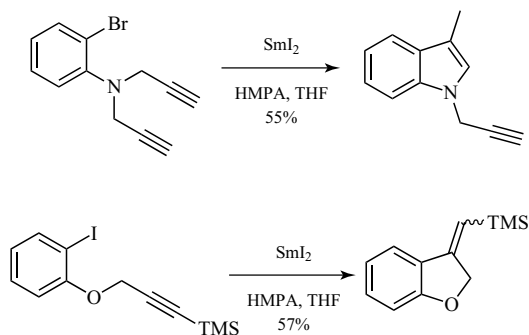
Aryl and alkenyl radicals also undergo cyclizations onto alkynes. Such ring closures are less efficient than examples involving sp^3 -carbon-centered radicals. Inanaga and Molander reported the application of aryl halide-alkyne cyclizations in the construction of the indole and naphthafuran frameworks using SmI_2 in THF–HMPA (Scheme 62).^{196,197}

8 SAMARIUM DIODIDE-MEDIATED BARBIER AND GRIGNARD REACTIONS

The reduction of alkyl halides with SmI_2 generates radicals which are reduced further by SmI_2 to give organosamarium intermediates. These intermediates add to carbonyl groups in reactions that are referred to as *SmI₂-mediated Barbier or Grignard reactions*.¹⁹⁸ Both intra- and intermolecular couplings can be carried out efficiently to yield products



Scheme 61 Radical-alkyne cyclizations in natural-product synthesis.



Scheme 62 sp^2 -Radical-alkyne cyclizations.

that can be difficult to access using more traditional methods.

Barbier reactions refer to procedures in which a mixture of the alkyl halide and carbonyl compound is treated with SmI_2 , whereas Grignard reactions involve the treatment of the alkyl halide with SmI_2 prior to the addition of the carbonyl compound. As organosamariums are formed from radical intermediates, competing radical processes may be problematic if they proceed faster than the reduction of the intermediate radical to the organosamarium. In general, Barbier conditions should be used when the organosamarium intermediate is prone to dimerization (e.g., allylic and benzylic organosamariums), decomposition (e.g., by elimination), or self-condensation. Grignard conditions suit reactions in which the carbonyl compound may be reduced faster than the alkyl halide, thereby

leading to competing reactions (e.g., aryl ketones and aldehydes).¹⁹⁸

In contrast to Barbier reactions mediated by other metals (e.g., Mg, Li, Zn), the SmI_2 -mediated Barbier reaction is homogeneous and often highly chemoselective, and, in general, organosamarium reagents undergo 1,2-addition to enones rather than 1,4-addition unless their reactivity is modified by transmetallation.¹⁹⁹

The expected order of reactivity is observed in SmI_2 -mediated Barbier and Grignard reactions ($\text{RI} > \text{RBr} \gg \text{RCl}$): alkyl iodides and bromides undergo facile reaction, whereas alkyl chlorides typically do not react (allylic chlorides react slowly).¹³

SmI_2 -mediated Barbier reactions are typically carried out in THF with additives such as HMPA,^{21,26,200} NiI_2 ,^{47,201,202} or ferric salts such as $\text{Fe}(\text{DBM})_3$ [dibenzoylmethido (DBM)].^{13,47,203} The role of metal salt additives is not yet clear.^{52,201,202,204} Although primary, secondary, allylic, and benzylic halides can be used in the transformation in THF, the use of THF as solvent is often beneficial.^{55,67,205} Generally, benzene is used as the solvent for SmI_2 -HMPA reactions employing aryl, vinyl, and alkynyl halides, in order to avoid hydrogen atom abstraction from THF by the intermediate radicals.^{55,67} Light activation has also been used to increase the rate of reactions.^{201,202} Table 1 summarizes the additives, solvents, and carbonyl electrophiles typically employed in SmI_2 -mediated Barbier reactions for particular classes of alkyl halide.

Table 1 Summary of the additives and solvents used in Barbier additions.

Alkyl halide (or equivalent)	Additives	Solvent	Carbonyl electrophile
Alkyl iodide	None, HMPA Fe(III), Ni(II)	THF	Aldehydes, ketones, esters, amides, imides, nitriles
Alkyl bromide	None, HMPA	THF	Aldehydes, ketones, esters, amides (imides)
Alkyl chloride	HMPA, Fe(III), Ni(II) and $h\nu$	THF	Aldehydes, ketones (esters)
Alkyl tosylate	NaI	THF	Aldehydes, ketones
Allylic/benzylic iodide/bromide	None	THF, THP	Aldehydes, ketones
Allylic/benzylic chloride	none HMPA	THF, THP	Aldehydes, ketones (esters)
Aryl/vinyl/alkynyl halide	HMPA	Benzene, THF	Ketones (and aldehydes)

8.1 The Mechanism of SmI₂-Mediated Barbier and Grignard Reactions

SmI₂-mediated Barbier and Grignard reactions permit the coupling of alkyl halides and carbonyl compounds to give alcohols (or ketones if esters are employed as the electrophiles). Under Grignard conditions, the mechanism of intermolecular coupling has been shown to be straightforward: the alkyl halide is reduced by 2 equiv of SmI₂ to give organosamarium species that react with carbonyl electrophiles (Scheme 63).²⁰⁶ The organosamariums formed under Grignard conditions using SmI₂ are typically not long-lived and must be used quickly.

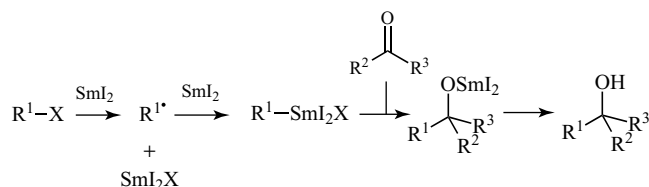
Determination of the mechanism of the intermolecular SmI₂-mediated Barbier reaction is more complex, as two reducible functional groups (the alkyl halide and the carbonyl group) are present in the reaction mixture with SmI₂. Curran proposed that the SmI₂-mediated Barbier reaction also involves the addition of an organosamarium, or carbanion, to a carbonyl group and this mechanism is widely accepted.^{67,206} With two reducible groups within the same molecule, the mechanism of the intramolecular SmI₂-mediated Barbier reaction is even less clear-cut and more difficult to investigate. Molander has produced evidence for the intermediacy of organosamarium species in these

processes,⁷⁵ and Curran has been integral in evaluating mechanistic evidence from Kagan's group and others.⁶⁷ However, despite extensive studies,²⁰⁷ the true nature of the SmI₂-mediated Barbier reaction has yet to be irrefutably elucidated; it now appears likely that the SmI₂-mediated Barbier reaction does not proceed by one discrete mechanism. In addition to substrate structure, many variables (including solvent, additives, and order of addition) may alter the reaction pathway.

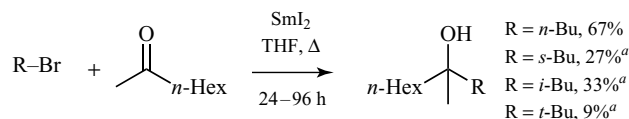
8.2 Intermolecular SmI₂-Mediated Barbier and Grignard Reactions

In 1980, Kagan demonstrated the clear difference in behavior of primary, secondary, and tertiary alkyl halides in SmI₂-mediated Barbier reactions (Scheme 64).¹³ The use of SmI₂ to mediate such additions is noteworthy, since the reaction of *i*-BuMgBr or *s*-BuMgBr with ketones typically leads to reduction of the carbonyl group.

Kagan also showed that allylic, benzylic, and propargylic halides undergo efficient reaction with ketones.¹³ Importantly, in the absence of ketone, these alkyl halides react rapidly with SmI₂ to yield Wurtz homocoupled products; thus the use of Barbier conditions is crucial. Kagan later found



Scheme 63 Basic mechanism of Barbier and Grignard reactions mediated by SmI_2 .

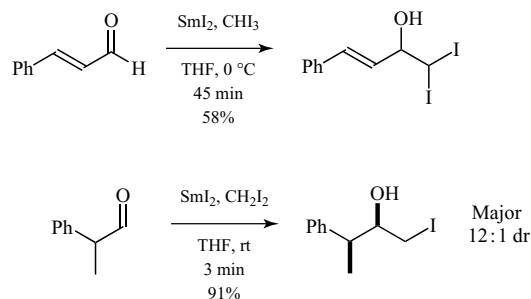


^a Recovered ketone predominated.

Scheme 64 Primary, secondary, and tertiary alkyl halides in Barbier reactions.

that THF was a better solvent than THF for the generation and reaction of allylic and benzylic organosamariums.²⁰⁵ When THF is used, the allylation of aryl ketones (that are prone to pinacol coupling) is possible, provided Grignard conditions are employed, and ketones that are prone to enolization are efficiently allylated under Barbier conditions.²⁰⁵ Vinyl, alkynyl, and aryl halides are reduced by SmI_2 in THF to form radicals, but it is thought that the reaction does not proceed to form organosamariums because of competing radical processes.^{53,208} To prevent competing hydrogen-atom abstraction from THF, the reactions of iodobenzenes,⁵⁵ iodoalkynes,^{209,210} and vinyl halides²¹¹ have been carried out with SmI_2 –HMPA in benzene. In some cases, vinylsamarium reagents have been generated and used in THF.²¹²

A variety of functionalized organic halides may be employed in SmI_2 -mediated Barbier and Grignard reactions. For example, benzyloxymethyl chloride can be used in conjunction with SmI_2 for the alkoxymethylation of ketones (in contrast to analogous organometallics, decomposition via α -elimination is not observed).^{213,214} In addition, polyhaloalkanes such as iodoform, diiodomethane,²¹⁵ and diiodoethane,²¹⁶ as well as fluorinated alkyl halides,²¹⁷ have been used in SmI_2 -mediated Barbier and Grignard reactions (Scheme 65), and iodomethylations of ketones have also been carried out using mixtures of Sm and CH_2I_2 .²¹⁴

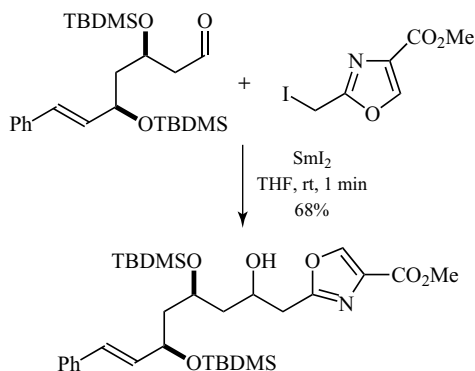


Scheme 65 Iodomethylations mediated by SmI_2 .

Although organosamariums can react with esters and lactones, they preferentially undergo addition to aldehydes or ketones, which allows ester-bearing organosamarium reagents to be employed in intermolecular Barbier couplings (Scheme 66).^{13,200} For example, Williams used SmI_2 to couple an aldehyde with a functionalized α -halo-2-methylazole (Scheme 66).²¹⁸

8.3 Intramolecular SmI_2 -Mediated Barbier Reactions

SmI_2 is the reagent of choice for the cyclization of a variety of halocarbonyl compounds,¹⁹⁸ giving cyclic systems, typically ranging in size from three- to nine-membered rings, often with high levels of diastereocontrol.^{219–222} The presence of



Scheme 66 Functional group tolerance in a Barbier addition.

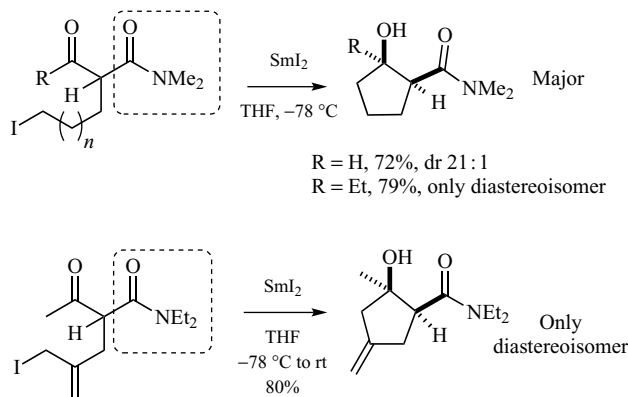
ester and amide groups (α to the carbonyl group undergoing attack) in haloaldehyde and haloketone substrates can lead to high levels of diastereocontrol (Scheme 67). The syn-diastereoselectivity of these cyclizations most likely arises from kinetic control, in which chelation of Sm(III) to the 1,3-dicarbonyl controls the orientation of the carbonyl group prior to addition of the organosamarium.²²³

The SmI₂-mediated Barbier cyclization of alkyl halides bearing cyclic ketones has been used extensively to form bicyclic systems.²⁰³ When the alkyl halide tether is attached α to the cyclic ketone carbonyl, cyclization typically proceeds to give syn products. For example, treatment of bis-bromide **64** with SmI₂ in THF–HMPA gave diol **65** in 68% yield (Scheme 68).²²⁴

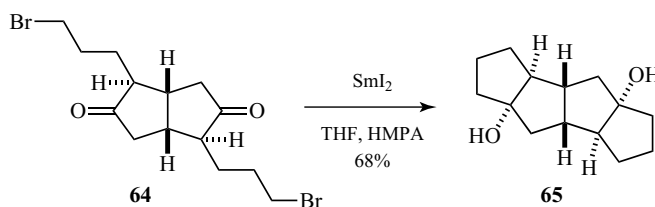
When the alkyl halide tether is not attached α to the cyclic ketone carbonyl group, SmI₂-mediated Barbier cyclizations result in bridged bicyclic systems. Molander found that these reactions were best carried out at low temperature in the presence of catalytic Fe(DBM)₃ (Scheme 69).⁷⁵

In the presence of catalytic Fe(III) salts, SmI₂ mediates intramolecular Barbier additions of alkyl and allylic halides to esters to give cyclic ketones (or cyclic hemiketals, if they prove to be stable).²²⁵ Reduction of the cyclic ketone product is not observed, suggesting that the tetrahedral intermediate (a samarium alkoxide of a cyclic hemiketal) is partially stable to the reaction conditions (Scheme 70).

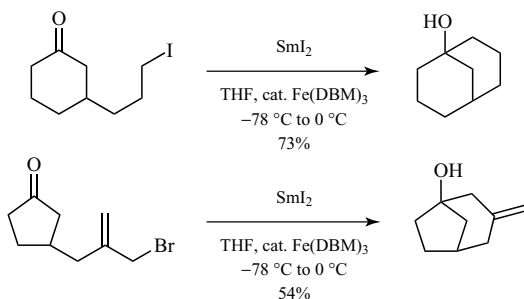
As alkyl iodides and bromides are reduced faster by SmI₂ than alkyl chlorides, sequenced Barbier



Scheme 67 Chelation control in SmI₂-mediated Barbier additions.



Scheme 68 Double Barbier cyclization.

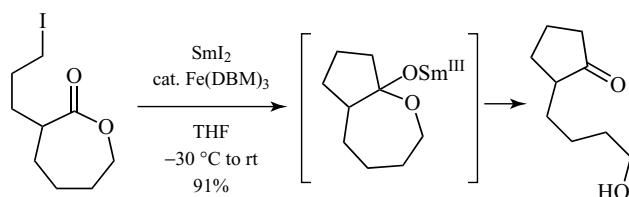


Scheme 69 Formation of strained bicyclics using Barbier cyclizations.

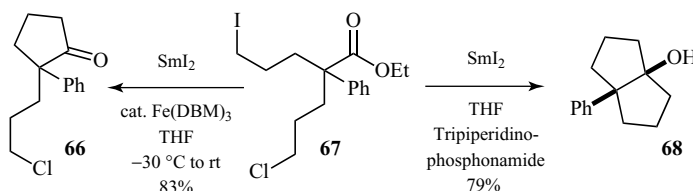
reactions involving dihaloester substrates are possible. For example, upon treatment of **67** under Molander's standard conditions, ketone **66** was obtained, whereas under more forcing conditions the alkyl chloride was also reduced, generating bicyclic alcohol **68** in good yield (Scheme 71).²²⁵

8.4 Intramolecular Barbier Additions to Imine Equivalents

Hydrazones^{136,226} and oximes^{227,228} are also effective participants in Barbier cyclizations. For example, treatment of the secondary iodide **69** with SmI_2 –HMPA gave cyclopentylhydrazine **70** with good diastereoselectivity (Scheme 72).^{136,226}



Scheme 70 Barbier addition to a lactone.

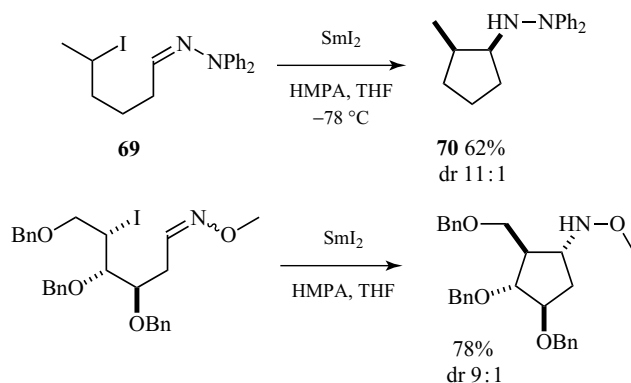


Scheme 71 Sequential Barbier reaction.

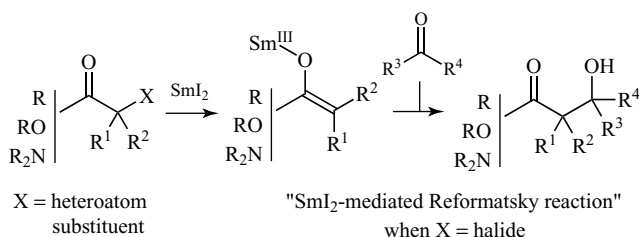
9 SAMARIUM DIIODIDE-MEDIATED REFORMATSKY AND ALDOL-TYPE REACTIONS

Sm(III) enolates can be exploited as nucleophiles in a number of reactions, although they behave differently to more conventional metal enolates.⁸² For example, there are few examples of the alkylation of Sm(III) enolates with alkyl halides. The reduction of α -heteroatom substituted carbonyl compounds is the most popular method for the generation of Sm(III) enolates, which can then be exploited as nucleophiles (e.g., they are known to undergo facile aldol reactions with aldehydes and ketones) or protonated to give the parent carbonyl compound. When the heteroatom substituent in the starting material is a halide, these reactions are commonly referred to as *SmI_2 Reformatsky reactions*, but it is important to recognize that these reactions are a subset of a much larger class of SmI_2 aldol-type reactions (Scheme 73).

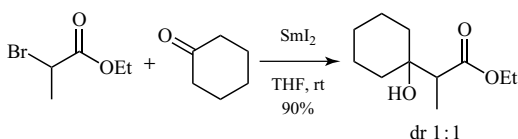
The SmI_2 -mediated Reformatsky and aldol reactions can be used in inter- and intramolecular fashion and proceed under mild, homogeneous conditions. The high chemo-, regio-, and diastereoselectivity of these reactions offer considerable advantages over other metal-mediated reactions. The chemoselectivity of SmI_2 and the low basicity of the resultant Sm(III) -enolate species make the lanthanide reagent ideal for sensitive substrates. Although α -halo esters are the most common substrates for the reaction, in principle, any α -halo



Scheme 72 Barbier cyclizations of imine equivalents.



Scheme 73 SmI₂-mediated Reformatsky and aldol reactions.



Scheme 74 Early example of a SmI₂-mediated Reformatsky reaction.

carbonyl compound may be employed. The reactions are most often carried out by the addition of SmI₂ to a 1:1 mixture of the α -halocarbonyl compound and the coupling partner (*Barbier conditions*).

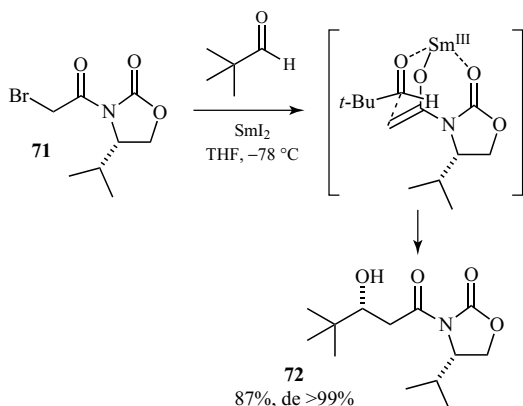
9.1 Intermolecular Reformatsky Reactions Using SmI₂

In 1980, Kagan reported the first example of a SmI₂-mediated Reformatsky reaction¹³ involving the coupling of ethyl α -bromopropionate with cyclohexanone (Scheme 74).

In the quest for an efficient catalytic SmI₂ reagent system, Namy has utilized mischmetal (La 33%, Ce 50%, Nd 12%, Pr 4%, Sm, and other lanthanides 1%) as the stoichiometric reductant for the regeneration of Sm(II) in several reaction types including Reformatsky reactions.^{229,230}

Analogous asymmetric SmI₂-mediated Reformatsky reactions of chiral 3-bromoacetyl-2-oxazolidinones have been described by Fukuzawa.²³¹ For example, reduction of **71** with SmI₂ generates a samarium enolate, which then reacts with pivalaldehyde to give β -hydroxy carboximide **72** in 87% yield and in high diastereoisomeric excess (Scheme 75).

As one would expect, coordination of the incoming electrophile to the Sm of the Sm(III)-enolate has an important influence on reactivity and diastereoselectivity in all SmI₂-mediated Reformatsky and aldol-type reactions. Lewis acid activation of the electrophile may explain why Sm(III)-enolate aldol-type reactions are relatively common while the reactions of Sm(III) enolates with alkyl halides are scarce.



Scheme 75 Asymmetric SmI_2 -mediated Reformatsky reaction.

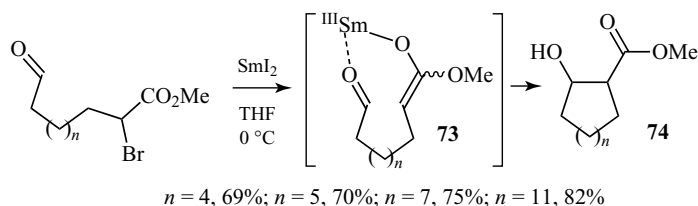
The use of α -haloketones in intermolecular Reformatsky reactions²³² is less common and is typically restricted to simple coupling partners, presumably because the product ketones can undergo further reduction by SmI_2 . Similarly, the intermolecular Reformatsky reactions of α -haloamides have received little attention.^{233,234}

9.2 Intramolecular Reformatsky Reactions Mediated by SmI_2

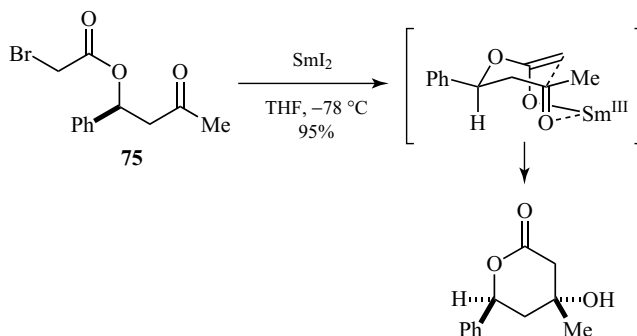
Intramolecular SmI_2 -mediated Reformatsky reactions have been used to great effect, and often proceed with high levels of selectivity. Interestingly, there are several examples of intramolecular SmI_2 -mediated Reformatsky reactions that employ protic solvents. In fact, in some of these cases, alcohol cosolvents are essential for efficient cyclization.

Inanaga reported the use of SmI_2 -mediated intramolecular Reformatsky reactions to access medium- and large-ring lactones²³⁵ and carbocycles.²³⁶ For example, the cyclization of the Sm(III) -enolate intermediates **73** gave carbocycles **74** in good yield. Inanaga suggests that the successful formation of such rings is assisted by the large ionic radius of samarium, its flexible coordination number, and its high oxophilicity, the lanthanide center effectively bringing the two reacting centers together through chelation (Scheme 76).²³⁶

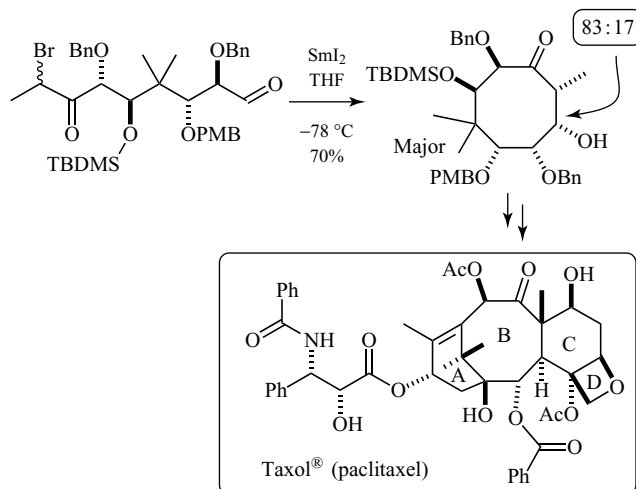
Molander showed that treatment of α -bromo esters such as **75** with SmI_2 resulted in a highly selective Reformatsky reaction to give lactones in excellent yield with high diastereoselectivity (Scheme 77).²³⁷



Scheme 76 Intramolecular Reformatsky reactions to access medium and large rings.



Scheme 77 Highly diastereoselective intramolecular Reformatsky reaction.



Scheme 78 Reformatsky cyclization to construct the B-ring of Taxol®.

Mukaiyama has used a SmI_2 -mediated Reformatsky cyclization to construct the B ring in an impressive total synthesis of Taxol® (Scheme 78).²³⁸

9.3 Intermolecular Aldol-Type Reactions Mediated by SmI_2

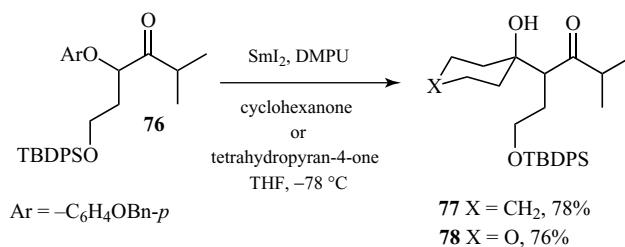
SmI_2 -mediated aldol-type reactions of other α -heteroatom-substituted carbonyl compounds in which the group expelled from the starting material is not a halogen (such as oxygen, nitrogen, sulfur, and selenium-containing substrates) are also possible.

For example, Procter reported that treatment of ketone **76** with SmI_2 in the presence of cyclohexanone or tetrahydropyran-4-one resulted in efficient aldol reaction to give adducts **77** and **78**,

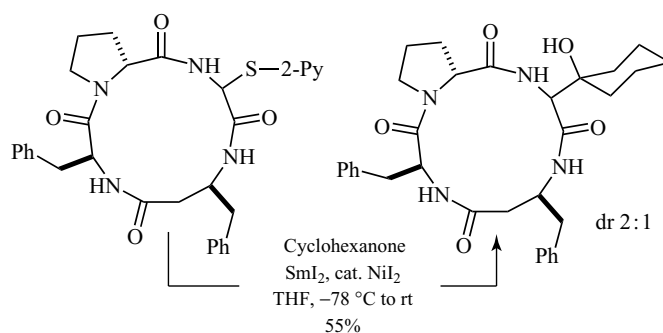
respectively (Scheme 79). Here, DMPU is employed as an additive to increase the reduction potential of SmI_2 and to facilitate Sm(III) -enolate formation.⁷⁶

Skrydstrup has utilized the aldol reactions of Sm(III) enolates generated from 2-pyridylsulfides to introduce nonnatural carbinol side chains to glycine residues in small peptide substrates (Scheme 80).^{239,240}

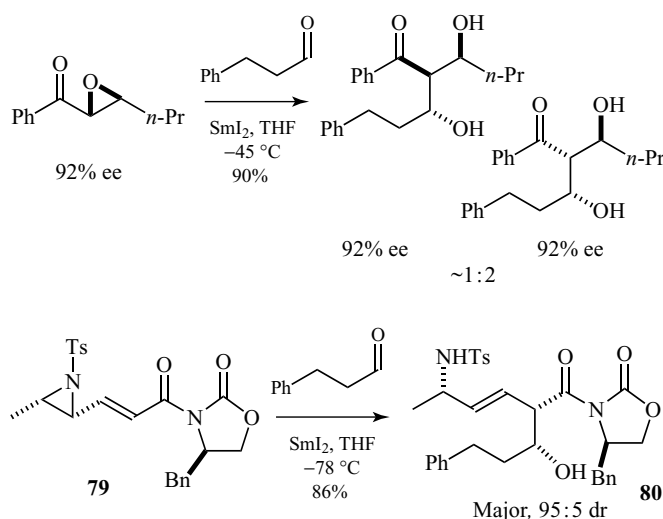
SmI_2 -mediated aldol reactions can also be carried out using epoxides and aziridines as precursors to the Sm(III) -enolate.²⁴¹ Mukaiyama reported the use of SmI_2 to mediate aldol reactions between aldehydes and aryl/alkyl oxiranyl ketones, resulting in the synthesis of unsymmetrical bis-aldol products (Scheme 81), and also reported an intramolecular variant of this aldol process.²⁴² Mukaiyama has examined an asymmetric aldol process using an unsaturated aziridine bearing an Evans oxazolidinone auxiliary. For example, on treatment with



Scheme 79 Aldol-type reactions of α -aryloxy carbonyl compounds.



Scheme 80 Aldol-type reactions of Sm(III) enolates derived from 2-pyridylsulfanylamides.



Scheme 81 Aldol reactions between aldehydes and oxiranyl/aziridinyl ketones.

SmI₂, aziridine **79** underwent smooth ring-opening, Sm(III)-enolate formation, and a highly diastereoselective aldol process to give diastereoisomer **80** in good yield (Scheme 81).²⁴³

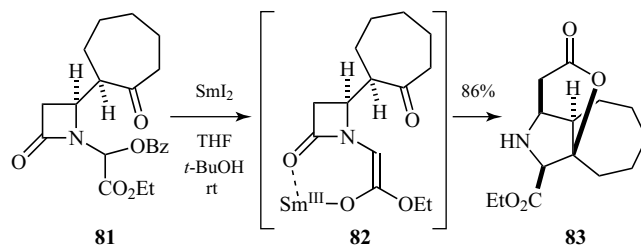
α -benzoyloxy esters, such as **81**, with SmI₂ led to the generation of a Sm(III)-enolate **82**, aldol cyclization, and addition of the resultant samarium alkoxide to the β -lactam carbonyl. The efficient sequential reaction gave proline derivatives, such as **83**, with high diastereoselectivity and in good yield (Scheme 82).²⁴⁴

9.4 Intramolecular Aldol-Type Reactions Mediated by SmI₂

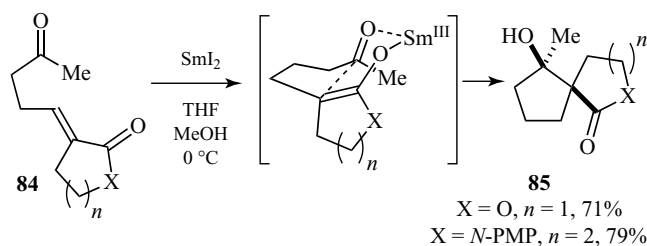
Intramolecular SmI₂ aldol-type reactions involving α -heteroatom-substituted carbonyl compounds have also been reported. For example, Skrydstrup reported the diastereoselective construction of functionalized prolines using a SmI₂-mediated aldol cyclization.²⁴⁴ Treatment of β -lactam-derived

9.5 SmI₂-Mediated Aldol-Type Reactions as Part of Sequential Processes

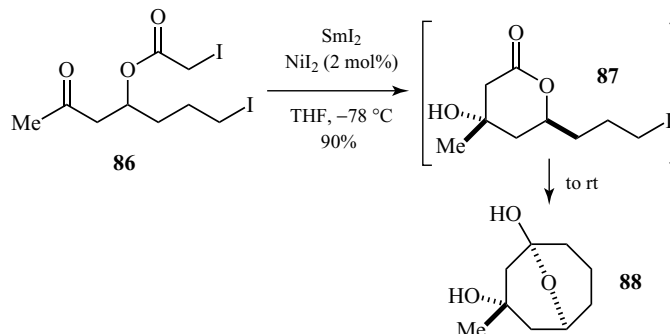
Other substrates react with SmI₂ to form Sm(III) enolates that undergo aldol-type reactions as part of sequential processes. For example, the conjugate



Scheme 82 Intramolecular SmI_2 aldol-type reaction.



Scheme 83 Conjugate reduction/aldol cyclization.



Scheme 84 SmI_2 -mediated Reformatsky/nucleophilic acyl substitution.

reduction of α, β -unsaturated carbonyl compounds is a potentially useful way of accessing Sm(III) enolates, which has yet to be widely exploited. Procter has reported the diastereoselective spirocyclization of unsaturated ketones **84** using SmI_2 ,^{34,245} which proceeds by conjugate reduction, Sm(III) -enolate generation, and chelation-controlled aldol cyclization to give syn-spirocyclic cyclopentanols **85** in good yield (Scheme 83). The success of the reductive aldol cyclization relies on the protic cosolvent, which presumably promotes the conjugate reduction step.^{34,245} SmI_2 ketyl-olefin couplings also generate Sm(III) enolates that can

be exploited in Reformatsky/aldol processes (see Section 10).

Molander has developed a sequential SmI_2 -mediated Reformatsky nucleophilic acyl substitution reaction for the synthesis of medium-sized carbocycles²⁴⁶: Treatment of α -iodoester **86** with SmI_2 generates iodo-lactone **87**, which then undergoes nucleophilic acyl substitution to give **88** as a single diastereoisomer (Scheme 84). The NiI_2 catalyst promotes reduction of the intermediate alkyl iodide to the corresponding alkylsamarium required for nucleophilic addition to the lactone carbonyl.²⁴⁶

10 SEQUENTIAL CARBON–CARBON BOND-FORMING REACTIONS MEDIATED BY SAMARIUM DIODIDE

Sequential reactions in which a number of transformations convert simple starting materials to complex products using a single reagent in a single synthetic operation are the holy grail of the synthetic chemist. Of the many reducing agents available to the synthetic chemist, SmI_2 is the one reagent able to orchestrate powerful sequential carbon–carbon bond-forming processes often with exquisite control of structure and stereochemistry.^{191,204,247}

10.1 Sequences Initiated by Radical Cyclizations

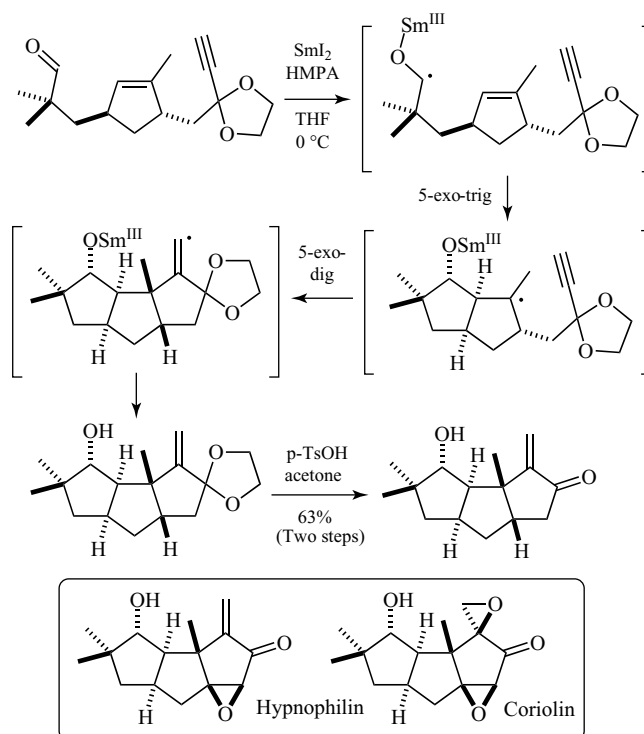
10.1.1 Radical/Radical Sequences

Curran's elegant approach to the natural products ($\pm$)-hypnophilin and ($\pm$)-coriolin consists of a

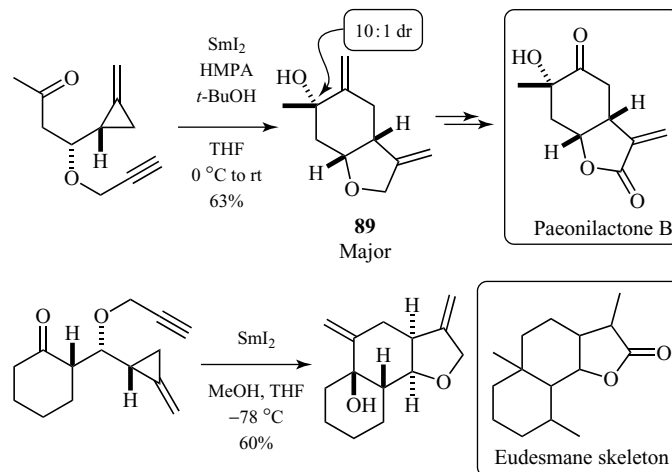
5-*exo*-trig cyclization followed by a stereoselective 5-*exo*-dig cyclization in a radical/radical cascade (Scheme 85).²⁴⁸ Attempts to mediate the sequence using Zn-TMSCl , or using photolysis, led to recovery of the starting material.

Kilburn has employed a SmI_2 -mediated radical/radical sequence involving a methylenecyclopropyl ketone in the preparation of paeonilactone B.^{249,250} Ketyl-olefin addition to the methylenecyclopropane, fragmentation of the resultant radical, and radical–alkyne cyclization gave **89** with good diastereocontrol (Scheme 86). A related radical/radical sequence has been used by Kilburn to access the tricyclic ether skeleton of the eudesmanes (Scheme 86).²⁵¹

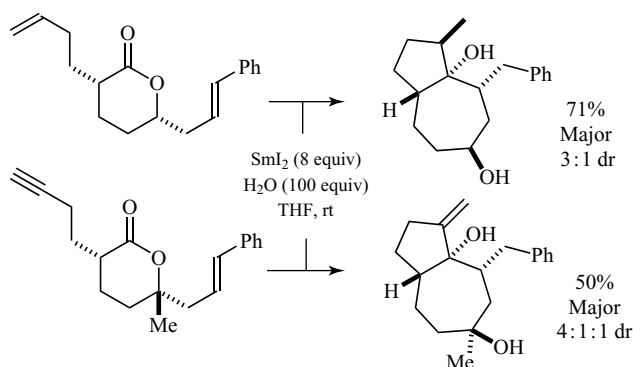
Finally, Procter has recently reported lactone radical/radical cyclization cascades using $\text{SmI}_2\text{--H}_2\text{O}$.^{38,64} Reduction of the lactone carbonyl using the activated reagent system triggers the conversion of simple lactones into complex products (Scheme 87).



Scheme 85 Radical/radical sequence toward ($\pm$)-hypnophilin and ($\pm$)-coriolin.



Scheme 86 Radical/radical sequences utilizing methylene cyclopropanes.



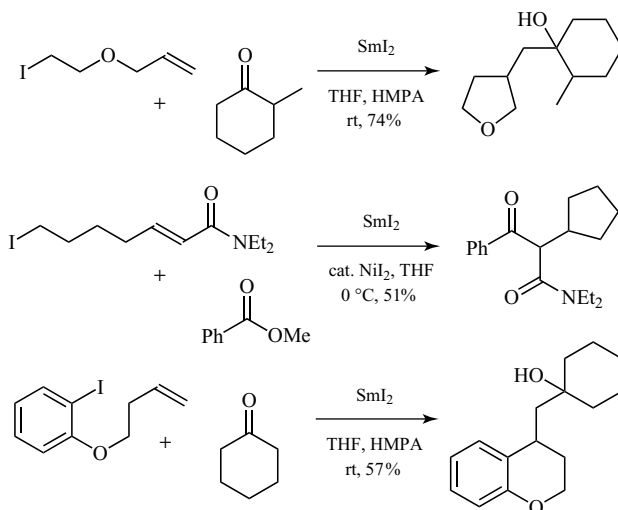
Scheme 87 Radical/radical cyclization sequences of lactones.

10.1.2 Radical/Anionic Sequences

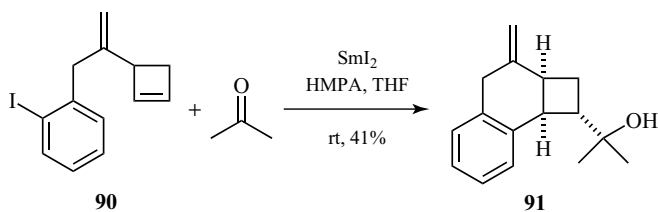
When planning sequences that require a radical cyclization, care must be taken, as radical intermediates are rapidly reduced by SmI_2 to give organosamariums (Section 3).⁵⁶ Provided that the desired radical cyclization is faster than reduction of the radical to the corresponding anion, radical cyclization–anionic sequences can be realized. For example, efficient 5-*exo*-trig radical cyclization/intermolecular Barbier additions,¹⁹⁷ 5-*exo*-trig radical cyclization/intermolecular Claisen reactions,^{204,247} and 6-*exo*-trig radical cyclization/intermolecular Barbier addition sequences are all possible (Scheme 88).¹⁹⁷

Curran has exploited a SmI_2 -mediated radical/anionic sequence in an approach to the BCD ring system of the penitrem indole alkaloids. Treatment of iodide **90** with SmI_2 and HMPA in the presence of acetone gave **91**, the product of radical cyclization/intermolecular Barbier addition (Scheme 89).²⁵²

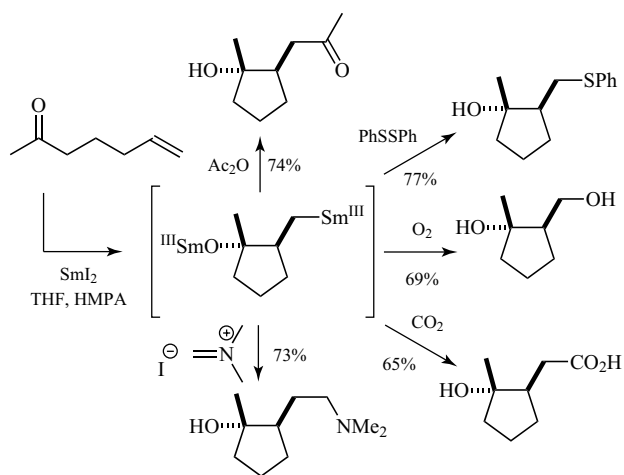
Radical cyclization/anionic sequences in which the radical cyclization involves the addition of a ketyl radical anion to an alkene are also possible. For example, carbonyl–alkene cyclization of hept-6-en-2-one and quenching of the resultant organosamarium with electrophiles allows access to an impressive range of cyclopentanol products (Scheme 90).²⁷



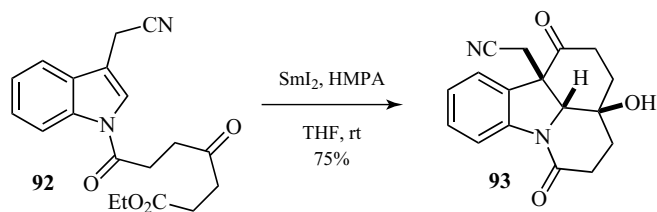
Scheme 88 Radical/anionic sequences.



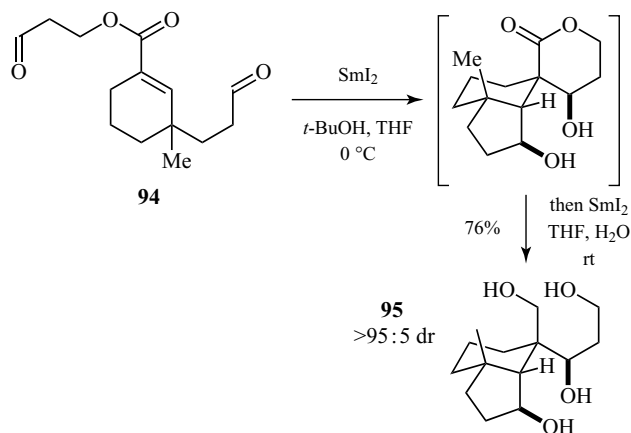
Scheme 89 Radical/anionic sequence toward the penitrem indole alkaloids.



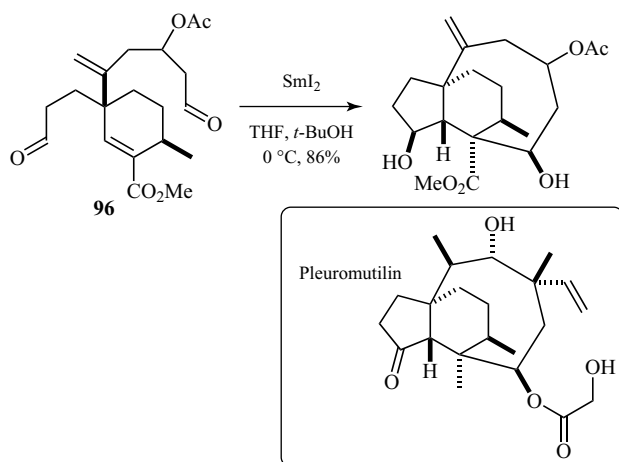
Scheme 90 Radical cyclization/anionic sequences.



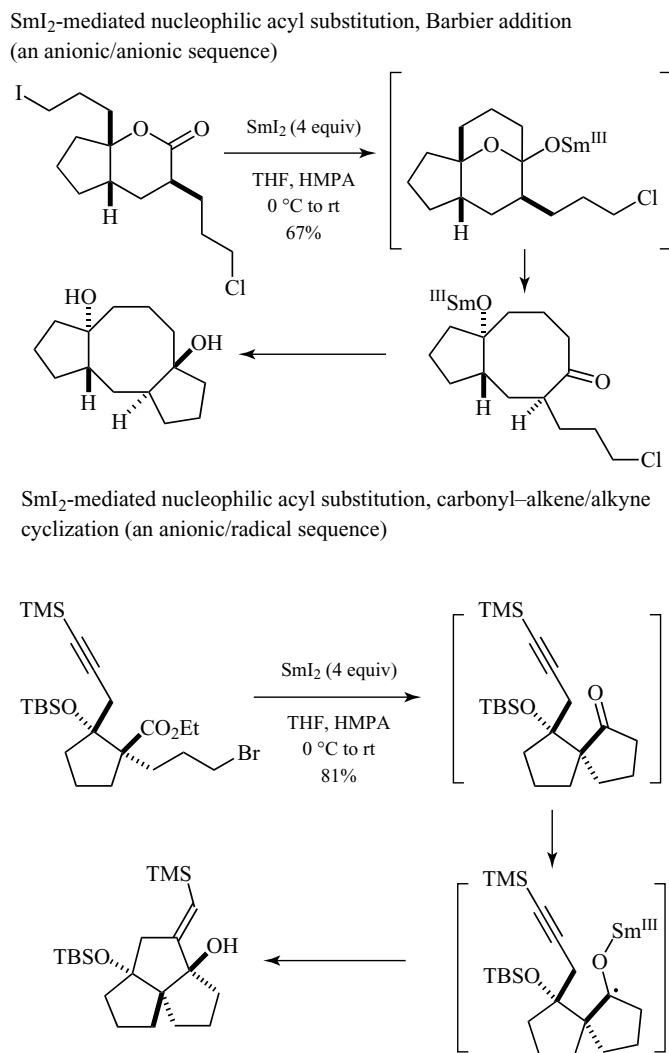
Scheme 91 Radical/anionic sequence involving ketyl radical addition to an indole.



Scheme 92 Radical/anionic sequence followed by $\text{SmI}_2\text{-H}_2\text{O}$ lactone reduction.



Scheme 93 Radical cyclization/intramolecular aldol sequence in an approach to pleuromutilin.



Scheme 94 Anionic/anionic and anionic/radical sequences.

Reissig has reported radical/anionic sequences that involve ketyl radical cyclizations on to indoles.²⁵³ Such a sequence has recently found application in a formal synthesis of strychnine (Scheme 91).²⁵⁴

Enholm has reported radical/anionic sequences involving ketyl radical cyclizations that culminate in intermolecular aldol reactions.²⁵⁵ Procter has recently shown that radical cyclization/intramolecular aldol sequences can also be carried out.²⁵⁶ For example, treatment of dialdehyde **94** with SmI₂ results in a sequential cyclization to

give **95** as a single diastereoisomer (Scheme 92). The diastereoselectivity of the sequence can be ascribed to the chelation of Sm(III) to intermediates. The sequence can be extended further by the addition of SmI₂–H₂O which “switches on” reduction of the lactone formed in the preceding steps (Scheme 92).²⁵⁷

Procter has recently utilized a radical cyclization/intramolecular aldol sequence of the dialdehyde substrate **96** to form the core of the antibacterial natural product pleuromutilin with complete diastereocontrol (Scheme 93).²⁵⁸

10.2 Sequences Initiated by Anionic Reactions

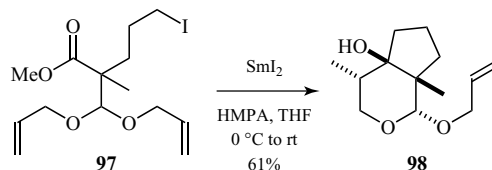
10.2.1 Anionic/Radical and Anionic/Anionic Sequences

Molander recognized the potential of the SmI_2 -mediated Barbier addition to esters for the initiation of sequential processes (Section 8.3). Two types of cascade have been developed that involve nucleophilic acyl substitution: the first type involves double intramolecular Barbier addition to an ester group (anionic/anionic sequences),²⁵⁹ the second type consists of a Barbier addition to an ester followed by a carbonyl–alkene/alkyne cyclization of the resultant ketone (anionic/radical sequences) (Scheme 94).^{193,260} Molander has shown that the double-Barbier anionic/anionic cascades can be used to access a range of fused polycyclic systems.²⁶¹

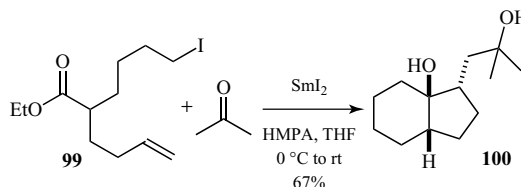
The sequential nucleophilic substitution–Barbier additions are controlled by the different rates of reduction of the alkyl halides or the tether length if the same halides are present in the substrate.²⁵⁹ Acetals such as **97** have also been used as substrates in anionic/radical cascades: Treatment of **97** with SmI_2 –HMPA gives bicyclic acetal **98** with excellent stereocontrol (Scheme 95).²⁶⁰

Molander has reported a variant of this sequential process that results in alkenyl transfer.²⁶² These anionic/radical sequences can be extended further and Molander has shown that anionic/radical/anionic sequences are possible.¹⁹³ Treatment of **99** with SmI_2 and HMPA in the presence of acetone gave bicyclic alcohol **100** in good yield (Scheme 96).

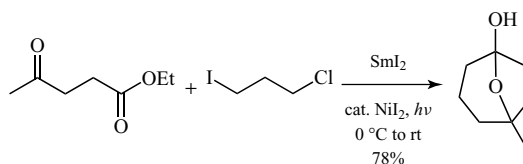
Molander has also studied the SmI_2 -mediated double-Barbier additions of alkyl dihalides to ketoesters.^{201,202} These anionic/anionic intermolecular/intramolecular sequences use NiI_2 as an additive and irradiation with visible light, and allow access to a range of bicyclic and tricyclic systems. The reactions proceed by reduction of the more reactive alkylhalide, intermolecular Barbier addition to the ketone, lactonization, and a second Barbier addition to the lactone carbonyl (Scheme 97).²⁰¹



Scheme 95 Anionic/radical sequence to form a heterocyclic product.



Scheme 96 Anionic/radical/anionic sequence.



Scheme 97 Intermolecular anionic/intramolecular anionic sequence.

The reagent's reducing power is accompanied by striking selectivity and it is this combination that continues to capture the imagination of synthetic chemists, and new applications are appearing at a significant rate over 30 years after the seminal work of Kagan. However, many challenges remain. For example, a complete understanding of the mechanism of reactions mediated by SmI_2 still eludes us, as does a full picture of the role additives play in modifying the active Sm(II) species present in solution. Furthermore, extension of the reagent's reducing range to new substrate classes, the development of new cascade processes, the discovery of ligand-controlled asymmetric processes, and the development of practical reagent systems that are catalytic in Sm are challenges for the future.

11 CONCLUSION

SmI_2 is set to retain its privileged status amongst reagents for synthesis for many years to come.

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The S_{RN}1 Reaction

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1 INTRODUCTION

Nucleophilic substitution is feasible through processes that involve electron transfer (ET) steps. In these reactions, a compound bearing a suitable leaving group is substituted at the ipso position by nucleophiles. The S_{RN}1 reaction, which stands for unimolecular radical nucleophilic substitution, is a chain process that involves radicals and radical anions as intermediates.

The S_{RN}1 mechanism was first proposed for the substitution of alkyl halides bearing electron-withdrawing groups (EWGs) in the α position and a suitable leaving group.^{1,2} In 1970, Bunnett applied this mechanism to unactivated aromatic halides.^{3,4} Later on, other substrates such as vinyl halides, perfluoroalkyl halides, alkylmercury chlorides, as well as cycloalkyl, bridgehead, and neopentyl halides were reported to react by this mechanism.

The process has a considerably wide scope. Many substituents, such as alkyl groups, OR, OAr, SAr, CF₃, CO₂R, NH₂, NHCOR, NHBoc, SO₂R, CN, COAr, NR₂, and F are compatible with the reaction. Even though the reaction is not inhibited by the presence of negatively charged substituents such as carboxylate ions, oxyanions, as a general rule, hinder the process. Normally, substituents such as NO₂ groups are not suitable for S_{RN}1 substitution on aromatic substrates, but are important EWGs on aliphatic substrates, favoring the ET process.

In addition to halides, other leaving groups are known, that is, (EtO)₂P(O)O[−], RS[−], ArOS[−], ArO₂S[−], PhSe[−], Ph₂S, RSN₂ (R = *t*-Bu, Ph), BF₄N₂, R₃N, N₂, N₃[−], NO₂[−], and HgX[−]. Thus, ArOH and ArNH₂ are ultimately the leaving groups through phosphate esters and ammonium salts.

Carbanions from hydrocarbons, nitriles, nitroalkanes, ketones, esters, *N,N*-dialkyl acetamides, and *N,N*-dialkyl thioamides, as well as mono- and dianions from β -dicarbonyl compounds are some of the most common nucleophiles through which a new C–C bond can be formed. C–C instead of C–O or C–N bond formation can be achieved by using ArO[−] ions or aromatic nitrogen nucleophiles in reactions with aromatic substrates. However, these nucleophiles afford O- and N-alkylation products in the reaction with alkyl halides bearing an EWG.

The S_{RN}1 mechanism has proved to be an important route to ring-closure reactions, mainly in aromatic systems. The synthesis of indoles, carbazoles, isoquinolones, and other heterocycles, as well as of a large number of natural products, has been achieved by this process.

Nucleophiles derived from Sn, P, As, Sb, S, Se, and Te react through the heteroatom to form a new C-heteroatom bond.

Several reviews have been published in relation to the S_{RN}1 mechanism of substitution at sp³ and sp² carbons,^{5,6} to aromatic photoinitiated substitutions^{7,8} to reactions performed under electrochemical catalysis,^{9,10} and to the synthetic applications of the process.^{11,12}

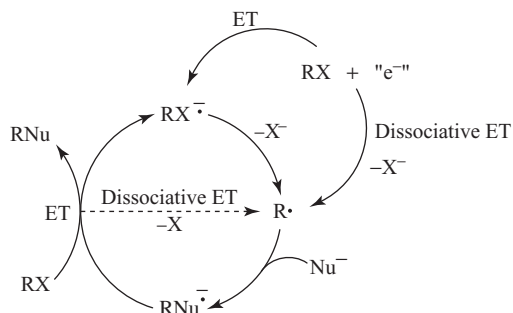
2 MECHANISM

The $S_{RN}1$ mechanism is presented in Scheme 1. In the initiation step, the radical anion of substrate $RX^{\cdot-}$ can be formed by an ET from the nucleophile or from a suitable electron source; the ET to unsubstituted alkyl halides is proposed to be a dissociative reaction.¹³ $RX^{\cdot-}$ fragments to afford the radical $R^{\cdot}$ and the anion of the leaving group. The radical thus formed can react with the nucleophile to give the radical anion of the substitution product $RNu^{\cdot-}$, which by ET to the substrate forms the intermediates required to continue the propagation cycle.

The mechanism has termination steps that depend on the substrate, the nucleophile, and the experimental conditions. Not many initiation events are needed, but in this case, the propagation cycle must be fast and efficient enough to allow long chains to be built up.

For a given aryl moiety, there is a broad correlation between the reduction potential and its reactivity in $S_{RN}1$ reactions.¹⁴ The order of reduction potential in liquid ammonia, $PhI > PhBr > PhNMe_3I > PhSPh > PhCl > PhF > PhOPh$, coincides with the reactivity order determined under photoinitiation. By competition experiments of pairs of halobenzenes toward $^-CH_2COt-Bu$ ions under photoinitiation, the span in reactivity from PhF to PhI was found to be $\sim 100\,000$.¹⁵

Radical probes (see **Radical Kinetics and Clocks**) have been used to demonstrate the formation of radicals along the propagation cycle and also as a synthetic tool to obtain heterocyclic compounds. Products from ring closure, ring opening, or from rearrangement of the radicals were thus taken as evidence for the



Scheme 1 Representation of the mechanism of the $S_{RN}1$ reaction.

presence of these intermediates. Inhibition by radical traps has been extensively used to provide mechanistic evidence. Those most frequently employed are di-*t*-butylnitroxide, or 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO), and radical anion scavengers such as *p*-dinitrobenzene.

Spontaneous or thermal ET is a possible initiation step depending on the relationship between the electron affinity of the substrate and the oxidation potential of the nucleophile. Even though photoinduction is a widely used initiation method, there have not been many mechanistic studies. These photoinduced ET can conceivably be accomplished in one of the following ways: (i) homolytic cleavage of the C–X bond; (ii) ET from the nucleophile to the excited ArX , generating a radical anion that enters the cycle; (iii) ET within an excited charge transfer complex; and (iv) photoejection of an electron from the excited nucleophile. Depending on the nature of RX , the nucleophile, and the experimental conditions, any of these mechanisms could probably be considered as an initiation step.

The process allows the possibility of affording the substitution of an unreactive nucleophile through *entrainment* conditions.¹⁶ Entrainment is useful when the nucleophile is rather unreactive at initiation, but quite reactive at propagation. Under these conditions, the addition of another nucleophile that is more reactive at initiation increases the generation of intermediates and allows the less reactive nucleophile to establish its own propagation.

Quantum yields of photoinitiated reactions have been used as a qualitative measure of the chain length. Quantum yields from 50 to 20 have been determined for the substitution of halonaphthoxide ions and PhI by $(EtO)_2PO^-$ ions.¹⁷ The quantum yields for the substitution of 4-nitrocumyl chloride with N_3^- ions and quinuclidine have been determined to be 6000 and 3.5, respectively.¹⁸ For the reaction of α -4-dinitrocumene with N_3^- ions, the quantum yield was 570.¹⁸

The photoinduced initiation reaction may have, however, a low quantum yield due to a fast backward ET that annihilates the ion pair before cage separation occurs. This will result in a less efficient source of radicals. In the case of nucleophiles reactive at the initiation and propagation pathways, the quantum yields for substitution (Φ_{global}) depend both on the efficiency of initiation and on the turnover in the propagation steps. Thus, the magnitude of the chain length of any $S_{RN}1$ reaction can

easily be derived from the overall quantum yield by knowing the quantum yield of initiation. The latter could be obtained if the propagation cycle is eliminated or markedly reduced in comparison with the initiation step. The chain length can then be obtained from (1):

$$\text{Chain length} = \Phi_{\text{global}} / \Phi_{\text{initiation}} = \Phi_{\text{propagation}} \quad (1)$$

The quantum yield for substitution of neophyl iodide by [−]CH₂COPh ion was determined to be 0.127.¹⁹ The quantum yield of initiation, evaluated by suppressing the propagation steps with the presence of di-*t*-butylnitroxide as radical trap, had a value of 10^{−3}. On the basis of both quantum yields, the chain length or Φ_{propagation} obtained for the reaction was approximately 127. This is the first report of Φ_{propagation}, which is a direct measure of the chain length for an S_{RN}1 process, demonstrating that overall quantum yields lower than unity cannot be taken as a criterion for the absence of a chain reaction.

Another method to initiate the S_{RN}1 reaction is the use of inorganic salts. Although several inorganic salts have been tested, the most commonly used is the ferrous ion. For instance, [−]CH₂CO*t*-Bu, *N*-acetylmorpholine, and a number of higher *N*-acylmorpholine ions react with ArX induced by FeSO₄ to give good substitution yields,²⁰ comparable to the substitutions of PhI with the enolate ions of 2-acetylfurane,²¹ 2-acetylthiophene,²¹ and 2-acetyl-*N*-methylpyrrole.²² The substitution of 1-iodoadamantane (1-AdI), neopentyl iodide, and 7-iodobicyclo[4.1.0]heptanes with carbanions from ketones²³ and of 1-AdI with the anion from thioacetylmorpholine²⁴ have been successfully achieved in the presence of FeBr₂ in dimethylsulfoxide (DMSO).

Electrons from alkali metal dissolved in liquid ammonia or Na(Hg) or from a cathode have also been used to initiate S_{RN}1 reactions. The solvated-electron initiation can be of importance whenever the products coming from a benzyne mechanism are to be avoided.^{4,25}

Electrochemical initiation is an approach that has been successfully applied in numerous cases with aromatic and heteroaromatic substrates.^{9,10} When the radical anion of the substrate fragments fast, reduction is the main reaction pathway; however, high yields of S_{RN}1 products can be obtained using redox catalysis. Electrochemical methods have been

used to determine the absolute rate constant of aromatic radicals with nucleophiles. A large number of these values are close to the diffusion limit.

The dissociation of the aromatic radical anion intermediates occurs through an intramolecular ET from the π system to the σ C–halogen bond. Both, theoretical and experimental evidences show the formation of π radical anions in the ET to ArX. In this family, the π and σ systems are adjacent and orthogonal. The main reaction coordinates for the intramolecular ET from the π to the σ state, which dissociates into aryl radicals and X[−] ions, are the C–X bond elongation and bending with respect to the aryl plane.^{26,27}

Relative reactivities for pairs of nucleophiles toward the same radical can be obtained from the ratio of the two substitution products in competition reactions. The span in reactivity is larger for aromatic ketones than for aliphatic ketones, with the following reactivity order: [−]CH₂COMe (1.00), [−]CH₂COPh (7.5), and anthrone anion (16.5).²⁸ In addition, the reactivity order of enolate anions of other aromatic ketones versus [−]CH₂COPh anion was determined to be as follows: carbanions from 2-acetylthiophene (0.49),²¹ 3-acetyl-*N*-methylpyrrole (0.73),²² 2-acetylfurane (0.83),²¹ 2-naphthyl methyl ketone (1.1), and 2-acetyl-*N*-methylpyrrole (2.6).²²

As opposed to the case of aryl radicals, limited information is available on the relative reactivities of nucleophiles toward aliphatic radicals. By competition experiments, it was found that 1-adamantyl radicals are more selective than phenyl radicals toward carbanions. The following relative reactivity order has been determined for the reaction of 1-adamantyl radical with the carbanions: anthrone (80)²⁹ > CH₃NO₂ (32)²⁹ > CH₃COPh (11)²⁹ > *N*-acetylthiomorpholine (3.3)²⁴ > CH₃COCH₃ (1.0).²⁹

One of the main goals of the S_{RN}1 mechanism lies in the possibility of obtaining disubstituted compounds when the reaction is performed with substrates bearing two leaving groups. This type of compounds may react to form monosubstitution and/or disubstitution products, depending on the leaving groups, their relative positions in the molecule, the nucleophile, and the solvent. For aliphatic substrates, reactivity also depends on the flexibility of the bridge. Few examples of trisubstitutions³⁰ or four consecutive S_{RN}1 substitutions are known.^{31–33}

3 S_{RN}1 REACTIONS WITH AROMATIC SUBSTRATES

3.1 Carbanions as Nucleophiles

The reaction with carbanions to afford a new C–C bond constitutes one of the more representative examples of S_{RN}1 reactions with aromatic substrates. Carbanions derived from hydrocarbons, such as 1,3-pentadienyl, 1-(4-anisyl)propenyl, fluorenyl, and indenyl anions, have been studied along this line. The regiochemistry of the coupling favors the formation of the more stable radical anion intermediate.⁵

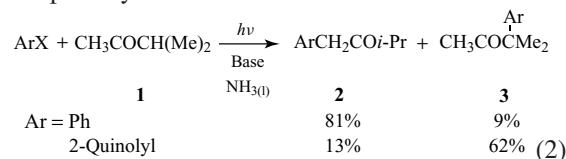
On the other hand, the enolate ions of aliphatic ketones are the carbanions most widely studied. The solvents and the reaction conditions of choice usually involve liquid ammonia or DMSO and irradiation. However, for some systems spontaneous initiation is also possible. For example, PhI reacts with [−]CH₂COR ions in DMSO in the dark; halo-heteroaromatic compounds are also substrates able to react in the dark in liquid ammonia.

The enolate ions of acetone, pinacolone, 3-pentanone, 4-heptanone, and 2,4-dimethyl-3-pentanone react through the S_{RN}1 mechanism to afford α-arylation products under photostimulation.⁵

In the reaction of the [−]CH₂COME ion with 2-chloroquinoline, the effect of solvent was studied, with the same reaction time and under photostimulation, from liquid ammonia (90%) to tetrahydrofuran (THF) (82%), DMF (74%), dimethoxyethane (28%), diethyl ether (9%), or benzene (4%).³⁴

In unsymmetrical dialkyl ketones, isomeric enolate ions can be formed. The equilibrium concentration of two possible enolate ions and the selectivity of the attacking radical largely determine the distribution of two possible arylated products. A case in point is the reaction of the anion from 2-butanone where phenylation occurs preferentially at the more substituted α-carbon, whereas,³⁵ with the anion from *i*-propylmethylketone **1**, 1-phenyl derivatives **2** predominate^{36,37}; when the same anion reacts with 2-chloroquinoline, the tertiary (**3**) to primary substitution ratio is approximately 4.8 (**2**).³⁸ Substituents located ortho to the leaving group of the substrate generally favors the attack at

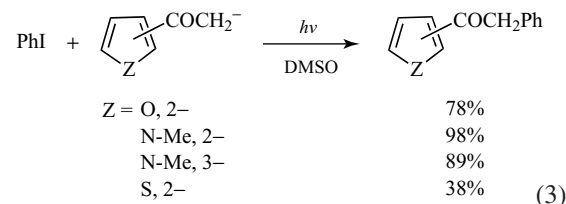
the primary α-carbon of the anion.⁵



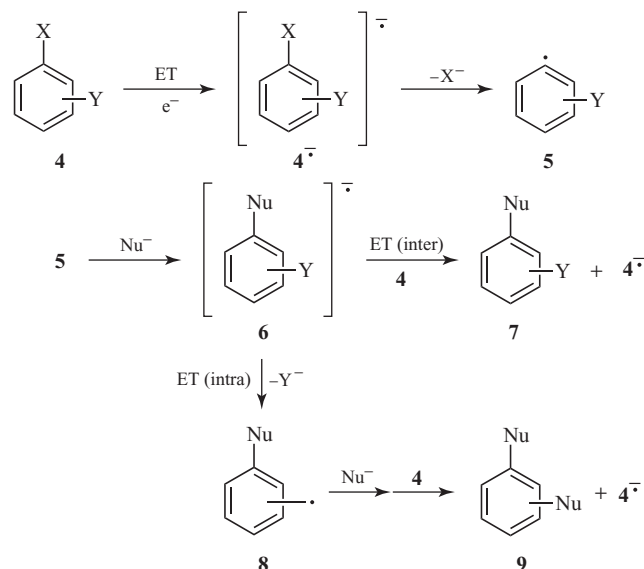
Products derived from α-arylation of cyclobutanone, cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and 2-indanone are obtained in good yields (58–95%) under irradiation in liquid ammonia.³⁹

The [−]CH₂COPh ion can be arylated in liquid ammonia by initiation with K metal or Na(Hg), or under photostimulation. In the coupling step, this anion demonstrated to be more reactive than [−]CH₂COME ion, yet the latter proved to be more reactive in the initiation step.²⁸

The anions from other aromatic ketones, such as methyl 2-naphthylketone, 2-acetyl furan, 2- and 3-acetylthiophene, 2- and 3-acetyl-*N*-methylpyrrole, anthrone, and tetralone, can also be arylated.⁸ Some examples are shown in (**3**).



When aromatic substrates with two leaving groups such as **4** (Scheme 2) react with enolate ions from ketones, mono and disubstitution products can be obtained, depending on the nature of the leaving group and their relative position in the molecule and on the nucleophile. Upon receiving an electron, substrate **4** forms the radical anion **4**^{•−}, which fragments at the more labile C–X bond to give radical **5**. Then, this radical intermediate **5** reacts with the nucleophile to form the radical anion **6**. This radical anion can transfer the extra electron to another molecule of **4** (ET_{inter}) to furnish product **7**, or to the second C–Y bond by an intramolecular ET (ET_{intra}). If ET_{intra} occurs, **6** fragments to afford radical **8**, which by coupling with the nucleophile followed by an ET reaction, generates the disubstitution product **9** (Scheme 2). This behavior is observed with dihalo substrates, not only with anions derived from ketones but with other nucleophiles as well.⁵



Scheme 2 Two possible pathways in S_{RN}1 reactions of a substrate with two leaving groups.

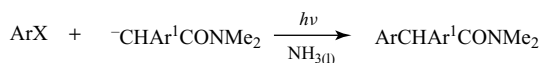
For instance, in the reaction of *o*-C₆H₄Br₂ with the [−]CH₂CO*t*-Bu ion, only disubstitution is observed,⁴⁰ while *o*-iodohalobenzene (X = Cl, Br, or I) reacts with several enolate ions from aromatic ketones to give the monosubstitution products with the retention of one halogen.⁴¹ The extent of dehalogenation is discussed in terms of the energies of the intramolecular ET from the π* molecular orbital (MO) of the ArCO to the σ* MO of the C–X bond in radical anions **6**, proposed as intermediates.

Other cases where disubstitution is achieved is in the reaction of 2,5- and 2,6-dibromopyridines, 2,3-, 2,6-, and 3,5-dichloropyridines, and 5,7-dibromo-8-methoxyquinoline with the [−]CH₂CO*t*-Bu ion^{42,43}; monosubstitution occurs from the selective displacement of chlorine from C4 of 4,7-dichloroquinoline when the same anion is used.⁴³

Carbanions derived from esters, carboxylate salts, *N,N*-disubstituted amides, thioamides, imides, and β-dicarboxylic compounds are used as nucleophiles to form new C–C bonds in S_{RN}1 reactions with aromatic substrates. α-Arylacetic esters are obtained by the reaction of ArX with the [−]CH₂CO₂*t*-Bu ion, under photo or Fe initiation. Lower yields of substitution are achieved with the anions of tertiary esters bearing β hydrogens. Other carbanions arylated under photostimulation includes the anions from ethyl phenylacetate, methyl diphenylacetate,

and *t*-butyl-3-butenate. For the last one, arylation occurs at the terminal site of the π system.⁵

On other hand, it is possible to obtain *N,N*-disubstituted-α-arylacetamides by the reaction of ArX with carbanions from *N,N*-disubstituted amides. Unsymmetrical α,α-diarylated amides can also be prepared by the reaction of the anions of the monoarylated products with ArX (**4**).^{25,44}

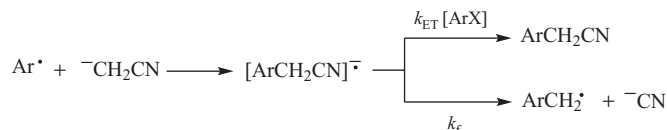


Ar = 1-Naphthyl, 9-phenanthryl or 9-anthracenyl. Ar¹ = Ph

Ar = Ph. Ar¹ = 9-Phenanthryl or 9-anthracenyl (4)

Stereoselective coupling of an aromatic radical with a nucleophile is found in the reaction of 1-iodonaphthalene with an imide ion containing a chiral auxiliary, where the diastereomeric isomers of the substitution compound are formed, depending on the metal counterion used. For example, the highest stereoselectivity is found with Li⁺ as a counterion at low temperature, and with Ti(IV).⁴⁵

1,3-Dianions from β-dicarbonylic compounds react quite well under irradiation through the terminal carbon site. Monoanions from β-dicarbonyl or β-cyanocarbonyl compounds react under electrochemical initiation with *p*-C₆H₅COC₆H₄Br and *p*-NCC₆H₄Cl, and in lower yields with



Scheme 3 Competition between ET and fragmentation of $[\text{ArCH}_2\text{CN}]^-$ radical anion.

2-chloroquinoline. An application of this reaction to obtain the natural product nebularine analog comprises the substitution of 2-methylsulfonylnebularine by ${}^-\text{CH}(\text{CO}_2\text{Et})_2$ ions.⁴⁶

The photoinitiated reactions of 2-bromobenzonitrile and 2-bromo-3-cyano-pyridine with the ethyl cyanoacetate ion afford the substitution product in good yields by an $\text{S}_{\text{RN}}1$ process.

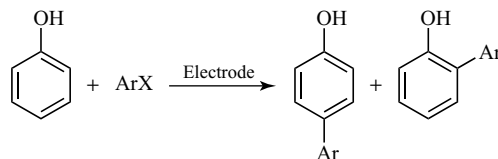
In the coupling reaction of phenyl radical with the ${}^-\text{CH}_2\text{CN}$ ion, the radical anion fragments into benzyl radical and CN^- ions ($\text{Ar} = \text{Ph}$, Scheme 3 lower case), where toluene is the principal product observed.^{47,48}

However, with 1-chloronaphthalene, polycyclic aromatic halides, substituted haloarenes with a $-\text{COPh}$ group, or halopyridines, substitution products ArCH_2CN are formed in good yields (upper case in Scheme 3). With these substrates, the extra electron of the radical anion resides in the aryl group and C–CN fragmentation is avoided. Other nitrile ions that can be used in this type of reaction include anions from phenylacetonitrile, 2-phenylbutyronitrile, and 2-cyclohexylidene-acetonitrile. For the last one, the substitution products are obtained at C γ position.⁴⁹

Nitronate ions can be used in $\text{S}_{\text{RN}}1$ reactions as nucleophiles, but only products of fragmentation of the radical anion of the substitution products are obtained.⁵⁰

One of the less reactive nucleophiles in $\text{S}_{\text{RN}}1$ is the CN^- ion.⁵ However, the substitution of $p\text{-C}_6\text{H}_5\text{COC}_6\text{H}_4\text{Br}$ is achieved under electrolysis, and the photoinitiated substitution of 2-methylsulfonylnebularine and 1-halo-2-naphthoxide ions has been reported. The diazosulfides ArN_2SPh are the best substrates to be substituted by the CN^- ion in DMSO, under irradiation or electrode stimulation. The system is favored by the positive reduction potential of the substrate with respect to the substitution products, which in turn helps the $\text{S}_{\text{RN}}1$ propagation cycle. When the aryl group is also substituted by Br or Cl, the introduction of two CN groups is achieved with good yields.⁵¹

Interesting examples in the aromatic family involve ArO^- ions, which react with ArX to give C–C instead of C–O bond formation. The reaction of PhO^- ions induced electrochemically with 4-bromobenzophenone or 4-chlorobenzonitrile, affords ortho (40%) and para (20%) coupling products (5).⁵²



(5)

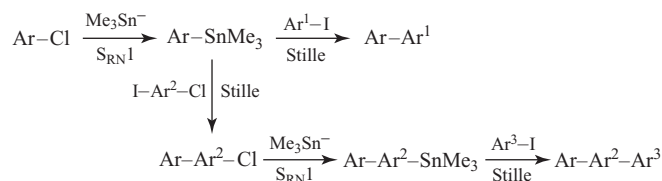
The 1- and 2-naphthoxide ions react under irradiation with different ArX . For 1-naphthoxide ions, a mixture of 2- and 4-aryl, together with 2,4-diaryl-1-naphthol products, is formed. Only substitution at C₄ occurs with the 2-methyl-substituted anion, while in the reaction with 4-methoxy-1-naphthoxide ion substitution takes place at C₂, accompanied by addition at C₄.⁵³

2-Naphthoxide ions react with ArX to give substitution only at C₁ of the naphthalene ring⁵⁴; 2,4 or 2,6-di-*tert*-butyl, $p\text{-MeC}_6\text{H}_4\text{O}^-$, and $p\text{-F}_3\text{COC}_6\text{H}_4\text{O}^-$ ions react under irradiation with $p\text{-FC}_6\text{H}_4\text{Br}$, $p\text{-CF}_3\text{C}_6\text{H}_4\text{Br}$, and $p\text{-F}_3\text{COC}_6\text{H}_4\text{Br}$ to give fluorinated biaryl derivatives.⁵⁵

The reaction of the 9-phenanthrenolate ion under photostimulation in DMSO with PhI affords the arylation product at C₁₀ position. In the reaction of this ion with *o*-diiodobenzene, substitution is obtained not only at C₁₀ but also at oxygen to give benzo[*d*]phenanthro[9,10-*b*]furan derivative.⁵⁶ This is a very rare example in which an aryl radical couples at oxygen.⁵⁷

3.2 Tin Nucleophiles

ArCl reacts in a photostimulated reaction with an R_3Sn^- ion by the $\text{S}_{\text{RN}}1$ mechanism, but ArBr and



Scheme 4 Synthesis of polyarylated products by S_{RN}1–Stille tandem reactions.

ArI react by the halogen metal exchange (HME) pathway.⁵⁸

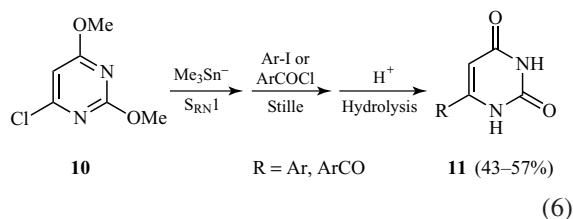
R₃Sn[−] ions from trimethyltin chloride and triphenyltin chloride can be prepared with Na metal in liquid ammonia. Competition experiments demonstrated that Me₃Sn[−] and Ph₃Sn[−] anions have the same reactivity in the propagation step, but the former is more reactive in the initiation step.⁵⁸

Disubstitution products are formed in high yields for the reaction of *o*-, *m*-, and *p*-C₆H₄Cl₂ under photostimulation. The trisubstitution product can be obtained from 1,3,5-trichlorobenzene.³⁰ Disubstitution products from pyridines also are acquired from dichloropyridines.³⁰

ArOH are readily converted into ArOP(O)(OEt)₂, which on reaction with Me₃Sn[−] and Ph₃Sn[−] ions afford ArSnMe₃ and ArSnPh₃ in good yields. This methodology is used for the synthesis of mono, di, and tristannylated products.^{59,60} On the other hand, ArNH₂ can be converted into ArNMe₃⁺ salts, which react with Me₃Sn[−] ions to give ArSnMe₃ in good yields.^{61,62}

This synthetic strategy has been employed to obtain a variety of stannanes, which have then been used in cross-coupling reactions to afford arylation products (Scheme 4). Thus, this sequence can be successfully applied to build large molecules.^{62,63}

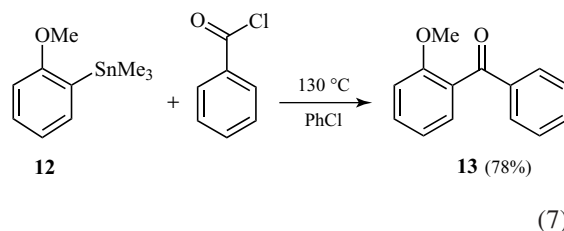
Recently, a similar approach to the synthesis of 6-substituted uracils **11** from 6-chloro-2,4-dimethoxypyrimidine **10** (6) was reported. By performing a three-step, one-pot reaction S_{RN}1–Stille–hydrolysis, it was possible to obtain 6-aryl- and 6-acyl-substituted uracils in good yields.⁶⁴



Other tin nucleophiles can be prepared by a Sn–alkyl bond fragmentation of a R₄Sn compound. When *p*-anisyltrimethyltin reacts with Na metal in liquid ammonia, the Sn–Me bond is cleaved to give the corresponding nucleophile. This reacts with *p*-chlorotoluene to afford the corresponding substitution product in high yields.⁶⁵

The dianion Me₂Sn^{2−} can be formed by the reaction of Me₂SnX₂ (X = Cl, Br) with Na metal, and affords Ar₂SnMe₂ in the photostimulated reaction with ArCl. A synthetic application of these stannanes involves the homocoupling of the aryl groups mediated by Cu.⁶⁶

The leaving group ability of the Me₃Sn group in electrophilic substitutions allows the synthesis of asymmetric diaryl ketones in good yields (40–78%) through the reaction of Me₃SnAr, synthesized by S_{RN}1 reactions, with ArCOCl. These reactions are completely regioselective, allowing the synthesis of diarylketones not usually available under Friedel–Crafts reactions. The reaction of stannane **12** with PhCOCl in PhCl as solvent, for instance, furnished diarylketone **13** in 78% yield (7).⁶⁷ Specific di- and triketones are obtained in good to excellent yields (45–83%).⁶⁸

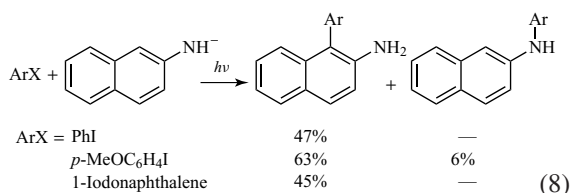


3.3 Nucleophiles Derived from N, P, As, and Sb

The first example of an S_{RN}1 type process was the reaction of ArX with the NH₂[−] ion.³ Thus, ArNH₂

products can be obtained by reaction with 1-chloro-2,4,5-trimethylbenzene and 1-chloro-2,3,5-trimethylbenzene, *o*-MeOC₆H₄X (X = Br or I), 2-iodo-1,3-dimethylbenzene, PhOPh, 3-bromothiophene, and ArOP(O)(OEt)₂, under K metal stimulation in liquid ammonia.⁴ NH₂[−] ions react under photoinitiation with 2-bromo-1,3,5-trimethylbenzene with good substitution yields (70%).⁶⁹

PhNH[−] ions reacts under K metal stimulation with PhI, and substitution occurs not only at nitrogen but also at the ortho and para carbons of the phenyl ring.⁴ On the other hand, the 2-naphthylamide ion reacts under photoinitiation with PhI, *p*-MeOC₆H₄I, and 1-iodonaphthalene in liquid ammonia to give 1-aryl-2-naphthylamines in good yields (8%).⁷⁰



Arylpyrroles, arylindoles, and arylimidazoles are synthesized electrochemically by the reaction of pyrrolyl, indolyl, and imidazolyl ions in liquid ammonia. For the pyrrolyl ion, substitution at C₂ on the heterocycle is the main product⁷¹; however, substitution at C₃ is obtained when C₂ and C₅ bear substituents.⁷²

For indolyl ions, substitution at C₃ is the major reaction observed.⁷² In the case of 4-methylimidazolyl ion, the yield of substitution product indicates that the C₅ position is more reactive than the C₂ position. For the 2-methylimidazole anion, the reaction becomes regioselective and only substitution at C₄ is obtained.⁷² This is also observed for the anions derived from 2-(*p*-anisyl)imidazole and 2-methyl-5-nitroimidazole in the reaction with ArI.⁷³

Electrochemical induction of different ArX bearing EWGs, in the presence of uracil ions in DMSO allows the synthesis of the corresponding 5-aryluracils.⁷³

The (EtO)₂PO[−] ion reacts with ArX to yield ArP(O)(OEt)₂ under irradiation either in liquid ammonia, MeCN/THF, DMF, or DMSO. The same anion also reacts under Fe²⁺ induction with ArI in liquid ammonia. Arylbromides ortho-functionalized by NH₂, OMe, or CONH₂ react under these

conditions to ArP(O)(OEt)₂ with low to excellent yields.⁵

When the (EtO)₂PO[−] ion reacts with haloiodobenzenes in liquid ammonia, the following behavior is observed: monosubstitution at iodine is obtained with *o*-, *m*-, and *p*-fluoro compounds; disubstitution is achieved with *o*- and *p*-chloroiodobenzenes; whereas meta isomers only afford substitution of iodine. With *o*-, *m*-, and *p*-dibromo and diiodobenzenes reaction with the (EtO)₂PO[−] ion gives mainly disubstitution products.⁷⁴

Other P-nucleophiles such as Ph₂P[−] ions react with different ArX to afford substitution products in good yields. The ions Ph(OBu)PO[−], Ph₂PO[−], (EtO)₂PS[−], (Me₂N)PO[−], and (C₆H₅CH₂)₂PO[−] react with PhI in liquid ammonia under photostimulation in nearly quantitative yields.⁵

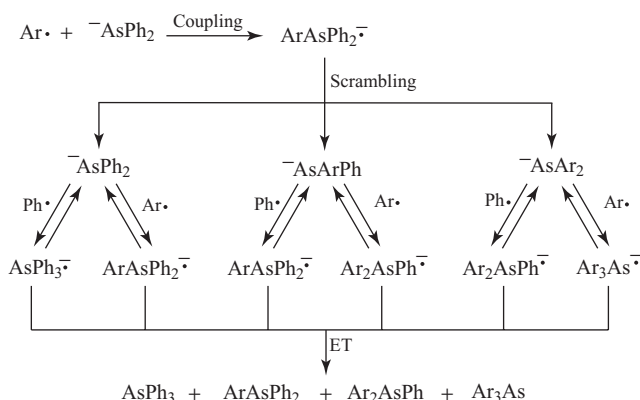
When Ph₂As[−] ions react under irradiation with *p*-halotoluenes, *p*-haloanisoles, 1-bromonaphthalenes, and 9-bromophenanthrene, arsines with scrambled aryl ring are formed. The S_{RN}1 mechanism, involving the formation of arsine radical anion intermediates, adequately accounts the products observed. For the radical anion intermediates formed, two possible reactions can occur: ET or C–As bond-breaking (Scheme 5).⁷⁵

When the substrate has a low-energy lowest unoccupied molecular orbital (LUMO), such as 4-chlorobenzophenone,⁷⁵ 2-chloroquinoline,⁷⁵ and 6-chloro-2,4-dimethoxypyrimidine,⁷⁶ the radical anion intermediates formed do not fragment, and the straightforward substitution products are obtained in 100%, 76%, and 70% yields, respectively.

3.4 Nucleophiles Derived from S, Se, and Te

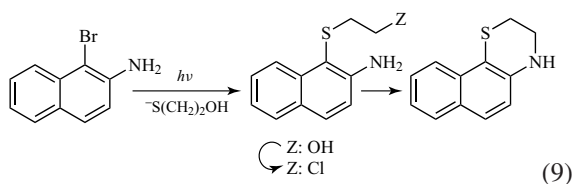
Sulfur-centered anions have been used in S_{RN}1 reactions and the results observed depend not only on substrates but also on the nucleophile applied. For alkanethiolate ions, depending on the nature of ArX and RS[−] involved, the fragmentation reactions may compete with the substitution process. Nevertheless, efficient substitution is obtained with compounds bearing EWGs as well as polycyclic or heterocyclic halides.⁵

The HO(CH₂)₂S[−] ion is used to obtain benzo[*e*]thiazine by an S_{RN}1 reaction with 1-bromo-2-aminonaphthalene followed by cyclization reaction



Scheme 5 Representation of the scrambling mechanism of aromatic moieties in the reaction of ArX with Ph₂As[−] ions.

after replacement of OH by Cl (9).⁷⁷



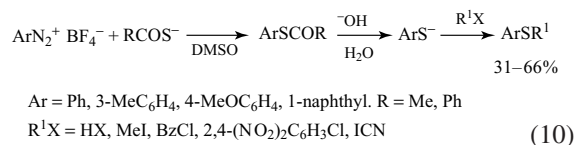
The same procedure has been applied to afford thiazines and benzo[*g*]thiazines by reaction of this anion with substituted *o*-bromoanilines, 2-amino-3-halo- or 3-amino-2-halopyridines, and with 1-amino-2-bromonaphthalene.⁵ By a double-S_{RN}1 reaction of 1- or 2-halonaphthalenes with [−]S(CH₂)_{*n*}S[−] dianions, the corresponding bis-sulfides are obtained.⁷⁸

Ar¹S[−] ions react with ArI in liquid ammonia under irradiation to form ArSAr¹ in good yields. ArBr reacts with PhS[−] ions under thermal, photochemical, or electrochemical initiation in DMF, MeCN, or DMSO. ArN₂BF₄ reacts with Ar¹S[−] to give ArSAr¹ via initial formation of the corresponding ArN₂SAr¹.⁵

Dihalobenzenes and ArN₂⁺ salts bearing a halogen substituent give mainly disubstitution in the reaction with PhS[−] ions. The synthesis of phenyl, naphthyl, and pyridyl derivatives bearing two ArS moieties or even two different ArS groups can be achieved by successive S_{RN}1 reactions.⁵

On the other hand, when 2-pyrimidinethiolate ions are allowed to react with *o*-, *m*-, and *p*-C₆H₄Cl₂, monosubstitution is the principal reaction observed, which can be explained on the basis of Scheme 2 (ET_(inter) > ET_(intra)).⁷⁹

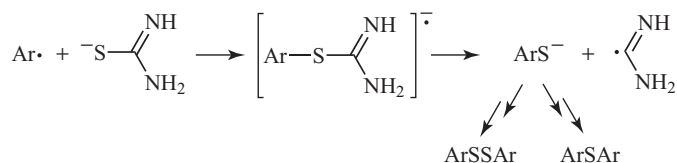
RCOS[−] ions represent another type of nucleophiles centered on sulfur which react in S_{RN}1 type processes. It is known that ArN₂BF₄ reacts with MeCOS[−] or PhCOS[−] ions to give arylthioesters, which can be either isolated or react further providing a convenient one-pot process to access other aromatic sulfur derivatives (10).⁸⁰



Aryl methyl and symmetrical diarylsulfides were prepared by photoinduced reactions of MeCOS[−] ions with ArX (X = Br or I) in moderate to good yields. For these reactions, *entrainment* conditions with *t*-BuOK are required. The yields of diarylsulfides increase when appropriate reactions conditions are chosen. For example, when 1-bromonaphthalene and the MeCOS[−] ion (0.125 M, ratio 1 : 1) react, 42% diarylsulfide is obtained. On the other hand, if the concentration of the nucleophile is increased to 0.25 M and the ratio substrate/nucleophile is 1 : 0.6, the yield of diarylsulfide is 83%.⁸¹

In addition, MeCOS[−] and NH₂(NH)CS[−] ions were used as nucleophiles in S_{RN}1 reactions with *p*-NCC₆H₄Cl and 2-, 3-, and 4-chloropyridines under electrochemical conditions to afford ArS[−], ArSAr, and ArSSAr (Scheme 6).⁵

A study on the reactivity of NH₂(NH)CS[−], MeCOS[−], and PhCOS[−] ions toward 1-naphthyl



Scheme 6 Generation ArS^- ions from reaction of $\text{Ar}^\bullet$ and $\text{NH}_2(\text{NH})\text{CS}^-$.

radicals determined by competition experiments indicates that all anions show similar rate constants for the coupling reaction (1×10^9 , 1.2×10^9 , and $3.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ respectively).⁸²

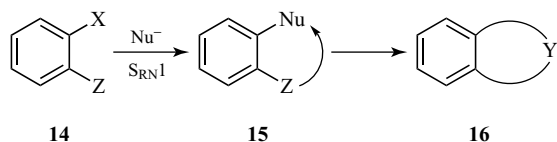
Although PhCOS^- is the most reactive anion in the coupling step, the overall reaction is the least efficient as compared to $\text{NH}_2(\text{NH})\text{CS}^-$ and MeCOS^- ions. A quantum yield higher than unity evidences a chain mechanism for $\text{NH}_2(\text{NH})\text{CS}^-$ and MeCOS^- ions. PhCOS^- adds to the 1-naphthyl radical, but is neither able to initiate the reaction nor to keep the propagation cycle.⁸²

The Na_2Se nucleophile can be formed by the reaction of Se and Na metals in liquid ammonia and reacts under irradiation with PhI to give $(\text{PhSe})_2$ (78%), after oxidation of the PhSe^- ions formed.⁸³ Z_2^{2-} ($\text{Z} = \text{Se}$ or Te) is also formed by electrogeneration from metals using sacrificial electrodes in MeCN. After that, the ions react with ArX to achieve ArZZAr .⁵ Finally, PhSe^- and PhTe^- substitute various ArX under irradiation; straightforward and scrambled products are obtained depending on both the nucleophile and the ArX employed.⁸⁴

3.5 Ring-Closure Reactions

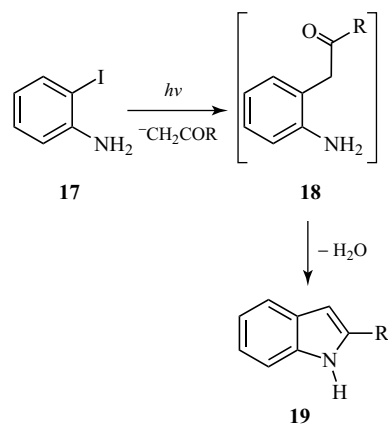
3.5.1 $\text{S}_{\text{RN}}1$ Reaction Followed by a Polar Reaction

One of the most widely studied approaches to ring-closure reactions is the $\text{S}_{\text{RN}}1$ substitution of aromatic compounds that have an appropriate ortho substituent Z to the leaving group, such as **14**, which can react with a nucleophile to afford product **15**. The ring-closure product **16** is obtained by the spontaneous reaction between the Nu and Z groups (11).



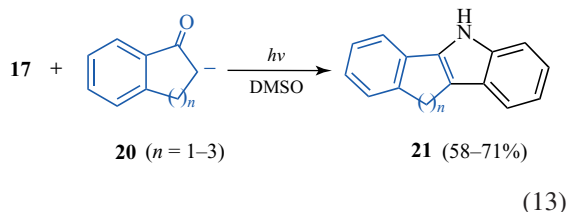
(11)

A significant example is the synthesis of indoles by the photostimulated reaction of *o*-iodoaniline **17** with $^- \text{CH}_2\text{COR}$ ions in liquid ammonia to give product **18**, which spontaneously cyclizes to the substituted indole **19** (12).⁸⁵ The analogous reaction of *vic*-aminohalo pyridines leads to azaindoles (70–95%).⁸⁶



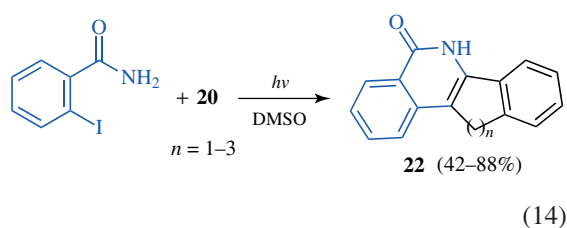
(12)

Photostimulated reactions of **17** with $^- \text{CH}_2\text{COAr}$ ions in DMSO afford 2-substituted indoles such as **19** [$\text{R} = \text{Ph}$ (88%), 1-Naph (73%), 2-Pyr (64%), and 3-Pyr (74%)], with heteroaromatic ketones, such as 2-acetylthiophene and *N*-methyl-2-acetyl-pyrrole, afford **19** with 82% and 93% yields, respectively.⁸⁷ Photostimulated reactions of **17** with enolate anions derived from cyclic ketones, such as **20**, afford the fused indoles **21** in moderate to high yields (13).⁸⁸

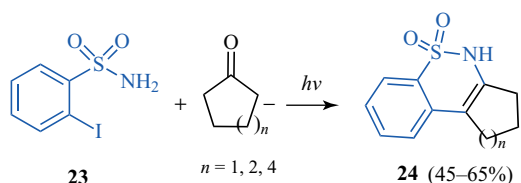


Benzo[*e*]- and benzo[*g*]indoles can be obtained through the reaction of 1-bromo-2-amino or 1-amino-2-bromonaphthalene, respectively, with the [−]CH₂CO*t*-Bu ion.⁷⁷

The synthesis of 3-substituted isoquinolin-1(2*H*)-ones can be achieved by photoinduced S_{RN}1 reactions in DMSO by reacting *o*-iodobenzamide with enolate ions of aromatic and aliphatic ketones in 68–87% yields. With cyclic ketones, these reactions afford fused isoquinolinones with moderate to good yields (14).⁸⁹

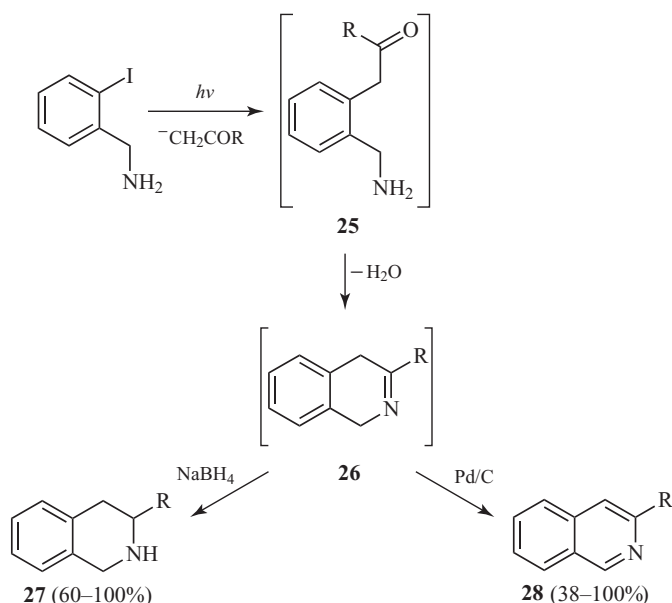


2-Iodobenzenesulfonamide **23** undergoes photo-stimulated S_{RN}1 reactions in liquid ammonia with ketone enolate ions, yielding 2*H*-1,2-benzothiazine-1,1-dioxides with fair to good yields (67–90%). With cyclopentanone-, cyclohexanone-, and cyclooctanone-derived enolates, fused benzo-thiazine-1,1-dioxides **24** were obtained (15).⁹⁰

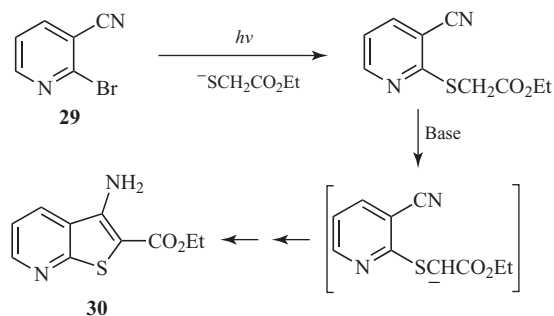


The S_{RN}1 approach can be a route to isoquinoline rings and derivatives by reaction of *o*-iodobenzylamines with [−]CH₂COR ions under irradiation. The substitution product **25** spontaneously reacts further by ring closure to give product **26**. If **26** is treated with NaBH₄, tetrahydroisoquinolines **27** are obtained. On the other hand, treatment with Pd/C provides isoquinoline derivatives **28** (Scheme 7).⁹¹

Thienopyridine rings such as **30** can be obtained by the reaction of EtO₂CCH₂S[−] ions with 2-bromo-3-cyanopyridine **29** (and 3-bromo-4-



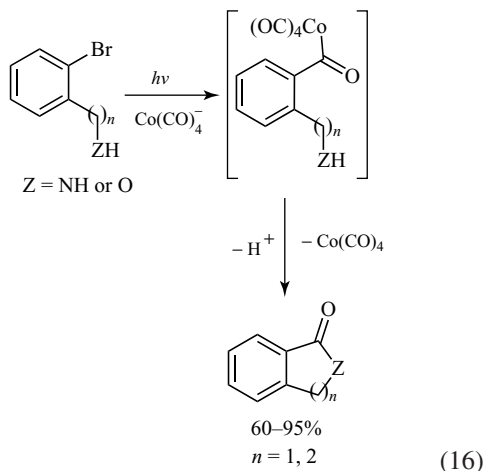
Scheme 7 Synthesis of tetrahydroisoquinolines (**27**) and isoquinolines (**28**) from *o*-iodobenzylamines and [−]CH₂COR anions by S_{RN}1-ring-closure sequence.



Scheme 8 Synthesis of thienopyridines **30** through the $S_{RN}1$ -nucleophilic addition-hydrolysis sequence.

cyanopyridine), in which the substitution product is deprotonated to afford ultimately **30** in 90% and 98% yields, respectively (Scheme 8).⁹²

An important approach to five- and six-membered ring benzolactams and benzolactones is the carbonylation under phase transfer catalysis (PTC) conditions of ArX bearing NH_2 or OH groups on a side chain ortho to the halogen atom (**16**). Although no mechanistic studies have yet been conducted, the authors suggest that reactions occur via an $S_{RN}1$ mechanism.⁹³

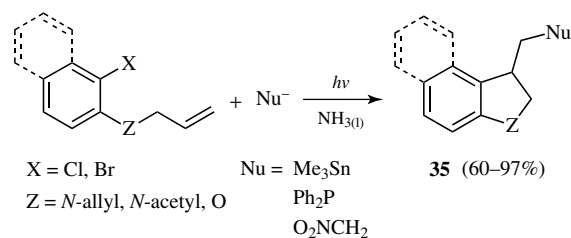


3.5.2 5-*exo* and 6-*exo* Radical Cyclization Followed by an $S_{RN}1$ Reaction

When an aromatic substrate has both a leaving group and a double bond at an appropriate distance as in **31** ($n = 1$ or 2), the radical **32** formed after the

ET and fragmentation can cyclized in a 5-*exo* or 6-*exo* fashion (see **Radical Kinetics and Clocks**), to generate the alkyl radical **33** which is able to react with nucleophiles by the $S_{RN}1$ mechanism to afford the ring-closure substitution product **34** (Scheme 9).

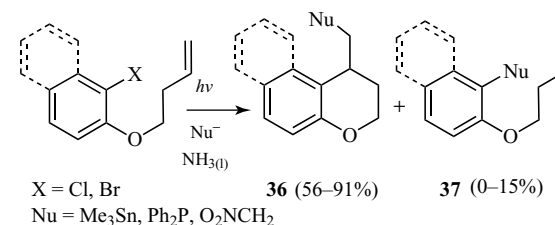
Using this approach, 3-substituted-2,3-dihydro-1-*H*-indoles, 3-substituted-2,3-dihydro-1-*H*-benzo[*e*]indoles (**35**, $Z = N-R$), 2,3-dihydrobenzofurans, and 2,3-dihydrobenzofurans (**35**, $Z = O$) are easily prepared via a 5-*exo* ring-closure process during the propagation cycle in the $S_{RN}1$ reaction (17).⁹⁴



(17)

With $^-CH_2NO_2$ ion as a nucleophile, the sequence provides the corresponding *N*-allyl-3-(2-nitro-ethyl)-2,3-dihydro-1-*H*-indole in 60% yield after a photostimulated reaction ($X = Br$), in the presence of the $^-CH_2COMe$ ion as an entrainment reagent.

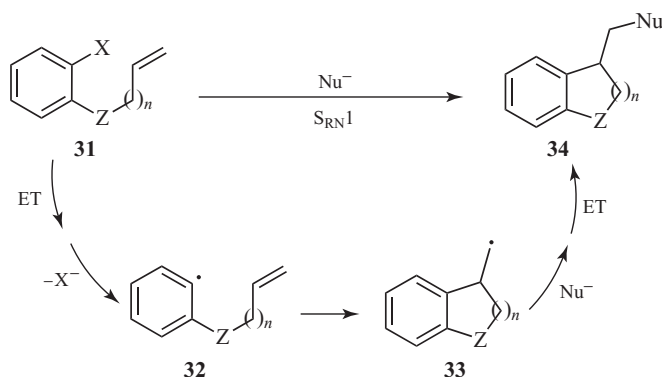
Tandem 6-*exo-trig* cyclization- $S_{RN}1$ reactions with 1-(but-3-enyloxy)-2-halobenzenes and 1-(but-3-enyloxy)-2-halonaphthalenes afford 4-substituted chromanes and benzo[*f*]chromanes **36** in good to excellent yields, along with the direct substitution product **37** (18).⁹⁵



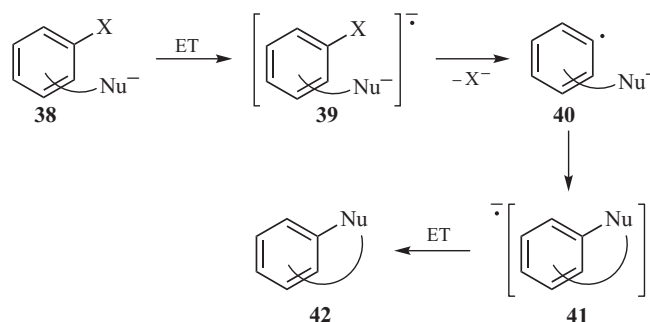
(18)

3.5.3 Intramolecular $S_{RN}1$ Reactions

When a substrate bears both the leaving group and also the nucleophilic center, the intramolecular $S_{RN}1$



Scheme 9 5- or 6-*exo* radical ring closure preceding the S_{RN}1 mechanism.

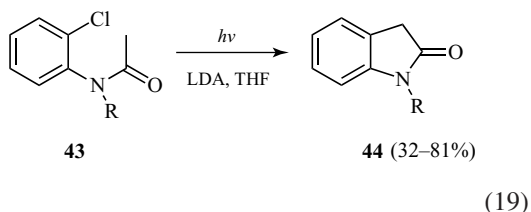


Scheme 10 Ring-closure reaction by an intramolecular S_{RN}1 reaction.

reaction directly leads to the ring-closure product (Scheme 10).

Substrate **38** receives an electron by ET and forms the dianion radical **39**, which by fragmentation of the C–X bond gives distonic radical anion **40**. This is a high-energy intermediate; the ring-closure product provides the more stable conjugated radical anion **41**. Finally, ET furnishes product **42**.

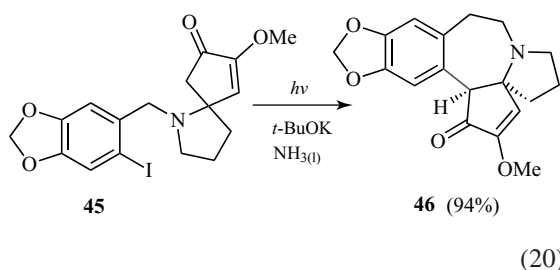
This strategy has been widely used to obtain heterocyclic compounds. For instance, oxindoles **44** were prepared by intramolecular cyclization of the anion of *N*-alkyl-*N*-acyl-*o*-haloanilines **43** (19).⁹⁶

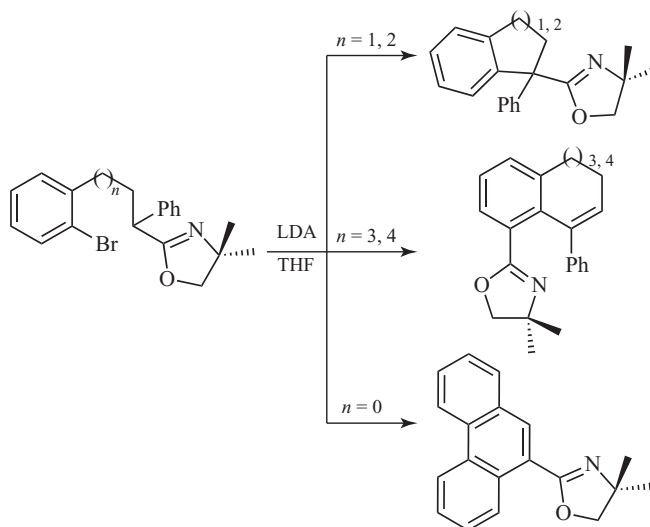


In a similar approach, 3-alkylideneoxindoles were obtained starting from *N*-methyl- α,β -unsaturated

anilides (63–100%) and 1,4-dihydro-2*H*-isoquinolin-3-ones by photocyclization of *N*-acyl-*N*-methyl-*o*-chlorobenzylamines (54–62%).⁵ 1-Phenyl-indanones, tetralin derivatives, and alkaloid structures were synthesized by the same strategy. For instance, alkaloids such as eupoulauramine, tortuosamine, and Ergot-type ones were obtained by intramolecular S_{RN}1 reactions as a key step.⁵

Cephalotaxinone **46**, a natural alkaloid, is the major product in the photoinduced reaction of iodoketone **45** (20).⁹⁷



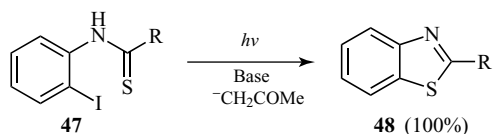


Scheme 11 Intramolecular reactions of 2-bromophenylalkyl-2-oxazolines. The products depend on the length of the alkyl chain spacers.

The length effect of alkyl chain spacers was studied using 2-halophenylalkyl-2-oxazolines (Scheme 11). When the spacer is $n = 1$ or 2, products from cyclization by $S_{RN}1$ reaction are obtained; for $n = 3$ or 4, the major product is a benzocycloalkane derivative in which the oxazoline has undergone an arenotropic migration from the end of the spacer to the benzo ring, whereas with $n = 0$, the 9-oxalinophenanthrene derivative is the main product observed.⁹⁸

In a similar approach, a tetracyclic isoquinoline derivative was synthesized using 3-[4-(2-bromophenyl)-2-phenylbutyryl]-4,4-dimethyloxazolidin-2-one as substrate. For this reaction, two mechanisms involving an $S_{RN}1$ -type process were proposed.⁹⁹

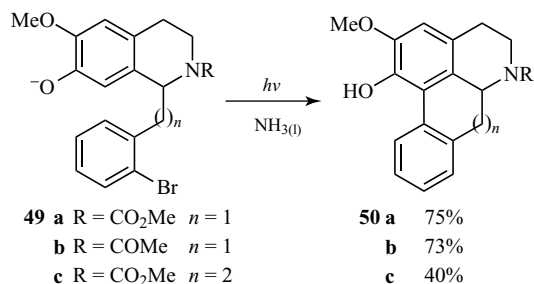
Benzothiazoles **48** can be obtained in excellent yields (100%) by reaction of **47** ($R = \text{Me}, \text{Ph}$) and acetone enolate ions as entrainment reagent (21).¹⁰⁰



(21)

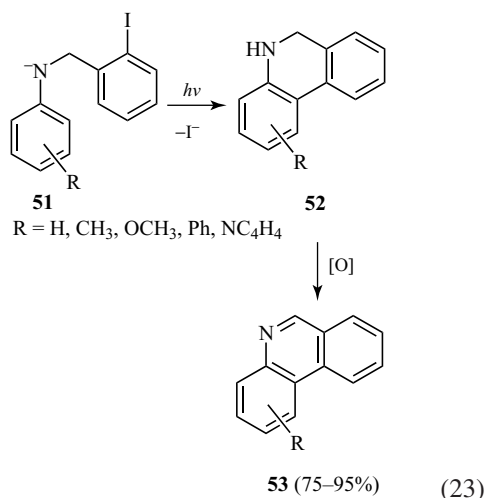
Photostimulated intramolecular ortho-arylation reactions of bromoarenes linked with pendant

phenoxy containing *N*-substituted tetrahydroisoquinolines such as **49** afford aporphine alkaloid derivatives **50** in good yields (22). This strategy was later extended to the synthesis of a homoaporphine alkaloid **50c** ($n = 2$) from **49c** in 40% yield.¹⁰¹

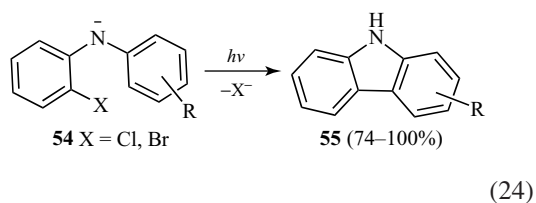


(22)

Following a similar approach and using the intramolecular arylation of iodobenzyl amide ions **51** with a pendant aryl moiety, the reaction affords phenanthridines **53** derivatives in very good yields.¹⁰² These reactions have been carried out under irradiation in liquid ammonia or DMSO. Dihydrophenanthridines **52** were the straight ring-closure products, which spontaneously oxidize during work-up to give **53** (23).



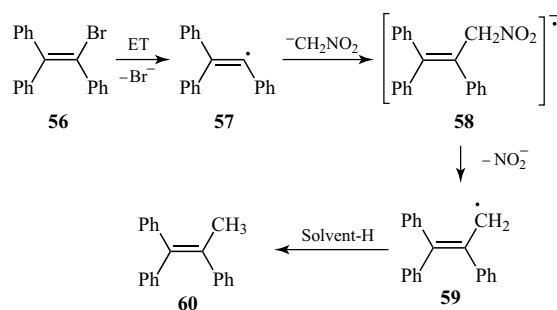
The synthesis of a series of substituted 9*H*-carbazoles by the photostimulated S_{RN}1 reaction of diarylamines as starting substrate was achieved via an intramolecular C–C bond formation. Anions **54** formed in liquid ammonia or DMSO reacted under irradiation in good yields to 9*H*-carbazoles **55** (R = H, 1-Ph, 1-pyrrolyl, 3-OMe, 3-*t*-Bu) (24).¹⁰³



4 S_{RN}1 REACTIONS WITH VINYLIC SUBSTRATES

Different mechanisms are possible for the nucleophilic substitutions of vinyl halides.¹⁰⁴ For a vinylic S_{RN}1 process, the substrate should not contain vinylic or allylic hydrogens so as to avoid the alternatives of α–β and α–β' elimination–addition reactions, respectively. On the other hand, the presence of a conjugated group such as aryl or 1,3-butadienyl is required to stabilize the intermediate radical anion of the substitution product. Nucleophilic addition to a rearranged radical from a 1,3-hydrogen shift is possible when the vinyl halides have γ-hydrogen atoms.¹⁰⁵

Triphenylvinyl bromide **56** reacts with the [–]CH₂CO*t*-Bu ion to yield the corresponding



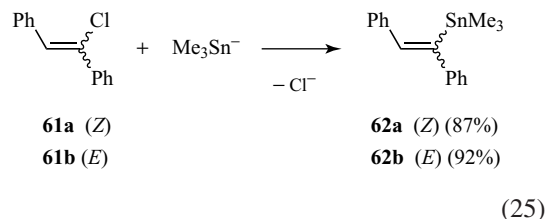
Scheme 12 Mechanism of the reaction of vinyl substrate **56** with the [–]CH₂NO₂ ion. Fragmentation of the intermediate radical anion **58** gives the final product **60**.

substitution product in 93% yield by an S_{RN}1 reaction. The anion [–]CH₂COPh does not react under irradiation; however, under *entrainment* conditions ([–]CH₂COMe anion as initiator), it affords 90% of the substitution product.¹⁰⁶

Under similar reaction conditions, [–]CH₂NO₂ ion as nucleophile yields 1,1,2-triphenylpropene **60** by the S_{RN}1 mechanism (Scheme 12).¹⁰⁶ When **56** accepts an electron, it fragments to afford the vinyl radical **57**. This radical then couples with the nucleophile to yield the radical anion **58** that fragments to afford the NO₂[–] ion and the allylic radical **59**, which is finally reduced to the product **60**.

A study was undertaken on the coupling of vinyl radicals with (EtO)₂PO[–], [–]CH₂COR-Bu, and PhS[–] ions, and the competing H-atom abstraction reactions from MeCN or DMSO. The rate constant for H abstraction in DMSO was, for radical **57**, 1.1 × 10⁵ M^{–1} s^{–1}, and that for the coupling of **57** with the PhS[–] ion was calculated to be 1.9 × 10⁷ M^{–1} s^{–1}.¹⁰⁷

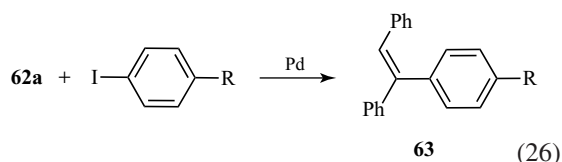
The reaction of (*Z*)-1-chloro-1,2-diphenylethene (**61a**) with the Me₃Sn[–] ion afforded the substitution product **62a** by the S_{RN}1 mechanism. Similar results were found with the isomer **61b** (25).¹⁰⁸



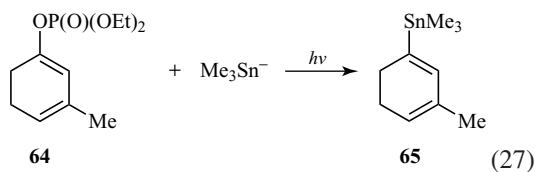
It is known that some vinyl radical intermediates are configurationally unstable, and from pure (*E*) or

(*Z*) substrate, the $S_{RN}1$ process yields a mixture of (*E*) and (*Z*) isomers.¹⁰⁴ The reaction of **61a** and **61b** with Me_3Sn^- affords only one isomer with retention of configuration, indicating that the inversion of these vinyl radical intermediates was slower than the coupling reaction of the radical with the Me_3Sn^- anion.¹⁰⁸

The stannanes thus obtained, such as the reactions of **62a**, can further react by Pd-catalyzed cross-coupling reaction with ArI to yield substituted alkenes **63** in high yields ($R = H, Me, OMe, Cl$, 87–98%) (26).¹⁰⁸



It has been reported that vinyl phosphate esters react with the Me_3Sn^- ion under irradiation to obtain vinyltrimethyl stannanes by the $S_{RN}1$ mechanism.¹⁰⁹ The reaction of Me_3Sn^- ions with 1-(diethoxyphosphoryl)oxy-1,3-cyclohexadiene **64** under irradiation affords the product **65** (59% yield) (27).¹¹⁰



However, the isomer 2-(diethoxyphosphoryl)oxy-1,3-cyclohexadiene reacts very slowly and no substitution product was identified. Thus, structurally similar compounds do not have the same reactivity. It is suggested that this behavior is mainly due to differences in the spin density of their radical anions, which influence their fragmentation rates.¹¹⁰

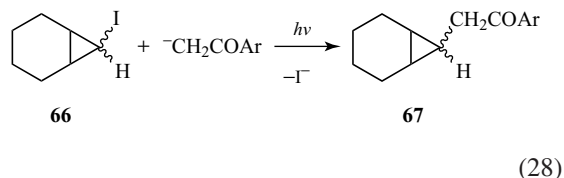
The $S_{RN}1$ mechanism has been proposed for the photoinduced catalytic carbonylation of vinyl bromides and chlorides with $NaCo(CO)_4$ under PTC conditions at atmospheric pressure, constituting a particularly interesting synthesis of unsaturated carboxylic acids.⁹³ Carbonylation can also be performed under atmospheric pressure of CO in the presence of a cobalt catalyst.¹¹¹

5 $S_{RN}1$ REACTIONS WITH ALIPHATIC SUBSTRATES

5.1 Cycloalkyl Halides

Substituted cyclopropanes react by the S_N1 mechanism through a disrotatory ring opening. This electrocyclic process has relatively high activation energy due to the fragmentation of two bonds in a concerted process. On the other hand, halocyclopropanes do not usually suffer nucleophilic substitution by the S_N2 mechanism. Instead, an elimination addition process occurs in the presence of strong bases.

In the reaction of carbanions with 7-iodonorcaradiene **66** (a mixture of circa 1:1 of *exo*:*endo* isomers), the substitution products **67** are 93–95% *exo* isomers, indicating that the coupling of the 7-norcaranyl radical with these carbanions is quite selective (28).¹¹² The same *exo* isomer yield (93–95%) obtained by reaction with $^-CH_2COPh$ ions initiated with inorganic salts ($FeBr_2$ or SmI_2)²³ evidences of the presence of 7-norcaranyl radicals as intermediates under both types of initiation.



Recently, the synthesis of new 1,1-bis(trimethylstannyl)cyclopropanes by the $S_{RN}1$ mechanism has been reported.¹¹³ 1,1-Dichlorocyclopropanes react under irradiation with the Me_3Sn^- anion in liquid ammonia to give the disubstitution products bis-stannylcyclopropanes in good to excellent isolated yield.

The photostimulated reaction of 2-iodoadamantane (2-AdI) with carbanions derived from MeCOPh, 2-naphthyl-methyl-ketone, *N*-acetylmorpholine, and anthrone affords substitution products in moderate yields (32–62%). The reaction with $^-CH_2COPh$ ions induced by $FeBr_2$ renders 88% substitution yield. The $^-CH_2NO_2$ anion reacts (in the presence of $^-CH_2COMe$ ions) to give 88% yield of substitution product.¹¹⁴

Excellent substitution yields are obtained with Me_3Sn^- ions and 2-AdCl (94%)¹¹⁵ and 2-AdBr

(80%) as substrates¹¹⁶ in liquid ammonia under irradiation.

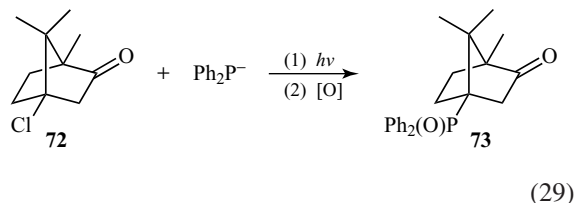
5.2 Bridged Halides

Bridged halides have a high energy barrier for a S_N1 mechanism owing to strain factors and they do not react by the S_N2 mechanism for steric reasons. Many of these halides have been found to react by the S_{RN}1 mechanism.

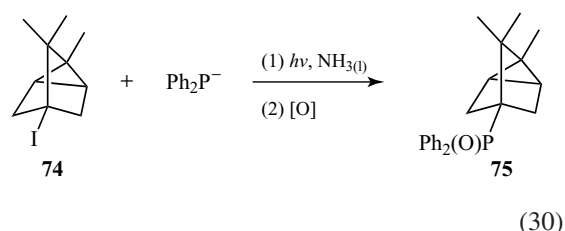
1-Iodobicyclo[2.2.2]octane reacts with Ph₂P[−] ions in liquid ammonia under irradiation to give the corresponding substitution product (87% yield). The chloro derivative is unreactive under irradiation.¹¹⁷ However, 2-oxo derivative **68** (with a C=O π electron acceptor) reacts to afford 69% yield of product **71** (Scheme 13).¹¹⁸ This increase in reactivity has been explained by an intramolecular entrainment reaction. It is proposed that **68** receives an electron in its antibonding carbonyl π* MO to form the radical anion **69**, which by an intramolecular ET to the antibonding σ* MO of the C–Cl bond forms the bridgehead radical **70** that propagates the chain reaction.^{118,119}

Similarly, 1-chlorobicyclo[2.2.1]heptane is unreactive toward Ph₂P[−] ions; however, 1-chloro-3,3-dimethyl-2-oxobicyclo[2.2.1]heptane reacts to give, after oxidation, the substitution product (93% yield). 4-Chloro-1,7,7-trimethyl-2-oxobicyclo[2.2.1]heptane **72**, in which the spatial distance between the leaving group and the C=O π is

increased with an extra C–C bond, also affords the substitution products **73** (80% yield) (29).¹¹⁹



4-Halotricyclanes are one of the most unreactive substrates in solvolytic reactions. Yet, 4-iodotricyclane **74** reacts with Ph₂P[−] ions under irradiation to afford **75** in 58% yield (30). The 1-chloro derivative is totally unreactive.¹²⁰

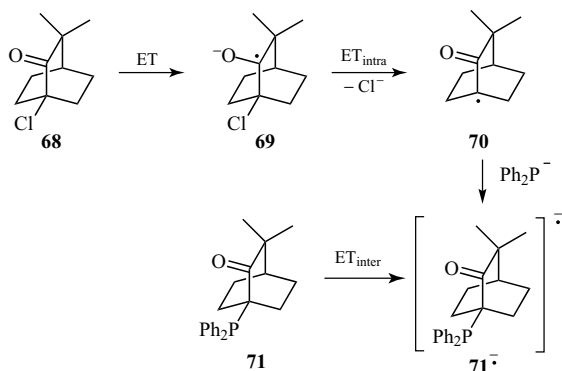


Substrate **76** reacts with Ph₂P[−] ions under irradiation to afford the rearranged substitution product **77** (83% yield, as the oxide). The ET to **76** gives the bridgehead radical **78** after fragmentation. This radical rearranges by a 1,5-hydrogen shift to afford radical **79**, which couples with the Ph₂P[−] ion to give the substitution product **77** after oxidation (Scheme 14).¹²¹

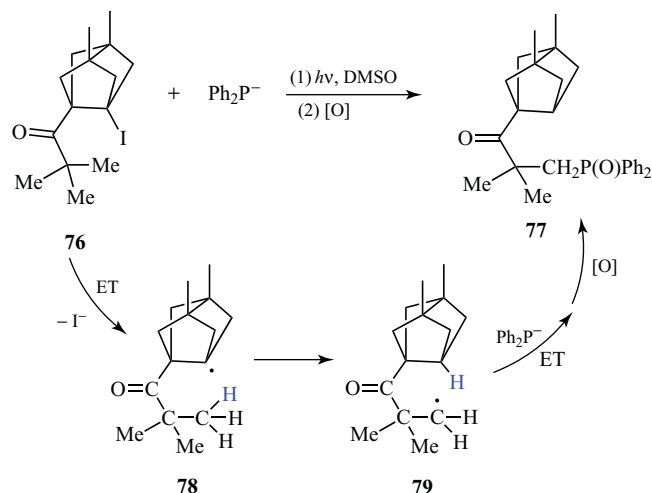
1-AdI reacts under irradiation with carbanions derived from ketones in DMSO (20–75% yield).²⁹ These reactions can also be induced by FeBr₂. Thus, [−]CH₂COPh ions afford the substitution product in 85% yield.²³ 1-AdCH(NO₂)R is also formed by the photostimulated reaction of 1-AdI with [−]CHR(NO₂) anions (R = H, Me, C₅H₁₁, (CH₂)₃CH=CH₂, 77–87% yields) in the presence of [−]CH₂COMe in DMSO.¹²²

Other nucleophiles that also react with 1-haloadamantanes are Me₃Sn[−] (80% yield),¹²³ Ph₂P[−] (70% yield),¹²⁴ Ph₂As[−] (65% yield),¹²⁴ ArS[−] (45–95% yield),¹²⁵ PhSe[−] (74% yield),¹²⁶ and PhTe[−] (69% yield)¹²⁶ ions.

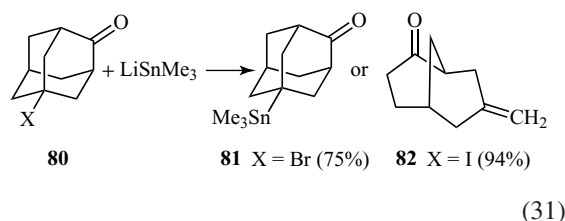
5-Bromoadamantan-2-one **80** reacts with LiSnMe₃ in THF to afford the substitution product **81** by a radical path; however, the iodo derivative furnishes the fragmentation product **82** by a polar reaction (31).¹²⁷



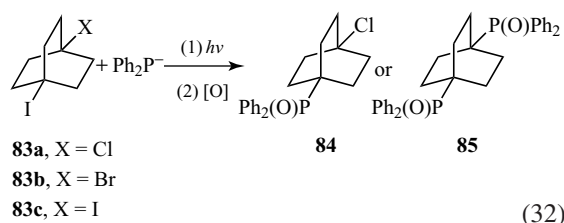
Scheme 13 Intramolecular redox catalysis in oxo derivatives of bridged halides.



Scheme 14 1,5-Hydrogen shift during an $S_{RN}1$ reaction.

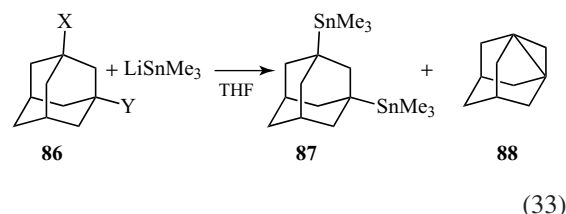


When the substrate has two leaving groups, and one of them is iodine, such as **83**, the products obtained depend on the nature of the second halogen. Thus, with **83a** only substitution at iodine occurs (compound **84**, 63% yield). Both halogens are substituted with **83b** and **83c**, affording **85** in 83% and 58% yields, respectively (32).¹¹⁸

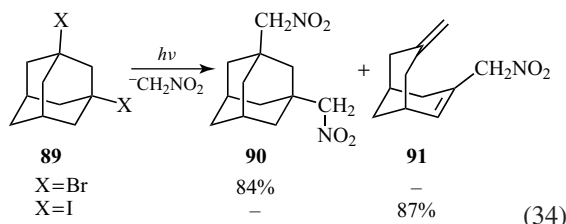


In the reaction of 1,3-dihaloadamantanes **86** with $M\text{SnMe}_3$ ($M = \text{Li}$ or Na), the products depend on the halogens. For example, when $X = \text{Cl}$ and $Y = \text{Br}$, the disubstitution product **87** is the main product (94–97% yield), whereas when $X = \text{Br}$, $Y = \text{I}$, or $X = Y = \text{I}$, propellane **88** is the major product (80–100% yield) (33). The $S_{RN}1$ mechanism accounts for **87**, but formation of **88** occurs

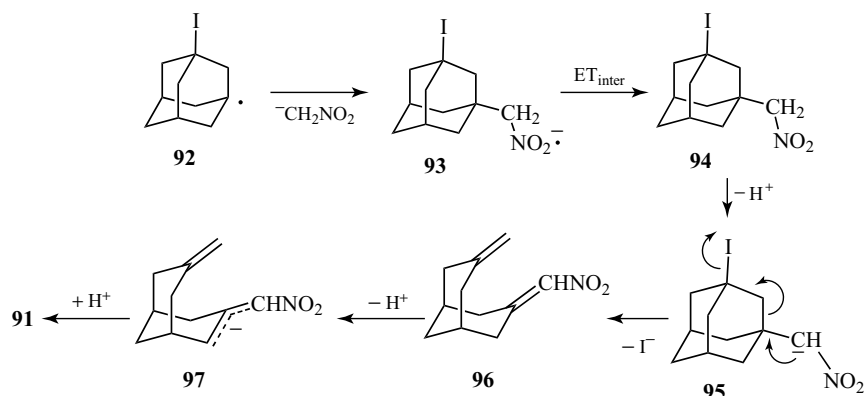
through a concerted process involving direct attack by the Me_3Sn^- ion on an iodine with synchronous cyclization and cleavage of the second $\text{C}-\text{X}$ bond.¹²⁸



In the photostimulated reaction of 1,3-dihaloadamantane with carbanions, the products also depend on the halogens. For instance, the photostimulated reaction of **89** ($X = \text{Br}$) with the $^-\text{CH}_2\text{NO}_2$ ion (and the $^-\text{CH}_2\text{COMe}$ ion as entrainment reagent) gives the disubstitution product **90** in 84% yield.¹²⁹ However, in the reaction with **89** bearing both iodo substituents, the rearranged monosubstitution product **91** is obtained in 87% yield (34).¹³⁰



When **89** ($X = \text{I}$) receives one electron, it fragments through a dissociative ET to give radical **92**

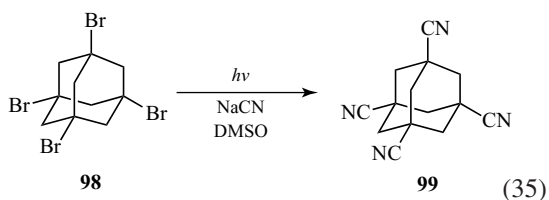


Scheme 15 Rearrangement of the monosubstitution S_{RN}1 product **94**.

that couples with the nucleophile to afford radical anion **93**, which, by an intermolecular ET to the substrate, affords substitution product **94** (Scheme 15). Compound **94** is deprotonated under the basic reaction conditions to yield carbanion **95**, which by a ring-opening reaction renders product **96**, in turn undergoing deprotonation to afford the carbanion **97**. After acidification, the most stable isomer **91** is obtained.¹³⁰

The fact that with 1,3-diiodoadamantane the intermolecular ET to the substrate to afford **94** as the intermediate is faster than the intramolecular ET to the other C–I bond accounts for the better electron acceptor capability of 1,3-diiodoadamantane as compared to the 1,3-dibromoadamantane.

CN[−] ions react in a photostimulated reaction (254 nm) with 1,3,5,7-tetrabromoadamantane **98**, affording tetrasubstituted product **99** in 73% yield by the S_{RN}1 mechanism (35).³²

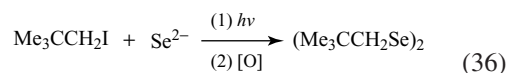


5.3 Neopentyl and Related Halides

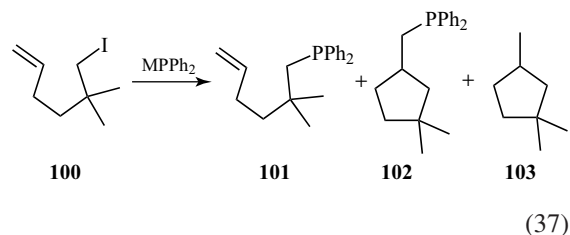
Several enolate anions such as [−]CH₂COMe ions fail to react with neopentyl bromide in liquid ammonia under irradiation. Reduction is the main reaction of neopentyl iodide in the presence of [−]CH₂COMe

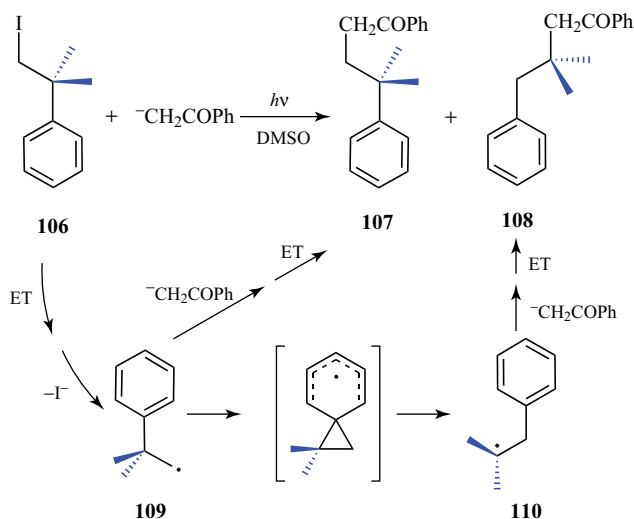
ions in DMSO, whereas substitution is achieved with [−]CH₂COPh ions (65% under irradiation,¹³¹ 92% when initiated with FeBr₂²³). Substitution by [−]CH₂NO₂ ions also occurs (69%, in the presence of [−]CH₂COMe ions).¹³¹

PhS[−], Ph₂P[−], and Ph₂As[−] ions react with neopentyl bromide under irradiation with 60%, 76%, and 82% yields of substitution, respectively.¹³² The Na₂Se salt reacts with neopentyl iodide to give dineopentyl diselenide (83% yield) as a result of initial S_{RN}1 reaction and subsequent oxidation of the neopentyl selenide ion intermediate (36).¹³³



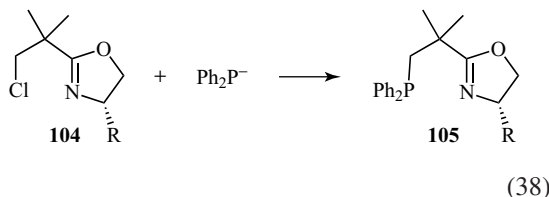
When MPPh₂ (M = Li, Na, or K) reacts with 6-iodo-5,5-dimethyl-1-hexene **100** in THF, the compounds indicated in (37) are formed by the S_{RN}1 mechanism.¹³⁴ The unrearranged **101** (17–43% yield), cyclized substitution **102** (48–75% yield), and cyclized hydrocarbon **103** (4–11% yield) products are obtained, and these yields depend on the counterion. The fact that rearranged products are obtained indicates that the radicals are intermediates.





Scheme 16 Neophyl rearrangement during the $S_{RN}1$ reaction of substrate **106**.

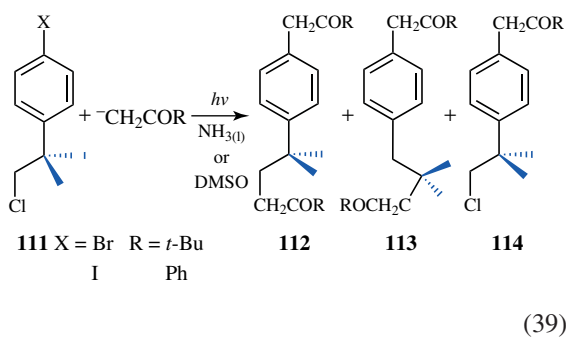
Recently, the reaction of a neopentyl chloride bonded to an oxazoline moiety **104** with Ph_2P^- ions by the $S_{RN}1$ mechanism has been reported to give the P–N ligand **105** with good yields (60–92% yield) (38). With these ligands **105**, new iridium complexes were synthesized and evaluated in the enantioselective hydrogenation of unfunctionalized olefins.¹³⁵



Neophyl iodide **106** reacts under irradiation with PhCOCH_2^- ions to afford the rearranged compounds **107** (50% yield) and **108** (16% yield), respectively.¹⁹ When **106** receives one electron, it fragments to afford radical **109**, which by a neophyl rearrangement gives radical **110**, which in turn reacts with the nucleophile to finally give **108** (Scheme 16).

Disubstitution at aromatic and aliphatic sites is achieved by the photostimulated reaction of $\text{CH}_2\text{CO}t\text{-Bu}$ and CH_2COPh ions with **111** (39).¹³⁶ In DMSO, the main reaction is $S_{RN}1$ to afford disubstitution **112** and rearranged disubstitution **113** products. In liquid ammonia, only substitution at the aromatic C-halogen site is observed

yielding **114**.



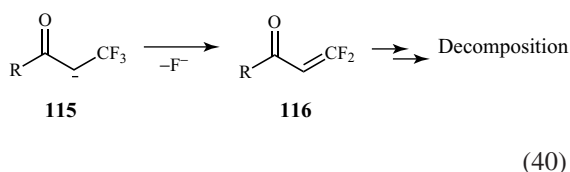
5.4 Perfluoroalkyl Halides

Perfluoroalkyl halides do not react by the S_N1 mechanism because of the low stability of perfluoroalkyl carbocations. They are precluded from undergoing S_N2 substitutions due to repulsion of the lone electron pairs of fluorine atoms to the backside attack by the nucleophile. However, R_fI are able to undergo a variety of nucleophilic substitutions by the $S_{RN}1$ mechanism. Some reactions occur in the dark and are accelerated by light, whereas others are induced electrochemically.

The reaction of the $\text{CMe}(\text{CO}_2\text{Me})_2^-$ ion with $n\text{-C}_8\text{F}_{17}\text{I}$ afforded only $n\text{-C}_8\text{F}_{17}\text{H}$ (27%).¹³⁷ These results seem to indicate that the $\text{CMe}(\text{CO}_2\text{Me})_2^-$ ion is able to transfer one electron to form radicals but is

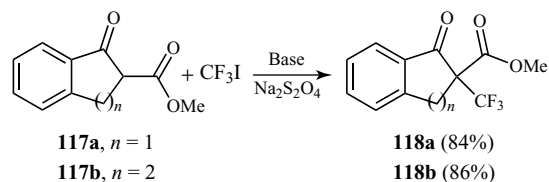
unable to couple with the R_f radical. The reaction of primary R_fI with the [−]CMe₂NO₂ ion occurs under mild conditions to give R_fCMe₂NO₂ in ~80%.¹³⁸

The CF₃ moiety in carbonyl compounds are useful synthetic intermediates. However, defluorination is problematic under the basic conditions of S_{RN}1 reaction. This difficulty has been found in the radical trifluoromethylation of enolate ions, which is the most direct way to synthesize CF₃ carbonyl compounds. It has been recognized that the highly basic conditions with enolate ions could not be applied to the trifluoromethylation. The substitution product is deprotonated to give anion **115**, which loses a F[−] ion to give an unsaturated ketone **116** that decomposes very fast (40).

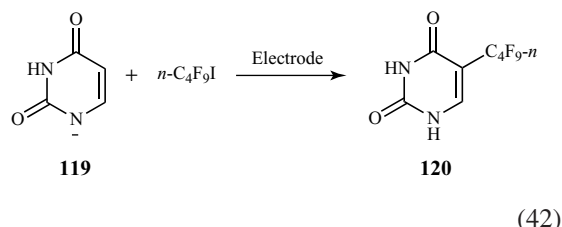


However, it has been found that the radical trifluoromethylation of the titanium ate enolate of ketone gives high yields of the products.¹³⁹ For instance, the titanium ate enolate cyclohexanone gave 81% yield of 2-(trifluoromethyl)cyclohexanone when treated with CF₃I and Et₃B to initiate the reaction. With only 1 equiv of lithium diisopropylamide (LDA) as base, it gave the same yield of the substitution product.¹⁴⁰ The radical trifluoromethylation of Ti ate and Li enolates has also been investigated by density functional theory (DFT) calculations.¹⁴¹

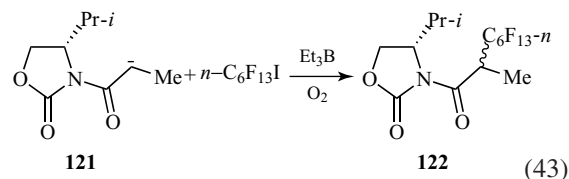
The radical trifluoromethylation of ammonium enolates derived from 1,3-dicarbonyl compounds with CF₃I in the presence of Na₂S₂O₄ to induce the reaction has been reported in MeCN–H₂O solution. The radical F₃C[•] is generated from the reduction of CF₃I with sulfur dioxide radical anion. Thus when substrates **117** were treated with a base and Na₂S₂O₄, products **118** were obtained (41).¹⁴²



The reaction of R_fI by electrochemical induction with several nitrogen nucleophiles is known to form a C–C bond with moderate yields. The reaction of uracil anion **119** with *n*-C₄F₉I, for instance, afforded the substitution product **120** in 65% yield (42).⁷³

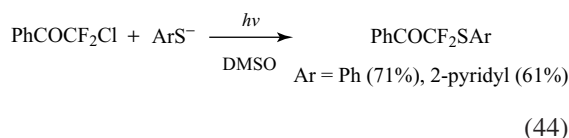


The reaction of R_fI with chiral imide enolate ions induced by Et₃B and oxygen gives substitution products with good diastereoselectivity. For example, the reaction of anion **121** with *n*-C₆F₁₃I gives the product **122** (79% yield, de 71) (43).¹⁴³



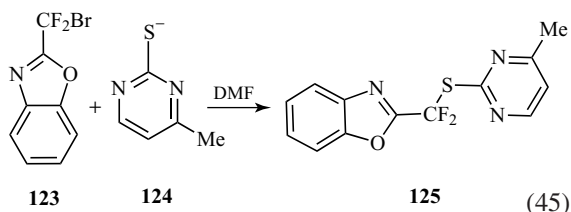
R_fI has been found to react with ArS[−] ions under irradiation.^{144,145} In this system, the ArS[−] ion containing both electron-donating groups and EWGs is readily converted into ArSR_f in good yields. With a primary or secondary R_fI, the substitution affords 60–85% yield of the product, but while using a tertiary R_f no reaction occurs.¹⁴⁶

Iodide is not the only leaving group for such processes; it is known that bromo and chloro groups can also act as leaving groups. A series of chlorodifluoromethylated ketones react with ArS[−] ions to afford new α-(heteroarylthio)-α,α-difluoroacetophenone derivatives with moderate to good yields (44).¹⁴⁷

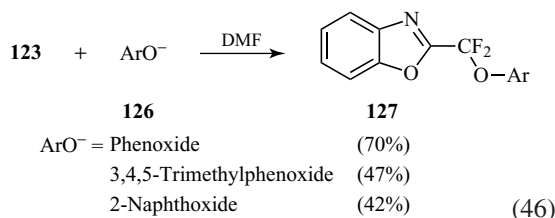


S_{RN}1 reaction of 2-(bromodifluoromethyl) benzoxazole **123** with a series of heterocyclic

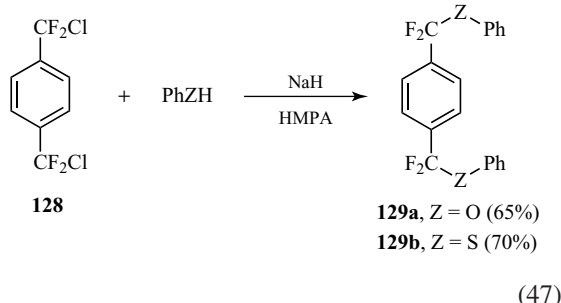
thiolate ions^{148,149} and phenolic compounds¹⁴⁹ affords substitution products in variable yields. For instance, when **123** was allowed to react with ion **124**, compound **125** was obtained in 62% yield (45).¹⁴⁸



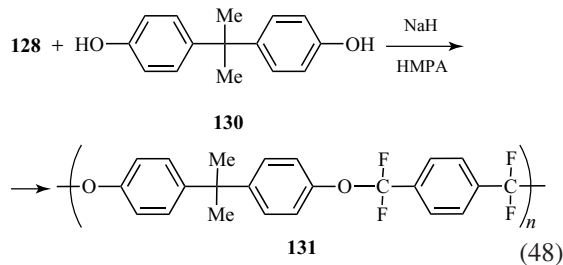
When **123** is allowed to react with ArO^- ions **126**, $\text{S}_{\text{RN}}1$ substituted products **127** are obtained from moderate to good yields (46).¹⁴⁹



Dichloride **128** reacts with PhS^- or PhO^- ions to afford the disubstitution product **129** (47).¹⁵⁰



In the reaction of bis-phenol **130** with NaH and **128**, a yellow solid is obtained in 81% yield, the structure of which is assumed to be the polymer **131** (48). The solid-state fluorine NMR spectrum indicates that it is a polymer of relatively uniform structure with a high molecular weight (36,000 g mol⁻¹).



Although this reaction occurs in the dark (70% conversion in 12 hours), under irradiation the reaction is accelerated (70% conversion in 3 hours) and inhibited by O_2 .¹⁵⁰

5.5 Alkyl Substrates with Electron-Withdrawing Groups

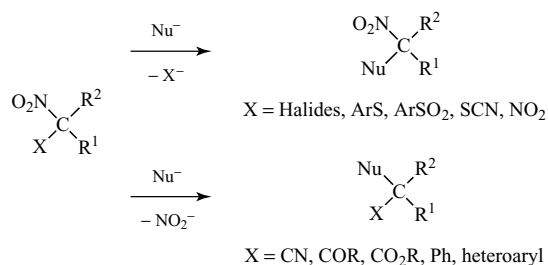
These types of compounds react through the $\text{S}_{\text{RN}}1$ mechanism with a great variety of nucleophiles centered on C, O, S, N, and P. In some cases, competition with other mechanisms, such as $\text{S}_{\text{N}}2$ or X-philic reactions, can take place, depending on the nature of the leaving group and the reaction conditions; however, it can be avoided via several approaches.⁵

5.5.1 α -Substituted Nitroalkanes and Other Activated Alkanes

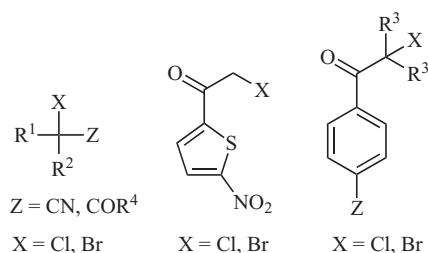
Compounds of the $\text{X-CR}^1\text{R}^2\text{NO}_2$ type are the most extensively studied with a leaving group at an sp^3 carbon. Reactions where $\text{X} = \text{halides, ArS, ArSO}_2, \text{SCN, N}_3, \text{ and NO}_2$ have been reported. The NO_2 group can act as a leaving group not only in dinitro compounds but also when X is $\text{CN, COR, CO}_2, \text{R, Ph, or heteroaryl}$ (Scheme 17).

EWGs other than NO_2 have also been reported to activate haloalkanes in the α position (Scheme 18); reaction with different nucleophiles give the product of substitution of the halogen (Cl, Br) by the $\text{S}_{\text{RN}}1$ mechanism.^{5,151} For instance, *p*-cyano- and *p*-nitro-substituted α -haloisobutyrophenones react with $^-\text{CR}_2\text{NO}_2$ ($\text{R} = \text{alkyl, cycloalkyl}$), $^-\text{CR}(\text{CO}_2\text{Et})_2$, and $^-\text{CMe}(\text{CN})_2$ to give the substituted products in good yields (39–85%).

A variety of carbon nucleophiles react with this type of substrates, as in the case of anions derived



Scheme 17 Leaving groups in α -substituted nitroalkanes. Different behavior of NO₂ group in S_{RN}1 reaction.



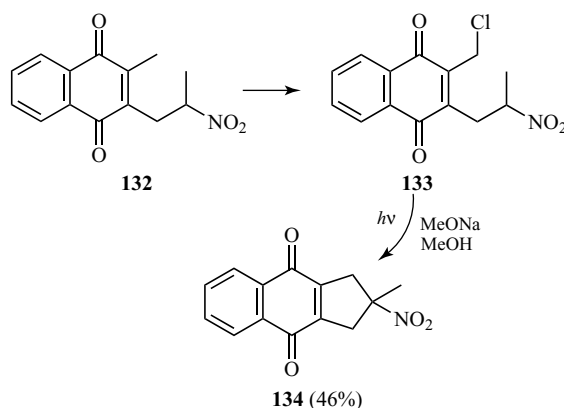
Scheme 18 α -Activated alkyl substrates with EWGs other than NO₂.

from nitroalkanes, ketones, disubstituted carbanions (β -dicarbonylic, α -cyanoesters, and α -sulfonyl esters derivatives), and those derived from substituted heterocycles.

Anions from nitroalkanes are the most widely studied, and even the synthesis of cyclic compounds by intramolecular reaction has been performed. For example, from 1,4-naphthoquinone **132** obtained by an intermolecular photostimulated S_{RN}1 reaction (85% yield), a new substrate **133** is synthesized,¹⁵² and the photostimulated reaction **133** with MeONa allows the formation of **134** by an intramolecular S_{RN}1 cyclization (Scheme 19).

The synthesis of nitro compounds by this approach have synthetic utility, such as the synthesis of tri- and tetrasubstituted olefins through the elimination of NO₂⁻ ions. For example, the S_{RN}1 photostimulated reaction of substrate **135** with 2-nitropropane anion afforded **137** from **136** (Scheme 20).¹⁵³

Within the nitrogen nucleophiles, N₃⁻ ion is the most frequently used; however, important nitrogenated nuclei have also been employed, such as anions from imidazole, triazole, purines, and cytosine, among others.⁵ The S_{RN}1 reaction of



Scheme 19 Synthesis of cyclic compounds by an S_{RN}1 reaction.

2-bromo-2-nitropropane with the anion of thymine provides an interesting example in which the disubstituted product is obtained (64% yield) without any formation of the monosubstituted product (Scheme 21).¹⁵⁴

α -Substituted nitroalkanes react with alkoxide anions to give disubstituted compounds through an S_{RN}1 coupled to an S_{RN}1-like reaction (Scheme 22).⁵

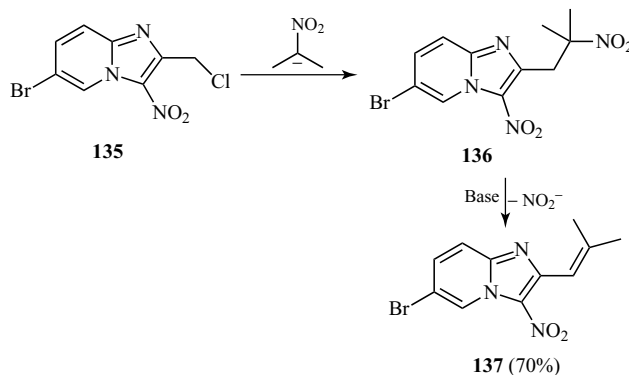
P-centered anions (⁻PO(OR)₃, ⁻PS(OR)₃) react with α -substituted nitroalkanes to give the S_{RN}1 product in moderate to good yields. However, there are some examples in which competition with X-philic mechanism can be observed.⁵

5.5.2 Activated Benzyl Derivatives

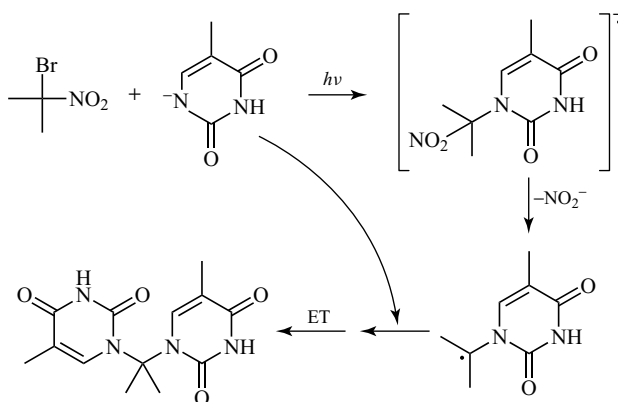
Benzylic substrates which have an EWG attached to the phenyl ring react by S_{RN}1 reactions (Scheme 23).^{5,155} Although the NO₂ group is the best and the most largely used EWG to facilitate S_{RN}1 reactions, other groups such as CN, C(=O)Ph, and CF₃ also participate in these reactions. Depending on the type of substrate and nucleophile, the S_{RN}1 reaction can be in competition with the S_N2 process.

Reactions occur with various X leaving groups, and even groups that have very low reactivity or are unreactive in polar processes (S_N2) can act as leaving groups in S_{RN}1 reactions.

Although the EWG group facilitates the reaction, it has been established that such activation of the

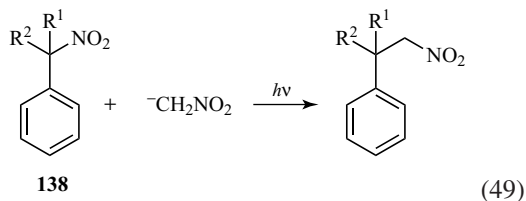


Scheme 20 $S_{RN}1$ reaction followed by base-promoted NO_2^- ion elimination.



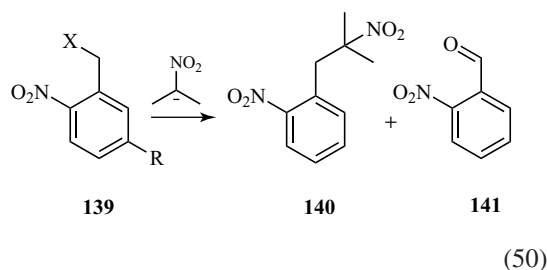
Scheme 21 Two consecutive $S_{RN}1$ reactions of 2-bromo-2-nitropropane with the anion of thymine.

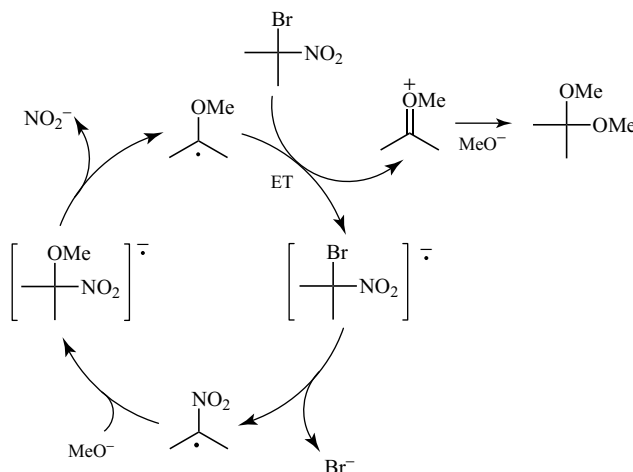
aromatic ring is not necessary for the reaction to occur. The reaction of **138** with $^-\text{CH}_2\text{NO}_2$ ions nicely illustrates this (49)¹⁵⁶; good yield of the $S_{RN}1$ product (circa 84%) was obtained despite the slower rate of the reaction resulting from the absence of an EWG in the aromatic ring.



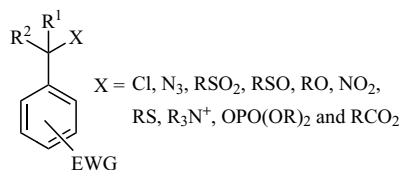
The most common is *p*-nitro substitution in such benzylic substrates; however, there are cases of substrates with ortho and meta NO_2 groups. In these two types of compounds, competition with S_N2 or other reactions are more important; yet, the

use of poor leaving groups and bulky groups in the α -carbon favors the $S_{RN}1$ route. For instance, the reaction of 2-nitropropane anion (50) with **139** ($R = \text{H}, X = \text{Cl}$) gave 32–45% yield of the $S_{RN}1$ product **140** and 52% yield of the S_N2 product **141**,⁶ and only the $S_{RN}1$ product (75% of the corresponding alkene after NO_2^- ion elimination) is found in the reaction with **139** ($R = \text{OMe}, X = \text{ArSO}_2$).¹⁵⁷





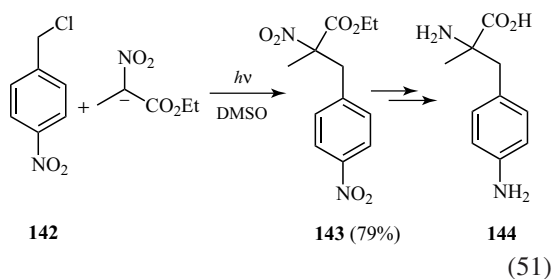
Scheme 22 S_{RN}1 coupled to an S_{RN}1-like reaction.



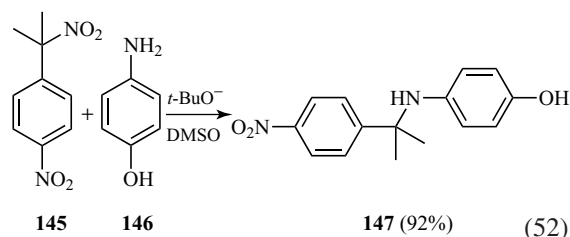
Scheme 23 Leaving groups (X) in activated benzylic substrates.

Carbanions derived from secondary and tertiary nitro compounds have been used in the reaction with *p*-nitro benzyl and cumyl derivatives to study the regiochemistry of the coupling of the radical with the nucleophile. In addition, the use of more complex nitro compounds derived from carbohydrates allows the synthesis of the corresponding alkylated nitro compounds in moderate to good yields.⁵

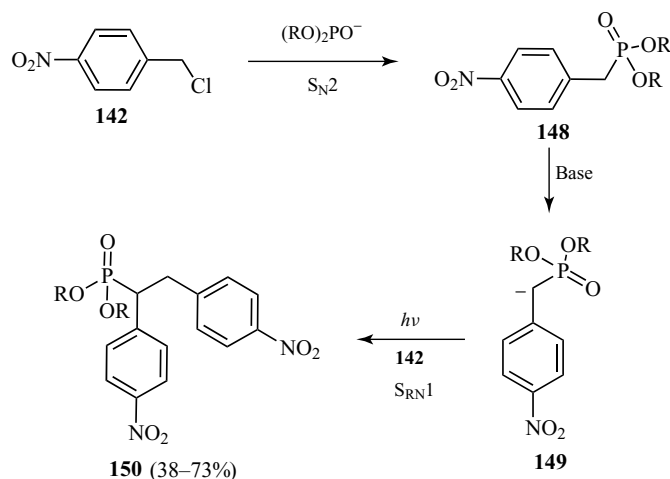
An interesting example of the scope of these reactions is the photostimulated reaction of ethyl 2-nitropropionate anion with *p*-nitrobenzyl chloride **142** to give the S_{RN}1 product **143**, which after reduction delivers the α -amino acid **144** (51).¹⁵⁸



Carbanions from β -dicarbonyls, β -dinitriles, α -cyano esters, uracil derivatives,⁵ and CN⁻ ions¹⁵⁹ have also been used in S_{RN}1 reactions with *p*-nitrobenzyl and cumyl derivatives to give the corresponding products with good yields. The nitrogen nucleophiles that react with *p*-nitro benzyl and cumyl derivatives are N₃⁻, NO₂⁻, as well as anions from imidazoles, benzimidazoles, and pyrazoles (26–100% yield). Neutral primary, secondary, and tertiary alkyl amines also react to give the products with good yields (66–96% yield). In a study of the base-promoted reaction of amine **146** with α -*p*-dinitrocumene **145**, the product of *N*-alkylation was obtained (**52**); it was concluded that the mechanism was partly S_{RN}1.¹⁶⁰



p-Nitrocumyl derivatives react with RO⁻ ions through an S_{RN}1 reaction to give the substituted products with a C–O bond formation. The reaction of MeO⁻, PhO⁻, and 1-methyl-2-naphthoxide ions with *p*-nitrocumyl derivatives allows the preparation of ethers (56–69% yield).⁵



Scheme 24 Intervening mechanisms in the formation of product **150** from **142** and $(\text{RO})_2\text{PO}^-$ anions.

Anions derived from thiols, 2-mercaptoazoles, and ArSO_2H also react with *p*-nitrobenzyl derivatives through an $\text{S}_{\text{RN}}1$ mechanism and good yields of the products are obtained (36–96% yield).^{5,159} However, with *p*-nitrobenzyl derivatives, the mechanism depends on the nucleophile used, in spite of the fact that the products obtained are the same.¹⁶¹

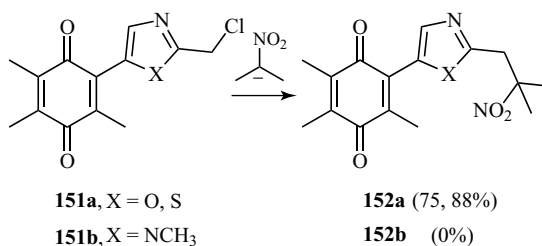
It is known that anions of phosphorus [$(\text{RO})_2\text{PO}^-$, $(\text{RO})_2\text{PS}^-$] react with *p*-nitrobenzyl halides through different mechanisms: $\text{S}_{\text{RN}}1$, $\text{S}_{\text{N}}2$, X-philic attack, and deprotonation to form benzyl anions; as a consequence, different products could be obtained depending on the conditions used. *p*-Nitrobenzyl chloride **142** reacts with $(\text{RO})_2\text{PO}^-$ ($\text{R} = n\text{-alkyl}, i\text{-propyl}, \text{Ph}$) in DMSO through the $\text{S}_{\text{N}}2$ mechanism to give the product **148**; however, an $\text{S}_{\text{RN}}1$ reaction takes place in THF or EtOH to give **148** in a photostimulated reaction.¹⁶² Carbanions **149** are formed *in situ* in the reaction described above in DMSO, and the disubstitution products are obtained in a photostimulated $\text{S}_{\text{RN}}1$ reaction (Scheme 24).¹⁶² The hindered $(t\text{-BuO})_2\text{PO}^-$ anion reacts with **142** in DMSO mainly through $\text{S}_{\text{RN}}1$, but as competition deprotonation of **142** occurs.¹⁶³

The bromide analog of **142** reacts by an X-philic mechanism to give the *p*-nitrobenzyl anion. The anions thus generated may react in some cases to di(*p*-nitrobenzyl) via an $\text{S}_{\text{RN}}1$ reaction with the substrate.¹⁶³

5.5.3 Heterocyclic Analogs of Benzyl Substrates

Various heterocyclic analogs of the benzyl derivatives react with nucleophiles through an $\text{S}_{\text{RN}}1$ reaction. Imidazoles are one of the most extensively studied and allow the preparation of new 5-nitroimidazoles and 5-nitro-1,2-fused-imidazoles bearing tri- or tetrasubstituted alkenes with good yields.^{5,164}

Methyl oxazoles and thioxazoles activated with a tetrasubstituted *p*-benzoquinone ring **151a** react by the $\text{S}_{\text{RN}}1$ mechanism to give substitution products **152a** with good yields (53). However, *N*-methylimidazole **151b** does not react under the same condition, a behavior that has been ascribed to the lack of coplanarity of the two rings due to the methyl group.¹⁶⁵

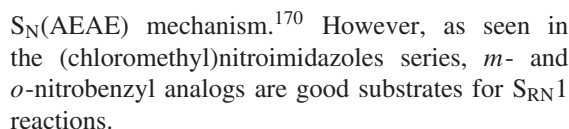


(53)

These analyses were confirmed by reaction of fused oxazoles and imidazoles that smoothly react



Competition with another mechanism can occur; for instance, 2-(halomethyl)-5-nitrofurans give substitution with $^-CMe_2NO_2$ ions by the $S_{RN}1$ pathway,¹⁶⁷ whereas they react by S_N2 with various RS^- ions.¹⁶⁸ Again, substitution at the benzylic carbon and poorer leaving groups favor the $S_{RN}1$ mechanism; the reaction of nitrofurans **153** and **154** with benzenesulfinate ions (54) clearly illustrates this.^{168,169}



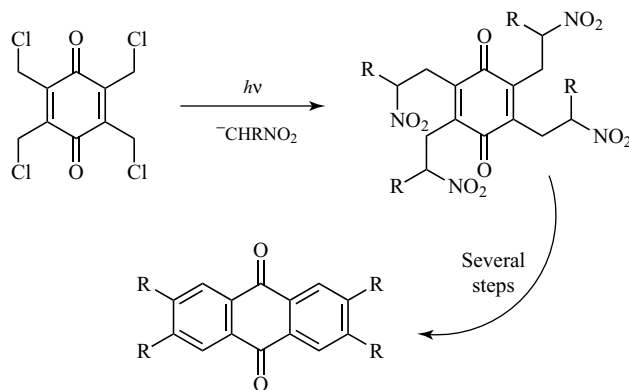
Nitroanions are the nucleophiles most extensively studied and give the corresponding olefins as the final products under classical reaction conditions (Scheme 25).^{5,153,171,172}

Carbanions from aliphatic, cyclic, heterocyclic, functionalized nitroalkanes, and 3-nitrolactams have also been used as nucleophiles.

Recently, an $S_{RN}1$ reaction promoted by microwave irradiation allowed the preparation of quinazoline derivatives starting from 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one and nitronate anion.¹⁷³ The products were obtained in yields higher than those found under classical conditions.

In addition to nitronate anions, other nucleophiles, such as carbanions from β -diesters, 4-hydroxycoumarin, PhCH_2S^- , and PhSO_2^- ions, have been used mainly in the synthesis of pyrimidinones.¹⁷⁴

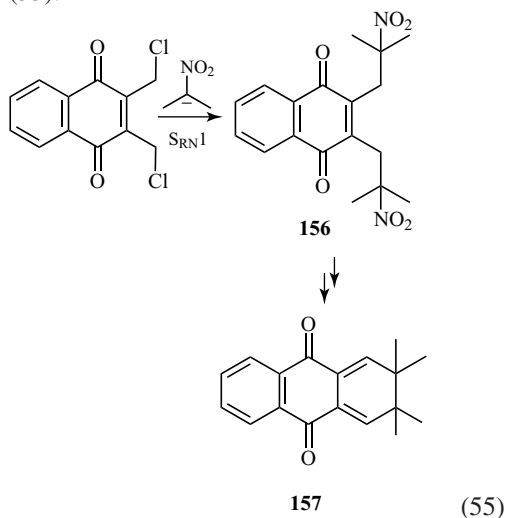
The position of the nitro group influences the competitive mechanism; for example, 5-nitro-2-(halomethyl)-thiophenes react by $S_{RN}1$; conversely, its 4-nitro analogs react by an



Scheme 26 Synthesis of 2,3,6,7-tetralkylantraquinones.

5.5.4 Other Activated Benzyl Halides

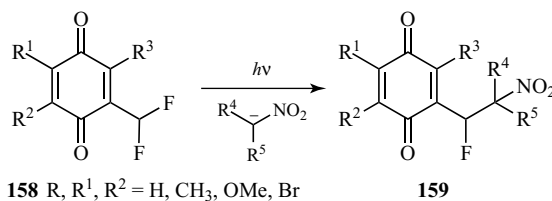
2,3-Bis(chloromethyl)-1,4-naphthoquinone reacts with the 2-nitropropane anion by the $S_{RN}1$ mechanism to give the disubstituted product **156**. After ring closure, compound **157** is obtained in good yield (55).¹⁷⁵



An interesting one-pot synthesis of dialkyl-substituted anthraquinones was conducted by this procedure using primary nitronate anions, which consists of two consecutive $S_{RN}1$ processes followed by base-promoted nitrous acid elimination, electrocyclic ring closure, and dehydrogenation. This new annulation method was also applied to synthesize dialkynaphthacene-5,12-di-ones and 1,4-naphthoquinones with acceptable yields.¹⁷⁵ The use of tetrachloride benzoquinone with nitronate

anion allows the preparation of the tetra-alkylated product after four consecutive $S_{RN}1$ reactions. The synthesis of 2,3,6,7-tetralkylantraquinones (40–46% yield) was achieved using the procedure described above (Scheme 26).

The reaction of 2-fluoromethyl-3,5,6-trimethyl-1,4-benzoquinone with the $^-CMe_2NO_2$ ion is the first example of displacement of F by $S_{RN}1$ at an sp^3 carbon.¹⁷⁶ The C-alkylation product was obtained in good yield (70%). Difluoride analogs **158** also react by the $S_{RN}1$ mechanism affording the monofluoro-product in good yields (56).¹⁷⁷ The high yield of the monosubstitution product **159** as compared to the disubstituted one can be explained on the basis of the high stability of the radical anion of the product due mainly to the nitro group.



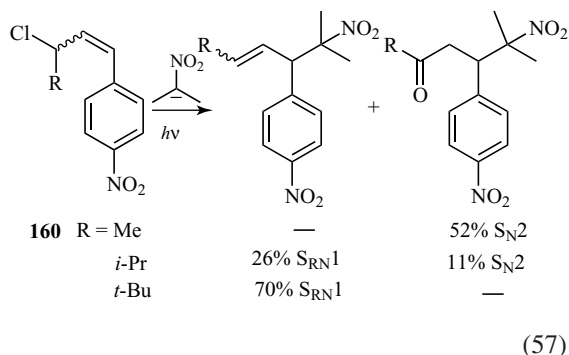
Other benzyl dihalides and analogs have been studied in the reaction with nitronate anions. For instance, *p*-nitrobenzylchloride reacts with the $^-CMe_2NO_2$ ion by an $S_{RN}1$ reaction, followed by an $E_{RC}1$ to give a mixture of products.⁵

Trichloromethyl 5-nitroimidazoles have been used to prepare derivatives bearing a tetrasubstituted double bond in moderate to good yield by reaction with nitronate anions.¹⁷⁸ As in the case

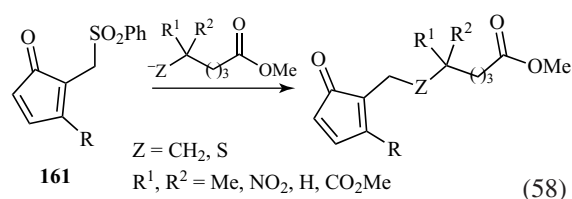
of dihaloderivatives, the reaction occurs by S_{RN}1 followed by E_{RC}1 reactions.

5.5.5 Activated Allyl Derivatives

Allyl systems substituted with *p*-nitrophenyl moiety react with different carbanions through various mechanisms: S_{RN}1, S_N2, and S_N2'. As we have already seen for other systems, the reaction outcome depends on the substrate and conditions. Thus in the series of compounds **160**, the S_{RN}1 component becomes more important for substrates bearing sterically hindered R substituents (57).^{179,180}



An interesting example of the application of these types of substrates in S_{RN}1 reaction is the synthesis of prostaglandin (PGB₁) analogs from 3-substituted-2-(phenylsulfonylmethyl) cyclopenta-2,4-dienone **161** (58).¹⁸¹



Other type of substrates studied involve α -substituted 3-cyclohexenones and mono and dichloride 5-nitroimidazoles, which react by various mechanisms in addition to S_{RN}1.⁵

6 CONCLUSION

The coupling between radicals and nucleophiles is a broad and general reaction. Reactions occur with

aryl, vinyl, and aliphatic radicals without EWGs (cycloalkyl, bridgehead, and neopentyl radicals), as well as perfluoroalkyl and alkyl radicals with EWGs at the α carbon. With the exception of substrates with EWGs in the α carbon, these radicals are derived from substrates that do not react or react slowly by polar mechanisms. We propose that any other substrates with the same reduced reactivity toward nucleophiles would also react by the S_{RN}1 mechanism.

The nucleophiles able to react with these radicals are carbanions and those with heteroatoms such as derivatives of Sn and elements from the 15 (N, P, As, and Sb) and 16 (O, S, Se, and Te) groups.

The monosubstitution product is not the only possible product to obtain, di-, tri-, and even tetrasubstitution with substrates bearing more than one leaving group is also viable.

One of the most widely studied approaches to ring-closure reactions is the S_{RN}1 substitution of aromatic compounds that have an appropriate substituent Z ortho to the leaving group, which can react with a nucleophile Nu to afford the substitution product. The ring-closure product is achieved by the spontaneous reaction between the Nu group and Z.

In an adequate distance with an appropriate combination of leaving groups and nucleophilic centers in the same molecule, the intramolecular synthesis of heterocycles can be achieved. The radical intermediates can also be trapped by an appropriate double bond, and the resulting radical intermediates can react with a nucleophile to give substituted heterocycles.

All these mechanistic possibilities open a wide area in physicochemical and synthetic organic chemistry.

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Halogen and Chalcogen Transfer Chemistry

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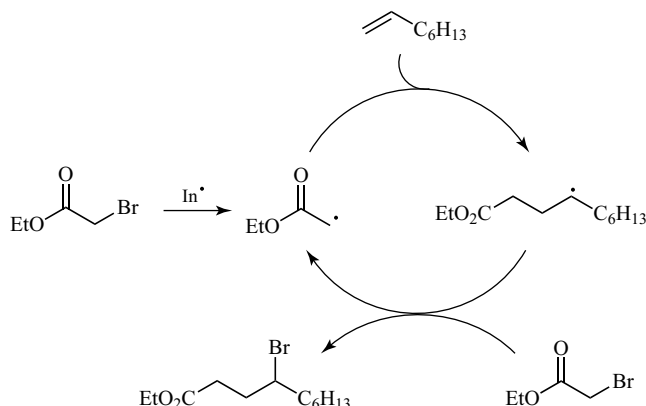
1 INTRODUCTION

Atom transfer reactions have emerged as one of the most important tools in the field of free-radical chemistry. The discovery of atom transfer reactions can be traced back to the year 1945 when Kharasch *et al.* reported the addition of CCl_4 to 1-octene in the presence of a catalytic amount of radical initiators.¹ A few years later, the Kharasch group showed that, with diacetyl peroxide as the initiator, ethyl bromoacetate was added to 1-octene to give the bromine atom transfer product ethyl 4-bromodecanoate upon thermolysis.² As a result, atom transfer radical addition (ATRA) is also called *Kharasch addition*. These studies did not receive much attention until the mid-1980s when Curran *et al.* first demonstrated the atom transfer radical cyclization (ATRC) reactions³ and their application in the synthesis of ($\pm$)-hirsutene.⁴ These works significantly encouraged further study in this type of transformations and enormous progress has been achieved ever since. Reactions involving transfer of halogens (I, Br, Cl) and chalcogens (SePh and TeAr) have been developed.⁵ This concept has been extended to atom transfer radical polymerization (ATRP), which has become an area of intensive research in recent years (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). In a broader sense, atom transfer reactions encompass radical

addition reactions in which carbon–heteroatom or heteroatom–heteroatom bonds add across $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, or other multiply bonded functionalities. In this article, we focus on the halogen and chalcogen transfer reactions involving carbon–carbon bond formation. The xanthate transfer chemistry is not included, which is discussed in other articles of this encyclopedia (see **Xanthates and Related Derivatives as Radical Precursors and Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).

2 MECHANISTIC CONSIDERATION

The mechanism shown in Scheme 1, originally proposed by Kharasch *et al.*,² represents the generally accepted mechanism for most atom transfer addition reactions. Once the substrate radical is initiated, it adds to 1-octene to give the adduct radical. The adduct radical abstracts the bromine atom of the substrate (ethyl bromoacetate) to give the ATRA product and another substrate radical, which then enters into the next circle. The overall reaction generates a new $\text{C}-\text{C}$ σ bond at the expense of the breakage of a $\text{C}-\text{C}$ π bond, providing the driving force for the chain process. All the atoms in the starting bromide and alkene are present in the product molecule,



Scheme 1 The typical mechanism for atom transfer radical addition.

making the transformation highly atom-economic in nature.

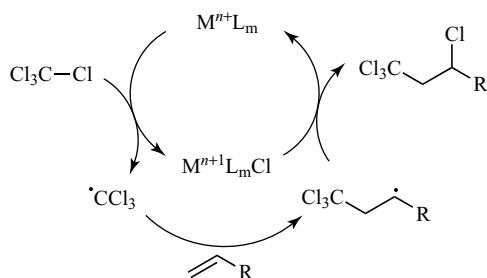
To have a successful atom transfer reaction, the following criteria should be satisfied. First, the carbon–heteroatom bond in the substrate should be relatively weak in order to facilitate initiation. Initiation can occur either thermally in the presence of a suitable initiator or under direct ultraviolet (UV) photolysis, depending on the substrate structures (see **Overview of Radical Initiation**). The most commonly used initiation system is the use of $(\text{Bu}_3\text{Sn})_2$ under sunlamp irradiation.³ While the tributyltin radical might be involved in the initiation step, the more critical role of $(\text{Bu}_3\text{Sn})_2$ is probably to scavenge radical chain suppressants such as I_2 .⁶ Another widely used initiator is BET_3/O_2 , the active species being the ethyl radical.⁷ Other initiators include diazo compounds such as 2,2'-azobis(2-methylpropionitrile) (AIBN), peroxides such as benzoyl peroxide (BPO), and even arenediazonium salts/ TiCl_3 .⁸

The second and also the most important requirement is that the adduct radical should abstract a heteroatom from the substrate (to give atom transfer product) much faster than its addition to an olefin (to give telomers). Indeed, the atom transfer step is quite fast in most successful ATRA reactions. A clear understanding on the rates of heteroatom abstraction of various alkyl radicals is thus essential in the design of ATRA reactions. An extensive list of rate constants for homolytic substitution reactions by alkyl radicals on a variety of alkyl halides and chalcogenides is now available in the literature.⁹ A typical set of rate constants is as follows. The rate constants for the halogen atom or aryl chalcogen

(X) transfer from $\text{XCH}_2\text{CO}_2\text{Et}$ to a primary alkyl radical in benzene at 50°C have been measured by Curran *et al.* to be about 7×10^4 (for Br), 1×10^5 (for PhSe), 2.3×10^7 (for PhTe), and 2.6×10^7 (for I) $\text{M}^{-1} \text{s}^{-1}$.¹⁰ These data reflect the general reactivity pattern in atom transfer reactions. On the other hand, the corresponding Cl atom or PhS group transfer occurs at a much slower rate^{10,11} and their use in ATRA reactions via the mechanism shown in Scheme 1 is not commonly observed.

Finally, the carbon–heteroatom bond formed in the product should be stronger than that broken in the reactant. This allows the chain-propagating steps to proceed as planned by selectively abstracting the heteroatoms from the substrate rather than from the product. As a result, the atom transfer product remains relatively stable under the reaction conditions. This difference in bond dissociation energy also provides an additional driving force for the atom transfer reactions.

Compared to the reductive radical addition processes typically mediated by tin hydride, the nonreductive ATRA is advantageous in that reactions involving slow olefin addition steps can proceed. The addition of substrate radical to a $\text{C}=\text{C}$ bond has only to be faster than radical–radical or radical–solvent reactions, and this can be easily met when the reactions are carried out in inert solvents such as benzene or dichloromethane. On the other hand, reductive radical addition reactions always suffer from the direct reduction of substrate radicals because of their fast H abstraction from tin hydride, especially when the radical addition is slow (see **Tin Hydrides and Functional Group Transformations**).



Scheme 2 The mechanism for transition metal-catalyzed chlorine atom transfer radical addition.

The radical addition step in atom transfer reactions is governed by the combination of steric and electronic effects as usual.¹² While nucleophilic alkyl radicals pair with electron-deficient alkene acceptors,¹³ electrophilic radicals such as malonyl radicals pair with electron-rich alkene acceptors in radical addition reactions. The latter case is more common in atom transfer reactions because the C–X bonds become weaker with one or more electron-withdrawing substituents. Steric factors may sometimes predominate in controlling the radical reactions. For example, malonyl radicals add faster to 1-octene than to the more electron-rich tetramethylethylene.¹⁴

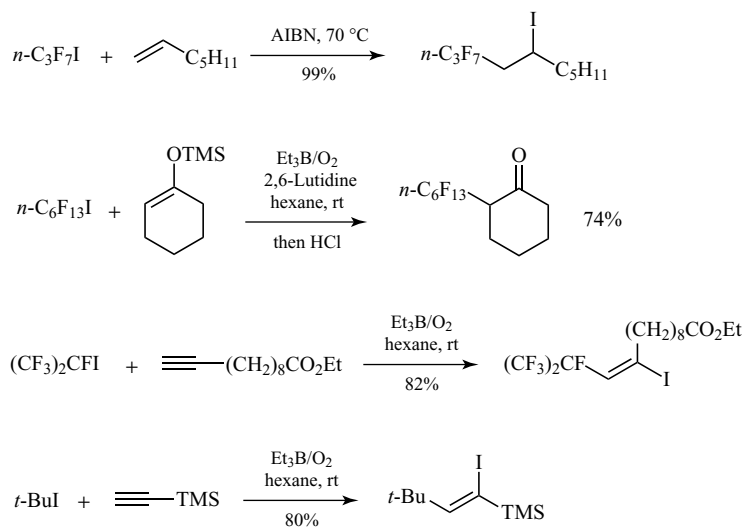
While chlorine atom transfer is rare in the above ATRA processes, it can be successfully implemented with the help of a suitable transition metal catalyst.¹⁵ This process, however, takes place via a different mechanism, as shown in Scheme 2. The catalytic circle starts with the homolytic cleavage of an alkyl chloride by a transition metal complex in the lower oxidation state ($M^{n+}L_m$) to generate an alkyl radical and the corresponding metal chloride in the higher oxidation state ($M^{n+1}L_mCl$, see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). The radical adds to an alkene to give the adduct radical, which is then trapped by the transition metal chloride in the higher oxidation state, which is a much more effective chlorine atom transfer agent than the substrate alkyl chloride, to afford the ATRA product. In the meantime, the transition metal complex in the lower oxidation state is regenerated and therefore enters into the next catalytic circle. Similar to the atom transfer process depicted in Scheme 1, this transition-metal-catalyzed process requires that (i)

the adduct radical is quenched by $M^{n+1}L_mCl$ at a much faster rate than its addition to another molecule of alkene and (ii) further activation of the product chloride should be avoided. The difference between the conventional ATRA and the transition-metal-catalyzed one is that the transition metal catalyst functions as both the radical initiator and the mediator for chlorine atom transfer in the latter case. A number of transition metals such as Cu,¹⁶ Fe,¹⁷ Ru,¹⁸ and Mn¹⁹ have been developed for these transformations.

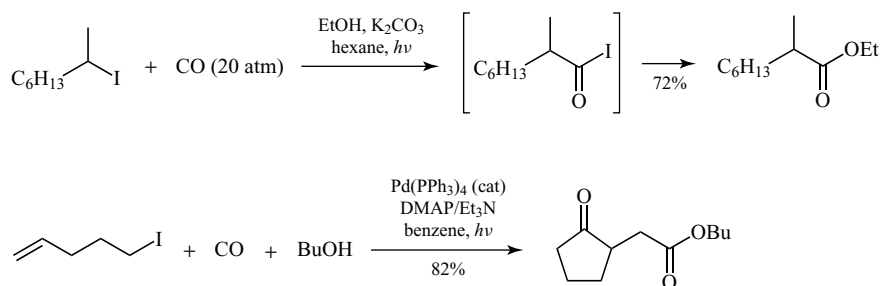
3 IODINE ATOM TRANSFER

Iodine atom transfer reactions are the most commonly studied type of reactions because of their easy initiation, the fast rate of iodine atom transfer, and the ready availability of alkyl iodides.

The first example of iodine ATRA reactions is the addition of perfluoroalkyl iodides to alkenes.²⁰ With the initiation of AIBN, perfluoroalkyl iodides add across monosubstituted alkenes in excellent yields, as shown in Scheme 3. The reactions can also be performed in hexane with Et_3B as the initiator, and allow the use of 1,2-disubstituted alkenes as the radical acceptor.²¹ In the presence of a base such as 2,6-lutidine, the reactions of perfluoroalkyl iodides with silyl enol ethers followed by treatment with aqueous HCl afford α -perfluoroalkyl ketones in good yields (Scheme 3).²² In contrast, ordinary alkyl iodides are not suitable for the ATRA reactions with alkenes. However, both ordinary alkyl iodides and perfluoroalkyl iodides can participate in the ATRA reactions with alkynes. Treatment of perfluoroalkyl iodides with terminal or internal acetylenes bearing a variety of substituents in the presence of a catalytic amount of Et_3B provides the corresponding perfluoroalkyl-substituted alkenes in high yields with an excellent *E*-stereoselectivity (Scheme 3).²¹ In a similar manner, secondary or tertiary alkyl iodides also undergo ATRA reactions with terminal acetylenes to give the corresponding alkenyl iodides in good yields with variable stereoselectivities, depending on the substrate structures.⁷ Exclusive *Z*-alkenes can be achieved in the cases of trimethylsilylacetylene, which may be attributed to the isomerisation of *E*-isomer to *Z*-isomer under the reaction conditions (Scheme 3).



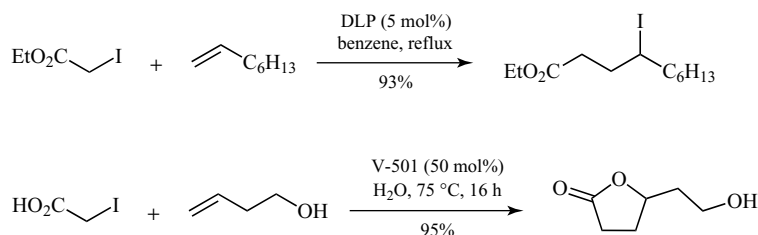
Scheme 3 Iodine ATRA reactions of perfluoroalkyl and alkyl iodides.



Scheme 4 Iodine ATRA reactions of alkyl iodides with CO.

In addition to alkenes and alkynes, carbon monoxide can also be employed as radical acceptor in the ATRA reactions with alkyl iodides.²³ Ryu have shown that the photoinduced reactions of RI, CO, and alcohols or amines provide the corresponding aliphatic carboxylic acid esters or amides (Scheme 4).²⁴ The atom transfer carbonylation proceeds efficiently with secondary and tertiary alkyl iodides, whereas a longer time of reaction is required for primary alkyl iodides. These processes can be effectively accelerated by photosensitizers²⁵ or by transition metal complexes such as $\text{Pd}(\text{PPh}_3)_4$.²⁶ As an example, the $\text{Pd}(\text{PPh}_3)_4$ -catalyzed irradiation of pent-4-enyl iodide with CO and butanol affords butyl 2-(2-oxocyclopentyl)acetate in 82% yield via the carbonylation–cyclization–carbonylation sequence (Scheme 4).

A large number of iodine atom transfer reactions involve the use of alkyl iodides with one or more adjacent carbonyl or nitrile substituents. The electron-withdrawing α -substituent lowers the C–I bond dissociation energies in the substrates, thereby facilitating the radical initiation and allowing the atom transfer step to be exothermic. Two typical examples of intermolecular iodine atom transfer addition to alkenes are listed in Scheme 5. With 5 mol% of dilauroyl peroxide (DLP) as the initiator, the reaction of ethyl iodoacetate with 1-octene in refluxing benzene affords the desired ATRA product in 93% yield.²⁷ A variety of substituted α -iodo esters, amides, nitriles, and sulfones can be utilized in these ATRA reactions. The alkenes are typically limited to mono- and disubstituted electron-rich alkenes. A number of functional groups such as –OH, OAc, and so on, can be well tolerated under



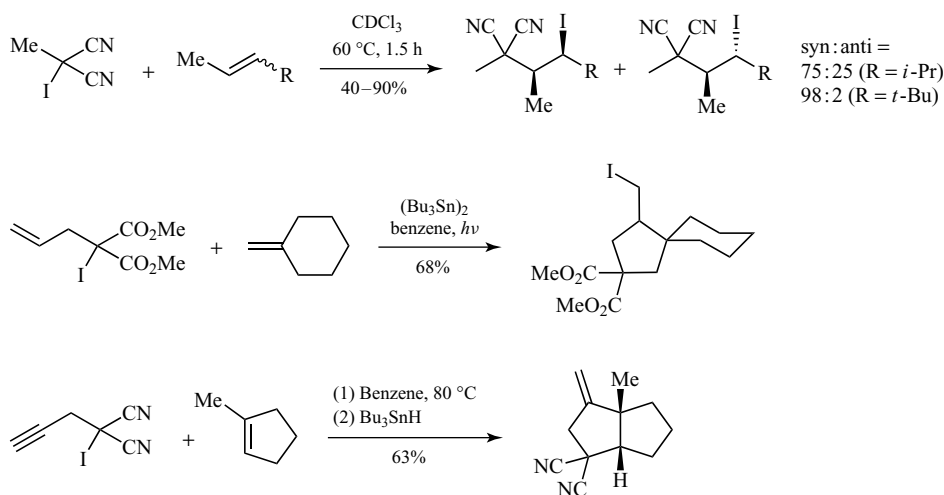
Scheme 5 Iodine ATRA reactions of alkyl iodides to alkenes.

the experimental conditions. $\text{Et}_3\text{B}/\text{O}_2$ can also be employed as the initiator.²⁸ These reactions can also be successfully carried out either in aqueous media with $p\text{-MeOC}_6\text{H}_4\text{N}^+\text{BF}_4^-/\text{TiCl}_3$ as the initiator⁸ or neat in the presence of copper powder.²⁹ The reactions of iodoacetic acid or iodoacetamide with alkenols in water under the initiation of water-soluble 4,4'-azobis(4-cyanopentanoic acid) (V-501) afford the corresponding γ -lactones in high yields (Scheme 5).³⁰ Similarly, reactions of iodine atom transfer addition to alkynes can be successfully implemented in high efficiency.^{31,32}

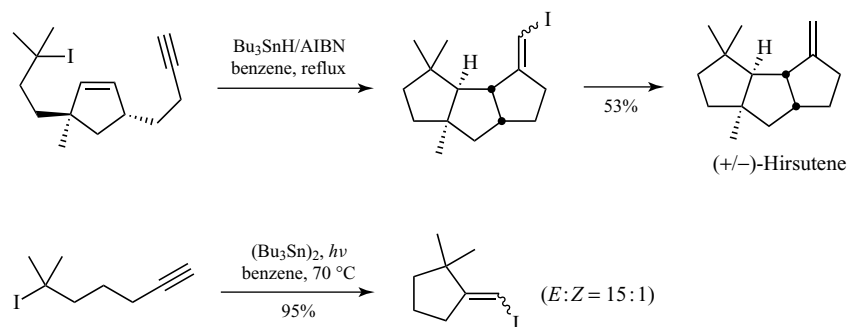
Iodomalonates or malononitriles are particularly reactive in ATRA reactions because of their weak C–I bonds and the high electrophilicity of the substrate radicals. They undergo efficient ATRA reactions with mono- or disubstituted alkenes via simple heating in the dark or in the presence of catalytic $(\text{Bu}_3\text{Sn})_2$ under sunlamp irradiation.^{33,34} The addition of methyliodomalononitrile to

dialkyl-substituted alkenes can be diastereoselective in some cases, depending on the size of the alkyl substituents, as shown in Scheme 6.³⁴ When allyl- or propargyliodomalonates are used, annulated products are formed.³⁵ The more reactive iodomalononitriles also add to trisubstituted alkenes upon heating in benzene. Further treatment with tin hydride affords the corresponding reduction products in good yields (Scheme 6).

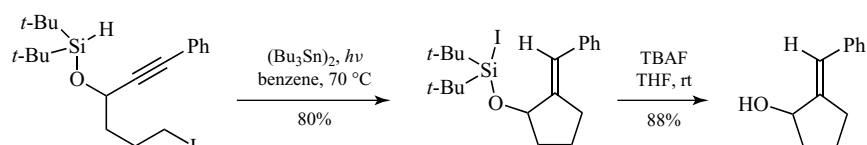
Perhaps the most exciting characteristic of atom transfer reactions is atom transfer cyclization. Curran's pioneering work in this area has not only demonstrated the potential of atom transfer cyclization in organic synthesis but also paved the ground for further research in ATRC reactions. One famous example is the synthesis of ($\pm$)-hirsutene shown in Scheme 7.⁴ The reaction can be extended to the 5-exo cyclization of alkenyl or alkynyl iodides.^{3,7,36,37} Good to excellent *E*-stereoselectivity is observed in the ATRC



Scheme 6 Addition and annulation reactions of malonates and malononitriles.



Scheme 7 Iodine ATRC of alkyl iodides.



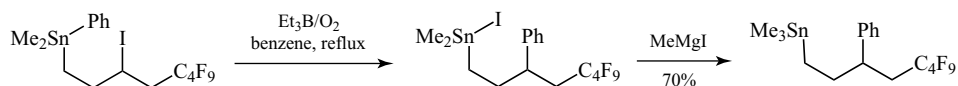
Scheme 8 Unimolecular chain transfer reactions of silicon hydrides.

reactions of alkyl iodides with terminal alkynes. For internal alkynes, the stereochemical outcome depends heavily on the alkyne substituents. Increasing the size of the substituent decreases the *E*-selectivity. When the starting alkynyl iodides are (prop-2-ynyl)silanes, the vinyl radicals generated via the initial 5-exo cyclization are quenched by intramolecular 1,5-hydrogen abstraction to afford the *E*-alkenes exclusively (Scheme 8).³⁸ These unimolecular chain transfer (UMCT) reactions³⁹ are advantageous over the analogous bimolecular chain reactions with Bu_3SnH in the control of stereoselectivity.

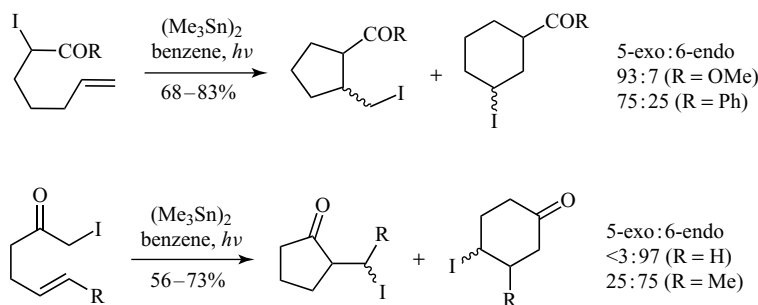
Alkyl iodides also undergo ATRC reactions with aromatic rings. An interesting example is the intramolecular aryl migration from tin to carbon via atom transfer cyclization reported by Oshima *et al.* (Scheme 9).⁴⁰ Upon initiation with Et_3B , the alkyl radical adds to the aromatic ipso-carbon in a 5-exo-like mode to give the cyclohexadienyl radical, which then undergoes $\text{Sn}-\text{C}$ bond cleavage to afford the stannyl radical. The stannyl radical then abstracts an iodine atom from another substrate

molecule to provide the stannyl iodide as the ATRC product in a high yield.

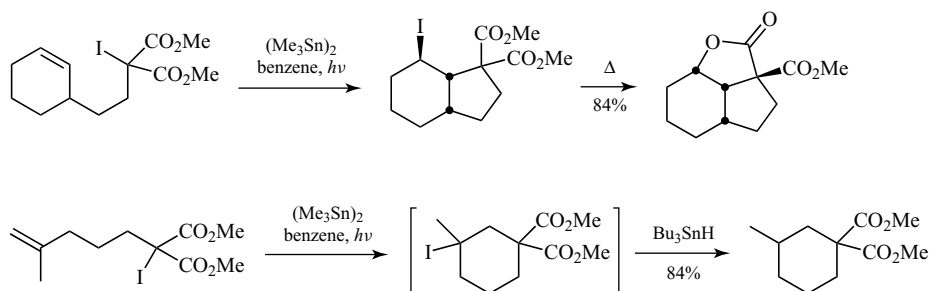
The atom transfer cyclization of α -carbonyl radicals has received considerable attention in the past two decades because of their versatility in the synthesis of functionalized carbo- and heterocycles of various sizes. A simple model is hex-5-enyl iodide bearing a 1-ester or carbonyl substituent (Scheme 10).^{41,42} The radical cyclization is kinetically controlled and irreversible.⁴¹ The α -ester radicals cyclize predominantly via the 5-exo mode. The regioselectivity is lowered when the α -ester radical is switched to an α -keto radical. Moreover, the endo mode becomes significantly preferred in the cyclization of α -keto radicals in which the carbonyl group is oriented inside the forming ring. For example, the reaction of 1-iodohex-5-en-2-one affords exclusively the 6-endo cyclization product (Scheme 10). Substituent effects also play a key role in controlling the regioselectivity of cyclization. For example, the malonyl radical adds to the cyclohexene moiety via the 5-exo mode, as shown in Scheme 11.⁴¹ On the other hand, the cyclization of



Scheme 9 Intramolecular aryl migration from tin to carbon.



Scheme 10 ATRC reactions of α -iodoesters and ketones.



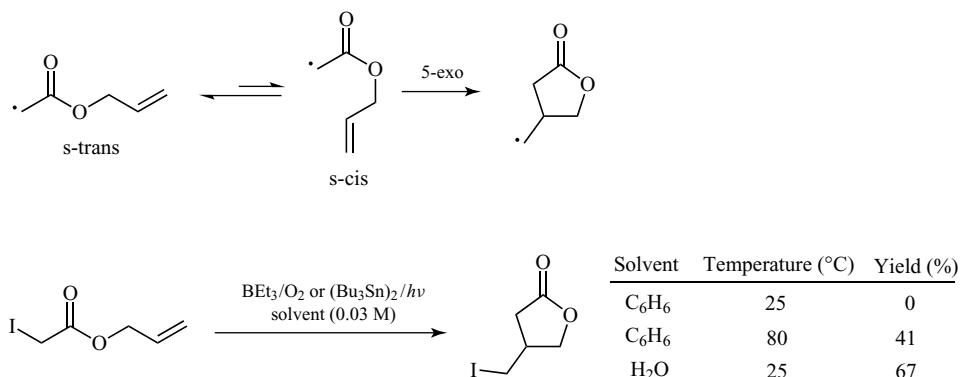
Scheme 11 Substituent effects in 5-exo versus 6-endo cyclization of malonyl radicals.

2-(4-methylpent-4-enyl)malonate proceeds via the 6-endo mode only (Scheme 11). As an extension, similar results can be obtained in the analogous 6-exo versus 7-endo cyclization reactions.⁴¹ It is worth mentioning that the stereoselectivity is typically poor in these cyclization reactions (Scheme 10). Nevertheless, stereoselective cyclization can be achieved in some cases, depending on the substrate structures.

Iodine atom transfer cyclization of α -ester or α -carbamoyl radicals also provides unique access to lactones or lactams of various sizes. *N,N*-Diallyliodoacetamide undergoes efficient ATRC at room temperature to afford the corresponding 5-exo cyclization product in almost quantitative yield.^{43,44} However, the sunlamp irradiation of allyl iodoacetate in the presence of catalytic $(\text{Bu}_3\text{Sn})_2$ at room temperature fails to give any expected cyclization product (Scheme 12).⁴³ These different behaviors should be attributed to the preferred *s*-trans conformations of esters and amides, whereas the 5-exo cyclization requires the *s*-cis conformation of the substrate radical. The energy barriers for the interconversion between *s*-trans and *s*-cis conformations are relatively high

for typical esters ($\sim 13 \text{ kcal mol}^{-1}$)⁴⁵ and amides ($16\text{--}22 \text{ kcal mol}^{-1}$).⁴⁶ The efficient cyclization of *N,N*-diallyliodoacetamide is due to the fact that the two rotamers are identical, and one of the allyl groups is always properly oriented for cyclization. On the other hand, the radical derived from allyl iodoacetate at room temperature is exclusively in the *s*-trans conformation and its lifetime is probably too short to surmount the barrier for ester bond rotation to the *s*-cis conformation. As a result, radical oligomerization rather than cyclization occurs.⁴⁷

In order to achieve efficient cyclization, several methods have been developed. Curran and Tamine have demonstrated that, by increasing the reaction temperature from room temperature to 80°C , the yield of the 5-exo cyclization product of allyl iodoacetate is increased from 0 to 41% (Scheme 12).⁴³ It is obvious that the ester bond rotation speeds up at higher temperature, allowing the substrate radical to adopt the *s*-cis conformation within its lifetime. The 5-exo cyclization then rapidly follows. In a similar manner, the ATRC reaction of *N*-allyl-*N*-methyliodoacetamide affords the 5-exo cyclization product in 87% yield at 80°C ,



Scheme 12 5-exo Cyclization of allyl iodoacetate.

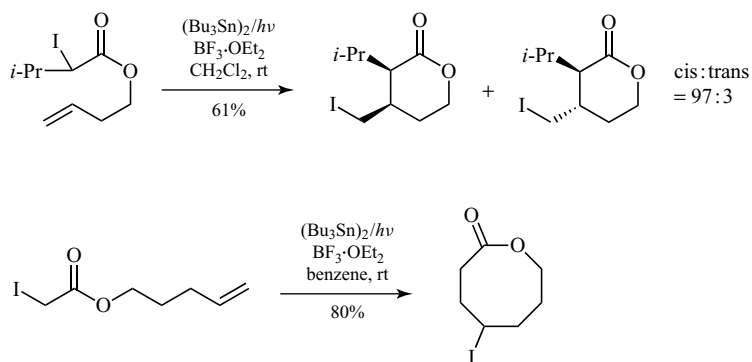
while only 39% yield is obtained at room temperature. An alternative method for the cyclization of α -carbamoyl radicals is to attach a bulky group such as the *tert*-butyl group to the amide nitrogen, thus locking the substrates in the conformations prone to cyclization.

Substrate concentrations are also an important factor. Barth and O-Yang have shown that, when the concentration of allyl iodoacetate is decreased from 0.5 to 0.008 M, the yield of the 5-exo cyclized product can be improved from 11 to 64%.⁴⁷ Apparently, the lower concentration suppresses the intermolecular addition, while the intramolecular addition is not affected much by the change of concentration.

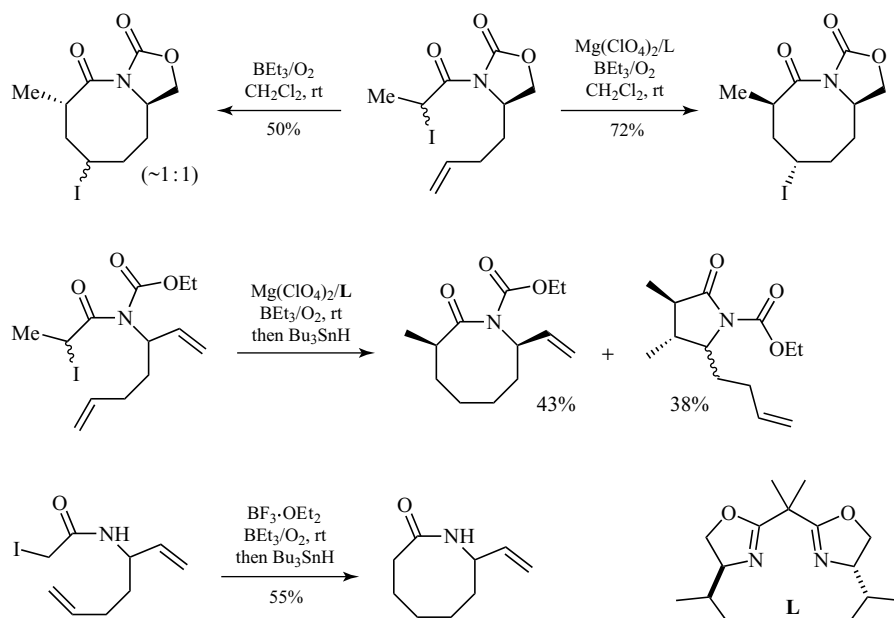
Solvents also play an important role in ATRC reactions of α -ester radicals. Oshima *et al.* have demonstrated that, when the Et₃B-induced ATRC reaction of allyl iodoacetate is performed in water at room temperature, the cyclized product is achieved in 67% yield (Scheme 12).⁴⁸ This is in sharp

contrast to the reaction in benzene at room temperature (0% yield of cyclization product). Further *ab initio* calculations have revealed that the large dielectric constant of water reduces the barrier to ester bond rotation to make rotation easier than in benzene. In the meantime, the activation energy for 5-exo cyclization is also lower in water than in benzene. Thus, radical cyclization becomes efficient in water even at room temperature.

In addition to the above temperature, concentration, and solvent effects, Lewis acids also play a vital role in the cyclization of α -ester or α -carbamoyl radicals.⁴⁹ α -Carbonyl radicals are ambiphilic in character.⁵⁰ The coordination of α -carbonyl radicals to Lewis acids significantly increases their electrophilicity, making their rates of addition to unactivated alkenes higher. In the meantime, the coordination of Lewis acids may help in directing the substrates to adopt the conformations required for cyclization. In addition, the coordination of Lewis acids to carbonyls makes



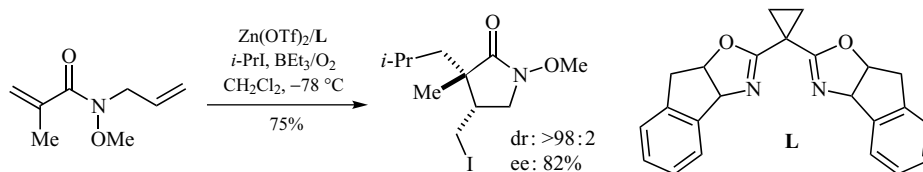
Scheme 13 Lewis acid-promoted cyclization of α -ester radicals.



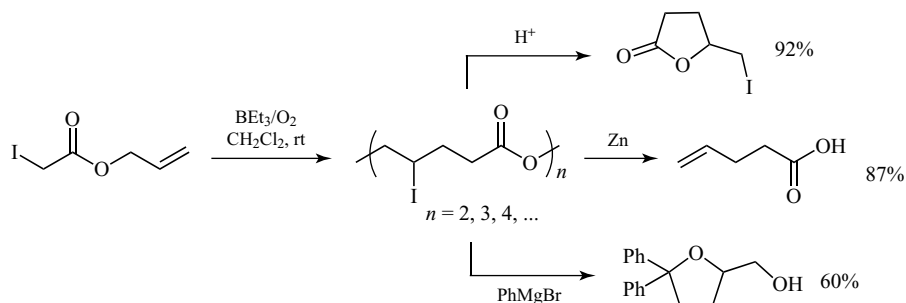
Scheme 14 Lewis acid-promoted cyclization of α -carbamoyl radicals.

the initiation of α -carbonyl radicals much easier by lowering the C–I bond dissociation energies. For example, the sunlamp irradiation of but-3-en-1-yl 2-iodoalkanoates with catalytic $(\text{Bu}_3\text{Sn})_2$ at room temperature offers no desired 6-exo cyclization product. However, with the presence of excess $\text{BF}_3 \cdot \text{OEt}_2$, the reactions proceed smoothly at room temperature to give the cyclized products in good yields (Scheme 13).⁵¹ Good to excellent stereoselectivities in favor of the cis isomers are observed. *Ab initio* calculations at the UB3LYP/6-31G* level on the cyclization reveal that the reactions are kinetically controlled and the transition states for the 6-exo cyclization are in boat conformations. Moreover, the cis-oriented transition states are of lower energy than the corresponding trans-oriented ones, resulting in the unique cis-stereoselectivity in the tetrahydropyran-2-one products. The effect of $\text{BF}_3 \cdot \text{OEt}_2$ can also be found in the 8-endo ATRC reactions of 4-pentenyl iodoacetates. The cyclization proceeds regioselectively at room temperature with the promotion of $\text{BF}_3 \cdot \text{OEt}_2$ to afford the expected 5-iodooxocan-2-ones in high yields.⁵² This ATRC method is advantageous over the reductive cyclization method with Bu_3SnH in that a significant amount of the uncyclized reduction products is always observed in the latter case.⁵³

The Lewis acid effect is even more crucial in promoting the cyclization of α -carbamoyl radicals.^{54,55} As shown in Scheme 14, the $\text{Et}_3\text{B}/\text{O}_2$ -initiated reaction of *N*-acyloxazolidinone substrate at room temperature gives the corresponding 8-endo ATRC product azocan-2-ones in 50% yield as a mixture of two stereoisomers, both having the 3,8-trans configuration. On the other hand, with the presence of $\text{Mg}(\text{ClO}_4)_2$ (150 mol%) and the bis(oxazoline) ligand **L** (150 mol%), the reaction proceeds at room temperature to afford exclusively the third isomer with 3,8-cis configuration in 72% yield.⁵⁵ The addition of the Lewis acid not only improves the yield of the cyclized product but also changes the stereoselectivity of cyclization. In addition, the I abstraction step also becomes stereoselective. Further density functional calculations at the UB3LYP/6-31G* level indicate that the 8-endo cyclization proceeds via the s-trans conformational transition states in the absence of a Lewis acid. On the other hand, with the Lewis acid able to form chelation with the substrate, cyclization takes place via the fixed s-cis conformational transition states. In both cases, 8-endo cyclization is fundamentally preferred over the corresponding 7-exo cyclization. Moreover, the chelation of Lewis acid to the substrate significantly decreases the activation



Scheme 15 Enantioselective iodine transfer radical cyclization.



Scheme 16 Oligomerization of allyl iodoacetate followed by deoligomerization.

energy of cyclization from ~ 14 to ~ 7 kcal mol $^{-1}$, resulting in the higher efficiency of cyclization. In the meantime, the more rigid structure by complexation also makes the I abstraction stereoselective. The Lewis acid effect also allows the direct competition between 5-exo and 8-endo cyclizations of α -carbamoyl radicals via fixed s-trans- or s-cis conformations. The results shown in Scheme 14 indicate that 8-endo cyclization is quite competitive to the common 5-exo cyclization for α -carbamoyl radicals even when the substrate conformations are fixed as s-cis. On the other hand, when the substrate conformations are fixed as s-trans, as in the case of *N*-(hepta-1,6-dien-3-yl)-2-iodoacetamide, only 8-endo cyclization occurs (Scheme 14).^{54–56}

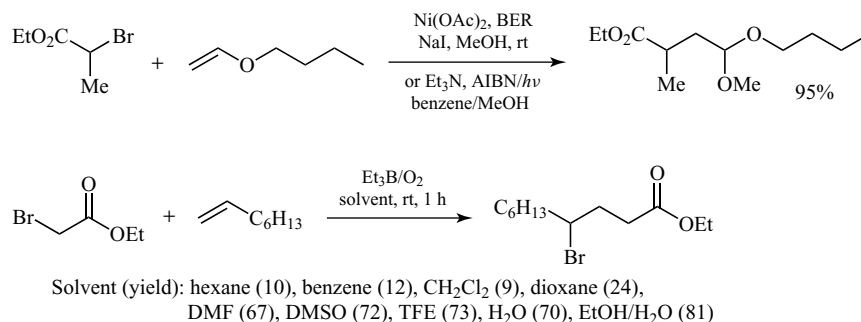
The introduction of a Lewis acid and a chiral ligand makes possible the enantioselective radical cyclization reactions (see **Stereoselective Radical Reactions**). An elegant example reported by Miyabe and coworkers is illustrated in Scheme 15.⁵⁷ In the presence of stoichiometric amounts of Zn(OTf)₂ and a bis(oxazoline) ligand, the Et₃B-initiated reaction of *N*-allyl-*N*-methoxymethacrylamide with excess isopropyl iodide at -78 °C provides the cyclized product in 75% yield with an 82% ee.

While most efforts in iodine ATRC reactions have been devoted to the inhibition of the competing intermolecular radical addition processes, it is interesting to note that the oligomerization

via intermolecular iodine ATRA is also useful in organic synthesis.^{56,58,59} Li and coworkers have demonstrated that, upon heating or treatment with an acid, the oligomeric mixture generated from the intermolecular ATRA reactions of allyl iodoacetate can be deoligomerized to afford 5-(iodomethyl)dihydrofuran-2(3*H*)-one in 92% yield (Scheme 16).⁵⁸ The oligomeric mixture can also be converted cleanly to pent-4-enoic acid on treatment with zinc or to 2,2-diphenyl-5-(hydroxymethyl)tetrahydrofuran by reaction with phenylmagnesium bromide (Scheme 16).⁵⁹ These results have illustrated that radical oligomeric mixtures not only serve as versatile intermediates in organic synthesis but also exhibit unique advantages in that the oligomeric mixtures are self-protected and the deoligomerization functions as the simultaneous deprotection.

4 BROMINE ATOM TRANSFER

Compared to iodine atom transfer, bromine atom transfer reactions are much less investigated, although they are among the earliest examples of ATRAs. This is probably because bromine atom transfer is much slower than the analogous



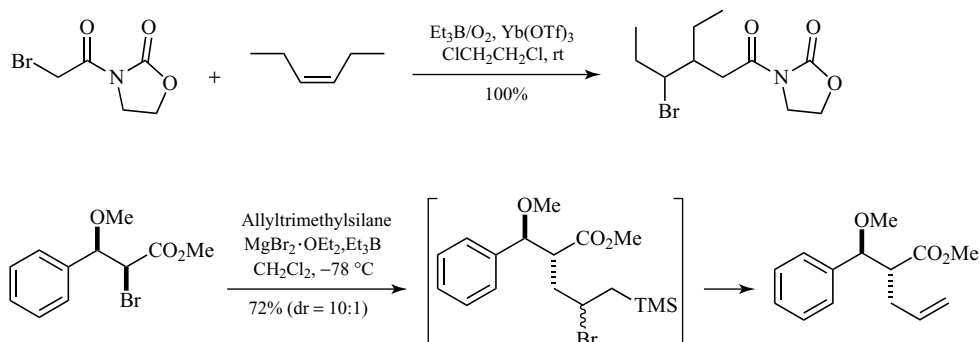
Scheme 17 Bromine ATRA reactions of α -bromo esters with alkenes.

iodine atom transfer, which makes the undesired radical telomerization competitive in some cases. Nevertheless, bromine atom transfer processes have advantages in that substrate bromides are much cheaper and the products are more stable.

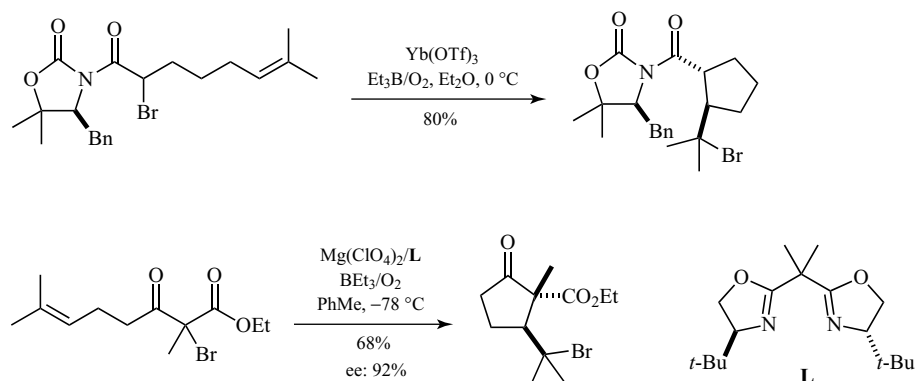
Active bromides such as phenyl tribromomethyl sulfone,⁶⁰ bromomalononitrile,⁶¹ or bromomalonates⁶² readily undergo ATRA reactions with a number of alkenes under direct UV photolysis without the help of an initiator. In the presence of Ni(OAc)₂, borohydride exchange resin (BER) and NaI, the reactions of α -bromo carbonyl compounds with enol ethers in methanol provide the radical addition products as the corresponding acetals, as shown in Scheme 17.⁶³ Further investigation by Curran and Ko has revealed that BER simply functions as a base and the same reactions can be carried out efficiently in the presence of triethylamine under the initiation of AIBN (Scheme 17).⁶⁴ With the initiation of Et₃B/O₂, ATRA reactions of α -bromo carbonyl compounds with mono- or disubstituted alkenes can be accelerated in polar

solvents such as *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), or protic solvents such as 2,2,2-trifluoroethanol (TFE) and aqueous media (Scheme 17).⁶⁵ *Ab initio* calculations indicate that a polar solvent tends to lower the relative energies of the transition states. The coordination of a carbonyl group to a proton in a protic solvent, such as a Lewis acid, may also increase the efficiency of the propagation.

Lewis acids also play an important role in bromine atom transfer reactions. For example, very poor conversion (<10%) is observed in the Et₃B/O₂-initiated addition of 3-(bromoacetyl)-2-oxazolidinone to 3-hexene. However, the addition of 1 equiv of Yb(OTf)₃ results in a clean bromine ATRA reaction with 100% conversion (Scheme 18).⁶⁶ Furthermore, control of stereochemistry in the atom transfer addition is possible by the use of chiral auxiliary oxazolidinones. Another example is the radical allylation of β -alkoxy esters using allyltrimethylsilane in the presence of MgBr₂·OEt₂ reported by Guindon *et al.*



Scheme 18 Lewis acid-promoted bromine ATRA reactions.



Scheme 19 Asymmetric bromine ATRC reactions.

(Scheme 18).⁶⁷ The chelation of the substrates to $\text{MgBr}_2 \cdot \text{OEt}_2$ allows excellent control over the diastereoselectivity. Both *syn* and *anti* bromides lead predominantly to the same *anti* product. As a comparison, the analogous *syn* iodide fails to give the allylation product; only hydroxylation occurs.

With the help of a chiral auxiliary, the Lewis acid-catalyzed ATRC reactions of unsaturated α -bromo oxazolidinone imides proceed with an excellent diastereoselectivity (Scheme 19).⁶⁸ The use of chiral Lewis acids allows enantioselective bromine ATRC reactions to occur, even in a catalytic manner.⁶⁹ Yang *et al.* have demonstrated that, in the presence of $\text{Mg}(\text{ClO}_4)_2$ (30 mol%) and a chiral bis(oxazoline) ligand (33 mol%), unsaturated α -bromo β -keto esters undergo 5-exo cyclization reactions to give the ATRC products in good yields with an enantiomeric excess up to 94% (Scheme 19).⁶⁹ These results have clearly illustrated the great potential of atom transfer processes in organic synthesis.

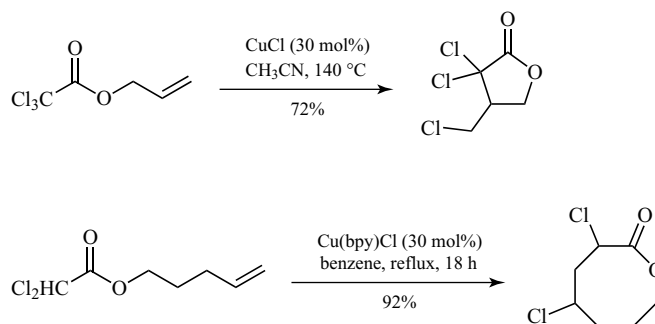
It should be pointed out that a number of ATRC reactions of unsaturated α -bromo esters or amides can be catalyzed by transition metal complexes such as Cu(I) complexes,^{15c} which will be discussed in the next section.

5 CHLORINE ATOM TRANSFER

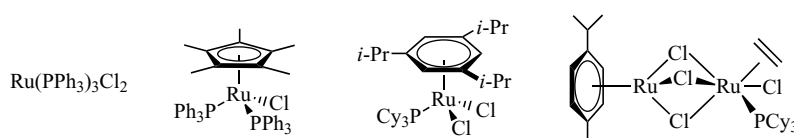
As discussed in Section 2, the majority of successful chlorine atom transfer reactions require the assistance of transition metal complexes and proceeds via the mechanism shown in Scheme 2. A number of

transition metals have been found to catalyze chlorine atom transfer processes. Among them, copper and ruthenium complexes have received the most attention.

Cuprous chloride has been shown to catalyze the intermolecular addition of polychlorinated compounds to alkenes.^{16,70} Of particular interest is its ability to catalyze the ATRC reactions of allyl trichloroacetates or amides to provide functionalized γ -lactones or lactams.⁷¹ The reactions are typically carried out in acetonitrile at high temperatures (Scheme 20). To improve the catalyst efficiency, a number of ligands have been introduced, including 2,2'-bipyridine (bpy),^{72,73} *N*-alkyl-2-pyridylmethanimines,⁷⁴ multidentate amines or pyridines,⁷⁵ bis(oxazoline),⁷⁶ and even *N*-heterocyclic carbene ligands.⁷⁷ The use of these Cu(I) complexes not only allows the reactions to be performed under milder conditions but also significantly extends the scope of reactions. Less reactive dichloroacetates can now undergo efficient ATRC reactions. For example, the $\text{Cu}(\text{bpy})\text{Cl}$ -catalyzed reaction of pent-4-enyl dichloroacetate in refluxing benzene offers the eight-membered lactone in 92% yield as a mixture of two stereoisomers in 70:30 ratio (Scheme 20).⁷³ The analogous cuprous bromide complexes can be employed to catalyze the cyclization of unsaturated α -bromo amides, as demonstrated by Clark *et al.*⁷⁸ Nevertheless, relatively high catalyst loading is required in these copper-catalyzed transformations. To partially deal with this problem, solid-supported reagents⁷⁹ and perfluorous catalysts⁸⁰ have also been developed to allow the recovery and reuse of catalysts.



Scheme 20 Cu(I)-catalyzed chlorine ATRC reactions.

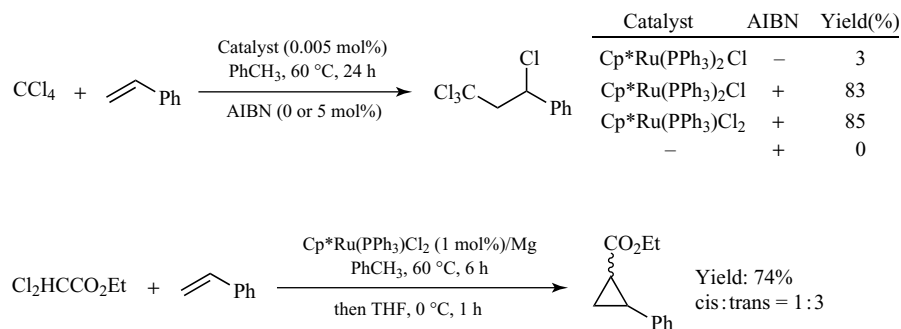


Scheme 21 Representative ruthenium catalysts for chlorine atom transfer reactions.

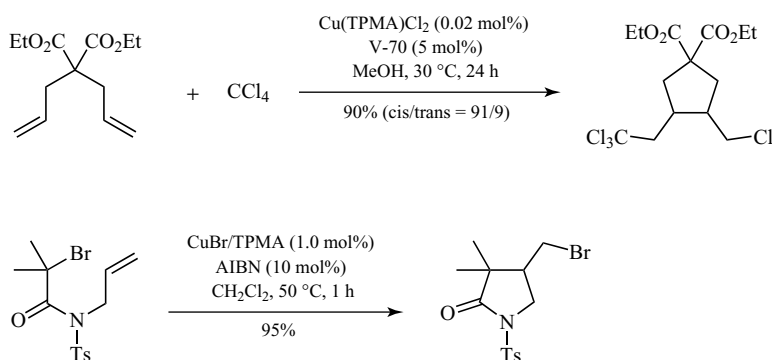
Ruthenium complexes have also been shown to catalyze chlorine atom transfer reactions. Among them, $(\text{Ph}_3\text{P})_3\text{RuCl}_2$ is the first Ru(II) catalyst developed for chlorine ATRA^{18,81} and ATRC⁸² reactions of chlorinated compounds to alkenes. Much effort has been made to improve the catalytic activity, leading to the development of a number of ruthenium catalysts of more complex structures, some of which are listed in Scheme 21.^{83–85} However, these Ru(II) complexes display low catalyst stability and consequently show low turnover numbers (TONs) typically.

In order to increase the lifetime of catalyst, Severin *et al.* have nicely demonstrated that the use of $\text{Cp}^*\text{Ru}(\text{PPh}_3)_2\text{Cl}$ or even $\text{Cp}^*\text{Ru}(\text{PPh}_3)\text{Cl}_2$ in the presence of AIBN leads to a dramatic increase in catalyst efficiency.⁸⁶ As illustrated in Scheme 22, when only 0.005 mol% of $\text{Cp}^*\text{Ru}(\text{PPh}_3)_2\text{Cl}$ is used for the reaction of CCl_4 with styrene at 60 °C, a conversion of only 3% is observed after 24 h. Apparently, the high concentration of CCl_4 relative to the catalyst leads to the rapid deactivation of the catalyst by turning the Ru(II) to inactive Ru(III)–Cl. However, in the presence of 5 mol% of AIBN, a complete conversion can be observed with the desired ATRA product in 83% yield (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). This is because the carbon-centered radical derived from AIBN can regenerate the Ru(II) catalyst by

abstraction of a chlorine atom from Ru(III)–Cl. Switching the Ru(II) complex to the more stable Ru(III) complex $\text{Cp}^*\text{Ru}(\text{PPh}_3)\text{Cl}_2$ also leads to the complete conversion with the mono adduct in 85% yield, which corresponds to a TON of 17 000 for the catalyst. A TON of 44 500 is observed in the $\text{Cp}^*\text{Ru}(\text{PPh}_3)\text{Cl}_2/\text{AIBN}$ -catalyzed reaction of CCl_4 with 1-hexene. In addition to AIBN, magnesium metal can also be used as the reducing agent, allowing the easy separation of the cocatalyst.⁸⁷ More importantly, the reactions can now be performed under milder conditions, resulting in a higher efficiency and better control over stereoselectivity. Further mechanistic studies⁸⁸ have revealed that the $\text{Cp}^*\text{Ru}(\text{PPh}_3)_2\text{Cl}$ - or $\text{Cp}^*\text{Ru}(\text{PPh}_3)\text{Cl}_2$ -catalyzed ATRA reaction is of zero order with respect to chlorinated compounds. This is in contrast to what is observed for less active catalysts such as $(\text{Ph}_3\text{P})_3\text{RuCl}_2$, which show a first-order dependence of the reaction rate on the chlorinated substrate. Furthermore, the kinetic data suggest that the metal catalyst is not directly involved in the rate-limiting step of the reaction. An interesting extension of the above processes is the cyclopropanation of alkenes by a sequential ATRA and dechlorination in the presence of a ruthenium catalyst and magnesium in a one-pot, two-stage manner, as shown in Scheme 22.⁸⁹



Scheme 22 Ruthenium-catalyzed ATRA reactions.



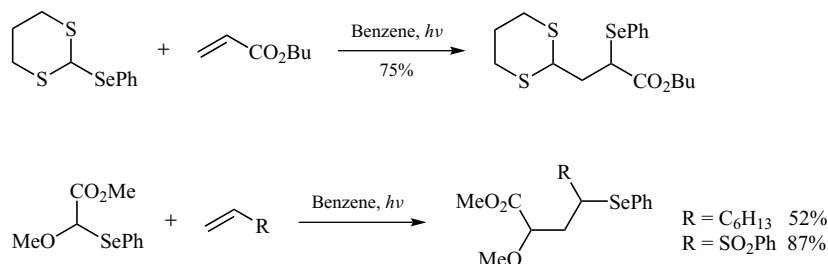
Scheme 23 Copper-catalyzed atom transfer reactions in the presence of AIBN or V-70.

The remarkable effect of AIBN is also observed in copper-catalyzed ATRA reactions of polyhalogenated compounds, as reported by Eckenhoff and Pintauer.⁹⁰ Both Cu(I) and Cu(II) complexes can be utilized as catalysts. Other than AIBN, the free radical initiator 2,2'-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70) can also be used in these processes.⁹¹ By taking advantage of the lower decomposition temperature of V-70, the ATRA reactions of polyhalogenated compounds with alkenes can be performed at a lower temperature, enabling selective formation of the mono adduct with highly active monomers such as methyl acrylate or vinyl acetate. The addition of CCl_4 to 1,6-dienes also proceed efficiently by catalysis of only 0.02 mol% of $\text{Cu}(\text{TPMA})\text{Cl}_2$ [tris(2-pyridylmethyl)amine (TPMA)] together with 5 mol% of V-70, furnishing the cyclopentane products in excellent yields (Scheme 23). Kinetic studies by Pintauer *et al.* have shown that in these ATRA reactions the rate of alkene consumption is dependent on the concentration and rate of

decomposition of AIBN, but independent of the concentration of the copper catalyst.⁹² This method is then successfully extended to bromine ATRA and ATRC reactions.⁹³ For example, in the presence of AIBN, the ATRA reactions of CBr_4 or CHBr_3 to alkenes can be successfully carried out via the catalysis of $\text{Cu}(\text{TPMA})\text{Br}$ or $\text{Cu}(\text{TPMA})\text{Br}_2$ of ppm concentrations.⁹³ Similarly, the ATRC reactions of *N*-allyl-2-bromoalkanamides proceed smoothly with the catalysis of only 1 mol% of CuBr/TPMA when 10 mol% of AIBN is also present (Scheme 23). Thus, these recent advances in transition-metal-catalyzed ATRA and ATRC reactions have clearly shown their great potential in industrial applications.

6 PHENYLSELENO GROUP TRANSFER

Like halogen atoms, chalcogens such as selenium and tellurium can also take part in ATRA and ATRC reactions. Among them, the phenylseleno transfer

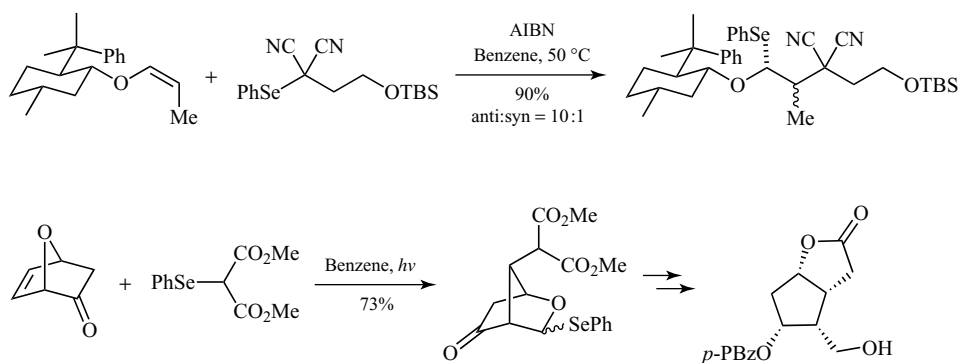


Scheme 24 ATRA reactions of α -heteroatom-stabilized radicals.

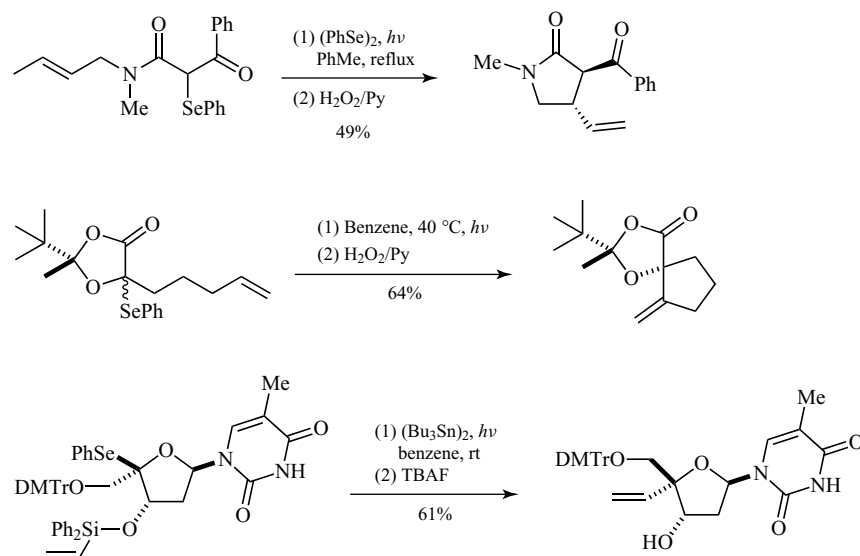
chemistry has been extensively investigated. In general, the transfer of phenylseleno group is of comparable rate to the analogous bromine atom transfer but is much slower than the iodine atom transfer. However, by taking advantage of the greater ionic stability of organoselenium compounds, the phenylseleno group transfer exhibits different behaviors in many cases.

The first examples of phenylseleno group transfer were reported by Byers and Lane.⁹⁴ Here, diethyl phenylselenomalonate undergoes the radical addition reaction with 1-octene upon sunlamp irradiation or heating in the presence of AIBN.^{94,95} Simple phenylselenenyl ketones, esters, nitriles, sulfones, and bisphosphonates can also be employed in these group transfer reactions.⁹⁶ Phenylselenotrichloromethane adds to alkenes upon photolysis, and the products can be converted to α,β -unsaturated carboxylic acids.⁹⁷ More importantly, the stability of α -heteroatom-substituted selenides now enables them to serve as the radical precursors for heteroatom-stabilized radicals. For example, 2-phenylseleno-1,3-dithiane adds to electron-deficient alkenes, while the

captodative radical derived from α -methoxy- α -phenylselenoacetate adds to both electron-deficient and electron-rich alkenes (Scheme 24).⁹⁸ In the meantime, the phenylseleno transfer addition of malonyl or malononitrile radical to heteroatom-substituted alkenes such as enol ethers or enamides readily proceeds to give the stable phenylseleno transfer products, whereas the analogous iodine atom transfer fails.⁹⁹ The addition of phenylselenomalononitriles to 1,2-disubstituted alkenes exhibits good to high stereoselectivity. An excellent diastereoselectivity is achieved in their reactions with (–)-8-phenylmenthol enol ethers (Scheme 25).⁹⁹ Taking advantage of the slow rate of phenylseleno transfer, Renaud and Vionnet have demonstrated that the regioselective radical addition of phenylselenomalonate to 7-oxabicyclo[2,2,1]hept-5-en-2-one is followed by rearrangement prior to phenylseleno transfer (Scheme 25), which serves as the key step for all-cis-Corey lactone synthesis.¹⁰⁰ Ryu *et al.* have shown that the radical addition of phenylselenoacetates to alkenes is followed by the trapping of CO prior to phenylseleno transfer, leading to the



Scheme 25 Phenylseleno transfer to α -heteroatom-substituted radicals.



Scheme 26 Stereoselective ATRC reactions of organoselenides.

isolation of acyl selenides as the three-component condensation products.¹⁰¹

Significant progress has also been achieved in phenylseleno group transfer cyclization. Allyl phenylselenoacetates and *N*-allyl-2- (phenylseleno) acetamides undergo preferably 5-exo cyclization reactions.^{102–104} For example, the cyclization of α -phenylseleno *N*-(2-butenyl)-*N*-methyl-3-oxo-3-phenylpropanamide followed by oxidation with H_2O_2 provides stereoselectively the corresponding γ -butyrolactam, which serves as the key intermediate for the synthesis of ($\pm$)-isocyanometrine (Scheme 26).¹⁰⁴ The cyclization of 5-(4-pentenyl)-5-phenylseleno-1,3-dioxolane-4-one also proceeds stereoselectively, leading to the synthesis of 1-hydroxycyclopentanecarboxylic acid derivatives (Scheme 26).¹⁰⁵ The radical cyclization onto vinyl silyl ethers followed by the cleavage of Si–C bond via tetrabutylammonium fluoride (TBAF) and subsequent β -elimination allows the stereoselective introduction of a vinyl group to the radical center (Scheme 26).¹⁰⁶

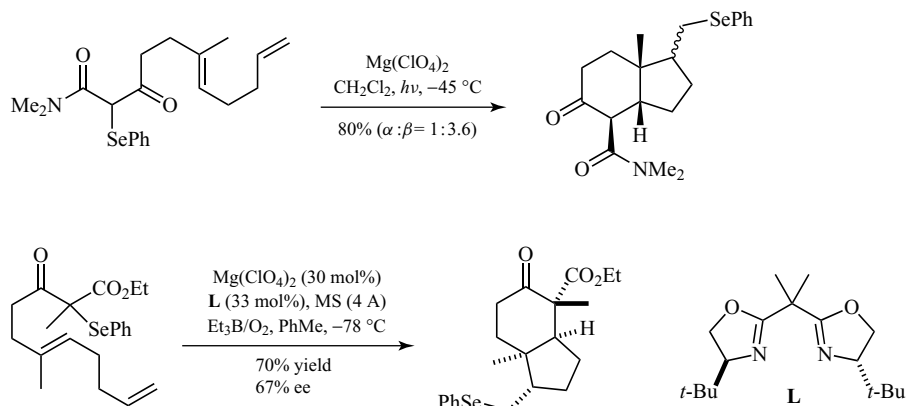
Phenylseleno transfer radical cyclization reactions can also be promoted by Lewis acids, allowing the reactions to be performed at a lower temperature with higher regio- and stereoselectivities. The cyclization of unsaturated α -phenylseleno β -hydroxy esters is significantly accelerated by Et_2AlCl and excellent diastereoselectivities are

achieved.¹⁰⁷ The cyclization via 5-exo, 6-endo, or 7-endo mode can thus be successfully implemented, depending on the substitution pattern of the C=C double bonds. In the presence of $\text{Yb}(\text{OTf})_3$ or $\text{Mg}(\text{ClO}_4)_2$, unsaturated α -phenylseleno β -keto amides undergo heteroatom transfer cyclization to give mono- or bicyclic products in a highly efficient regio- and stereoselective manner (Scheme 27).¹⁰⁸ Enantioselective phenylseleno group transfer tandem cyclization can also be designed with the catalysis of chiral Lewis acids, as demonstrated by Yang *et al.* (Scheme 27).¹⁰⁹

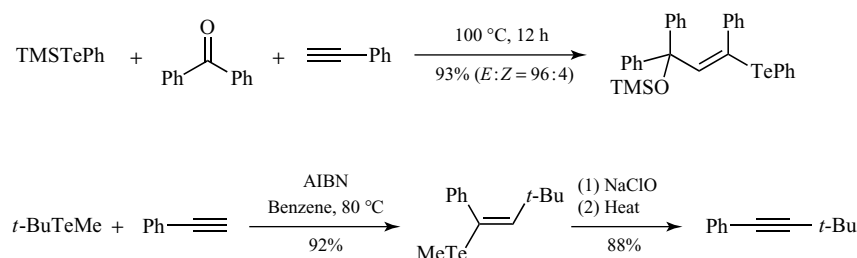
7 ARYTELLURO GROUP TRANSFER

Organotellurium compounds exhibit unique characteristics in halogen and chalcogen transfer chemistry.¹¹⁰ In general, the rate of ArTe group transfer is comparable to that of the iodine atom transfer but much faster than that of the PhSe group transfer (see **Sb, Bi, Te, and I-Transfer Polymerization and Applications**). The high rates of aryltelluro group transfer, together with the ionic stability of organotellurides, allow a number of ArTe group transfer processes to take place, whereas the analogous halogen or phenylseleno transfer fails.

Carbotelluration of alkynes proceeds upon photolysis or heating in the presence of AIBN to



Scheme 27 Lewis acid-promoted tandem radical cyclization reactions.

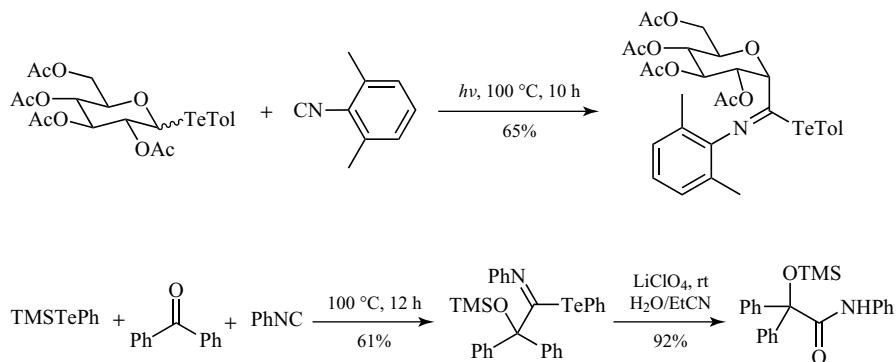


Scheme 28 Carbottelluration of alkynes.

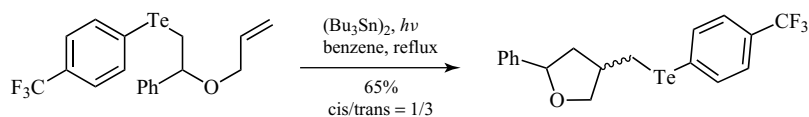
afford the corresponding vinyl tellurides in good yields.¹¹¹ Primary, secondary, and tertiary alkyl and benzyl tellurides are all suitable substrates for the carbottelluration. Alkynes bearing an aryl or electron-withdrawing substituent undergo carbottelluration very efficiently, while alkyl-substituted alkynes give moderate to poor yields of adducts. The stereochemistry is kinetically controlled and mainly affected by steric effect. The competitive reaction of PhTe^iPr and ^iPrI with phenylacetylene indicates that the addition of PhTe^iPr is about 10 times faster than that of ^iPrI , revealing the ease of phenyltelluro transfer. In a similar manner, vinylic *C*-glycosides can also be prepared from the addition of telluroglycosides to alkynes.¹¹² An interesting extension of carbottelluration involves the three-component condensation of trimethylsilyl phenyl telluride, carbonyl compounds, and alkynes, as reported by Yamago and Yoshida.¹¹³ The reaction of silyl telluride with carbonyl compounds proceeds first to give the α -silyloxy tellurides, which then add to alkynes to afford the corresponding silylated allylic alcohols with high *E*-stereoselectivities

(Scheme 28). It should be noted that vinyl tellurides are versatile intermediates in organic synthesis.¹¹⁴ For example, vinyl tellurides prepared by carbottelluration of terminal alkynes followed by oxidation with NaClO and subsequent pyrolysis furnish the internal alkynes in good yields (Scheme 28).¹¹⁵

Carbottelluration of isonitriles has also been proven successful. Organotellurium compounds as precursors for benzyl, α -alkoxy, α -amino radicals add to isonitriles to provide the corresponding imidoylated products.¹¹⁶ For example, telluroglycosides react with isonitriles (see **Unusual Radical Acceptors**) under photothermal conditions to give 1-telluroimidoylglycosides (Scheme 29). Good yields are obtained in the reactions of aromatic isonitriles, whereas the less reactive alkyl-substituted isonitriles give poor yields of products. The three-component condensation of silyltellurides, carbonyl compounds, and isonitriles leads to the formation of α -silyloxy imines, which can be converted to a variety of α -hydroxy carbonyl compounds such as α -hydroxy amides by exploiting the reactive C–Te bond (Scheme 29).



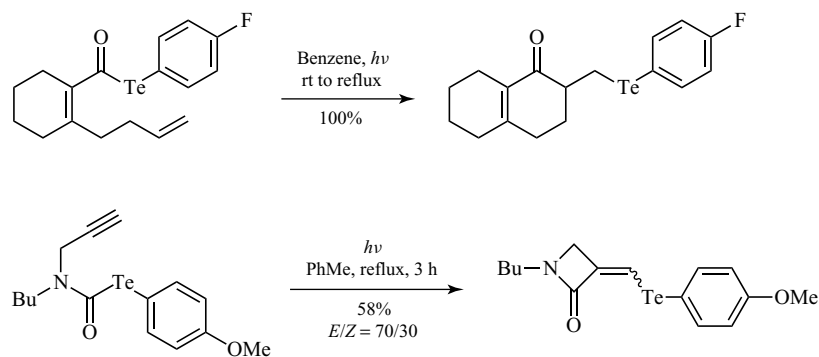
Scheme 29 Carbottelluration of isonitriles.



Scheme 30 Group transfer cyclization of organotellurides.

Intermolecular group transfer addition of organotellurides to alkenes is rare if any presumably because of the lack of sufficient driving force and poor stability of the related organotellurium compounds. However, group transfer cyclization of organotellurides has been demonstrated to be successful by Engman and Gupta.¹¹⁷ For example, β -(allyloxy)alkyl aryl tellurides undergo group transfer 5-exo cyclization to afford substituted tetrahydrofurans upon photolysis with catalytic $(\text{Bu}_3\text{Sn})_2$ (Scheme 30). As a comparison, the analogous selenides fail to undergo group transfer cyclization because of the much lower rate of phenylseleno group transfer.

Acyl tellurides of aryl and vinyl carboxylic acids, which can be readily prepared by the reaction of sodium aryl tellurides with acyl chlorides or mixed anhydrides, are excellent sources of acyl radicals as demonstrated by Crich *et al.*¹¹⁸ Upon photolysis with a simple white light source, acyl tellurides are shown to participate in very efficient group transfer cyclization reactions onto alkenes with the formation of five-, six-, and even eight-membered rings (Scheme 31). Again, the analogous phenylselenenides fail to undergo group transfer cyclization. Acyl tellurides also react with isonitriles to give the corresponding group transfer imidoylation products.¹¹⁹ Carbamottelluroates are shown to



Scheme 31 Cyclizations of acyltellurides.

add to acetylenes to yield β -telluroacrylamides.¹²⁰ When the reactions are carried out intramolecularly, α -alkylidene- β -lactams can be obtained via 4-exo cyclization (Scheme 31).¹²¹

8 CONCLUSION

Atom transfer radical reactions have become an indispensable tool for carbon–carbon bond formations. They provide a powerful, atom-economic, and nonreductive complement to the tin hydride method for conducting radical addition reactions. The halogens or chalcogens are retained in the products, allowing further transformations. The introduction of Lewis acids increases the efficiency and regio- and stereoselectivity in many cases. Enantioselective atom transfer reactions can also be successfully implemented with the help of chiral Lewis acids. Transition metal catalysts, in combination with reducing agents, make the ATRA and ATRC reactions more efficient and environmentally friendly. The rich and versatile atom transfer chemistry should be of increasing importance in organic synthesis in the near future.

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Xanthates and Related Derivatives as Radical Precursors

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1 INTRODUCTION

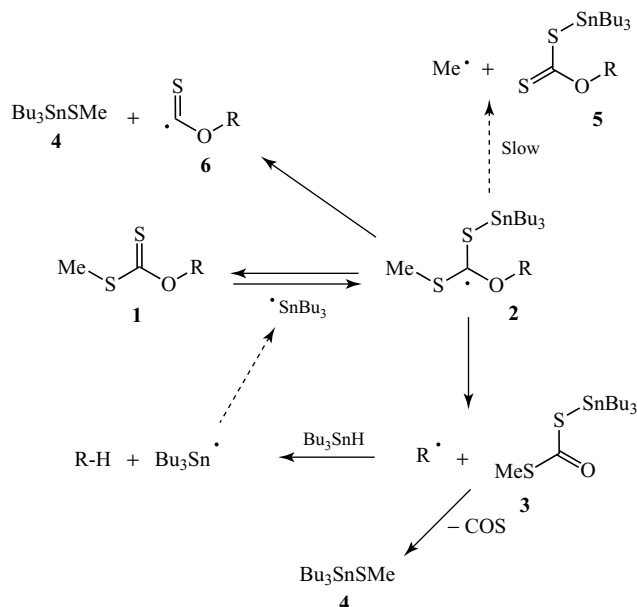
Xanthate salts or (or dithiocarbonates, $R-O-C(=S)-SM$), derived by the simple reaction of an alcoholate with carbon disulfide, were discovered by Zeise nearly two centuries ago.¹ They have found extensive use as flotation agents in the mining industry and in the manufacture of viscose (artificial silk) and cellophane wrapping films.² The thermal fragmentation of xanthate esters to give olefins is called *Chugaev elimination*, a well-known but infrequently applied reaction.^{3,4} An infinitely more powerful transformation involving xanthates was reported in the early 1970s by Barton and McCombie.⁵ It is a radical process that was initially designed to deoxygenate secondary alcohols $R-OH$ through *cleavage of the R-O bond* in the corresponding xanthate $R-O-C(=S)-SMe$ (or, more generally, in compounds of structure $R-O-C(=S)-Z$), but which ultimately emerged as an extremely versatile method for generating carbon radicals that can be incorporated in numerous radical sequences.^{6–11} The Barton–McCombie deoxygenation reaction represents a major advance in the application of radical processes to synthetic problems: spectacular deoxygenations on incredibly complex structures that still cannot be accomplished by known ionic and organometallic methods nearly 40 years later.

More recently, the cleavage of the $R-S$ bond in xanthates of type $R-S-C(=S)-OEt$, and more generally in dithiocarbonyl compounds of gross structure $R-S-C(=S)-Z$, has constituted the basis of

a versatile degenerate radical transfer of xanthates and related groups. Both the Barton–McCombie deoxygenation and the degenerative transfer are discussed in the present chapter.

2 MECHANISM AND SYNTHETIC APPLICATIONS OF THE BARTON–MCCOMBIE DEOXYGENATION

The Barton–McCombie deoxygenation proceeds by the mechanism displayed in Scheme 1, which is a slightly modified version of the one originally proposed by Barton and McCombie. The modification concerns the first propagation step, namely the addition of the tributylstannyl radicals to the thiocarbonyl group of the xanthate, which was found to be fast and reversible.^{12,13} The slow rate-determining step is the irreversible fragmentation of intermediate **2** to give radical $R^\bullet$ and *S*-tributylstannyl dithiocarbonate **3**. Hydrogen abstraction from the stannane is fast and irreversible, furnishing the alkane, RH , and tributylstannyl radicals to propagate the chain. The main driving force is the conversion of a $C-S$ π bond into the much stronger $C-O$ π bond. Stannyl dithiocarbonate **3** may be observed by ^{119}Sn NMR below $-20^\circ C$, but above this temperature it swiftly extrudes carbon oxysulfide to give tributyltin sulfide **4**.¹⁴ Placing a methyl group on the sulfide sulfur of the xanthate disfavors the unwanted scission of the $C-S$ bond in intermediate **2**, for this would lead to a



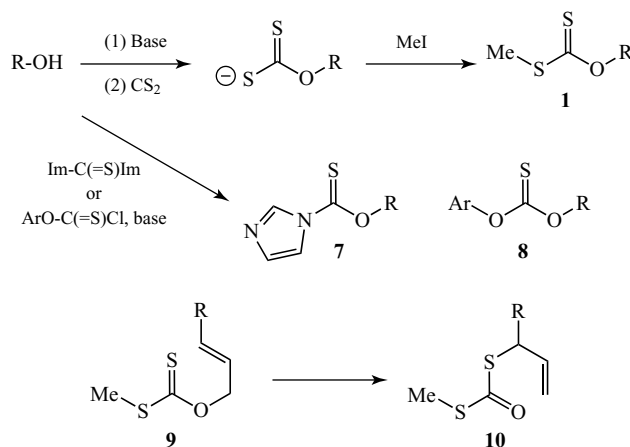
Scheme 1 Mechanism of the Barton–McCombie deoxygenation.

high-energy methyl radical as well as to stannyl xanthate **5**. Hence, in most structures, the fragmentation proceeds preferentially in the desired direction, on the side of the oxygen. In some cases, side products are observed that are derived either by premature reduction of intermediate **2** by the stannane or, more likely, by further reduction of the thionoformate derived from alkoxythiocarbonyl radical **6**.^{12,13,15–18} Incidentally, it was also demonstrated that radicals **6** can undergo extrusion of carbon oxysulfide to give radicals $\text{R}^\bullet$.^{17,18}

In practice, the Barton–McCombie reaction is best suited for deoxygenating secondary alcohols. Xanthates of tertiary alcohols are usually thermally unstable, decomposing readily into an alkene through the Chugaev elimination, sometimes even below room temperature. The deoxygenation is nevertheless highly efficient in cases where the Chugaev elimination is sufficiently slow at ambient temperature to allow handling of the xanthate.¹⁹ Xanthates derived from bridgehead tertiary alcohols belong to this category. If needed, the chain reaction may be initiated at low temperature using a combination of triethylborane and oxygen for example.²⁰

In the case of primary alcohols, the hurdle is the greater energetic cost of forming a primary carbon radical from intermediate **2**.²¹ The competition

between the expulsion of a primary radical by scission of the C–O bond and a methyl radical by cleavage of the C–S bond is no longer totally biased toward the former mode. The collapse of **2** is a unimolecular step with a large positive entropy of activation; it is therefore highly temperature-sensitive and can be accelerated considerably by operating at higher temperatures. However, this does not obviate the danger of competitive C–S bond cleavage, which is also a unimolecular fragmentation with an equally large positive entropy of activation. In this respect, it is usually advantageous to start with other thiocarbonyl derivatives pictured in Scheme 2, such as thiocarbonyl imidazolides **7**,^{5–11} *O*-arylthionocarbonates **8**,^{22–24} or thionocarbonates,²⁵ where the fragmentation of the intermediate radical adduct corresponding to **2** can occur only on the side of the oxygen. These alternative thiocarbonyl derivatives are also suitable substrates for the deoxygenation and follow the same mechanism (the –SMe group in the xanthate is just a spectator in the addition–fragmentation process outlined in Scheme 1). These precursors are often easier to prepare than xanthates, but are more expensive. As for the xanthates themselves, they are readily obtained by treatment of the requisite alcohol with a strong base, carbon disulfide, and methyl



Scheme 2 Synthesis of precursors for the Barton–McCombie deoxygenation.

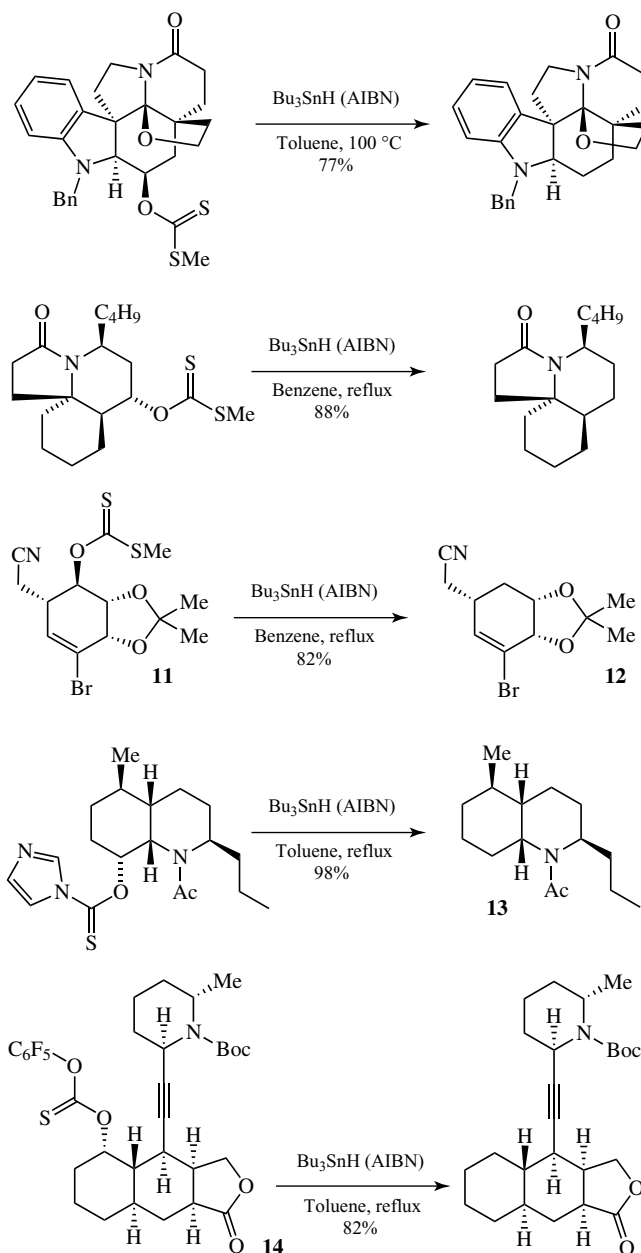
iodide, normally in this order (Scheme 2), but variations have been reported where all the ingredients are mixed in the presence of a phase transfer catalyst.^{26,27} A word of caution must be said concerning xanthates **9** derived from allylic (and propargylic) alcohols, which can undergo a relatively easy [3,3]-sigmatropic rearrangement into allylic dithiolcarbonate **10** as indicated in Scheme 2.²⁸

The Barton–McCombie deoxygenation has been applied on more than a thousand natural products and synthetic intermediates, and several reviews have already appeared.^{6–11} An *Organic Reactions* chapter devoted to this transformation, by McCombie, Motherwell, and Tozer, is in press and will soon be published.¹¹ The process is tolerant of many of the functional groups encountered in modern organic synthesis, in line with typical stannane chemistry, and can be applied with success to quite complex structures, even late in a synthetic scheme. Replacing the regular triorganotin hydride with the deuteride or the tritide allows the specific replacement of an alcohol group by a deuterium or a tritium atom. As a consequence of the *reversibility* of the addition of the stannyl radicals to the thiocarbonyl group and the rate-limiting, irreversible fragmentation of intermediate **2** discussed above, it is relatively easy to deoxygenate a secondary alcohol in the presence of a primary alcohol by using a limited amount of stannane.²⁹ In the case of 1,2- and 1,3-diols, selective reductions can be accomplished by use of cyclic thionocarbonates. Bisxanthates derived from 1,2-diols generally lead to alkenes in good yield.^{6–11}

The recent examples listed in Scheme 3 are representative of the unique synthetic potential of the Barton–McCombie deoxygenation. The first two correspond to important steps in the concise total synthesis of (+)-fendleridine and lepadiformine **C** by the groups of Boger and Aubé, respectively.^{30,31} The third transformation (**11** → **12**), taken from Banwell's route to Nobilisinine **A**, showcases the possibility of reducing a xanthate in the presence of a vinylic bromide.³² The use of a thiocarbonyl imidazolide precursor is illustrated by the last step in the synthesis of (±)-*epi*-pumiliotoxin **C** (**13**) reported by Fearnley and Thongsornkleeb.³³ The reduction of lactone **14**, an intermediate in the formal synthesis of (+)-himbacine by Wong and Sherburn, involves the deoxygenation of a thionocarbonate derivative.³⁴

3 TIN-FREE MODIFICATIONS

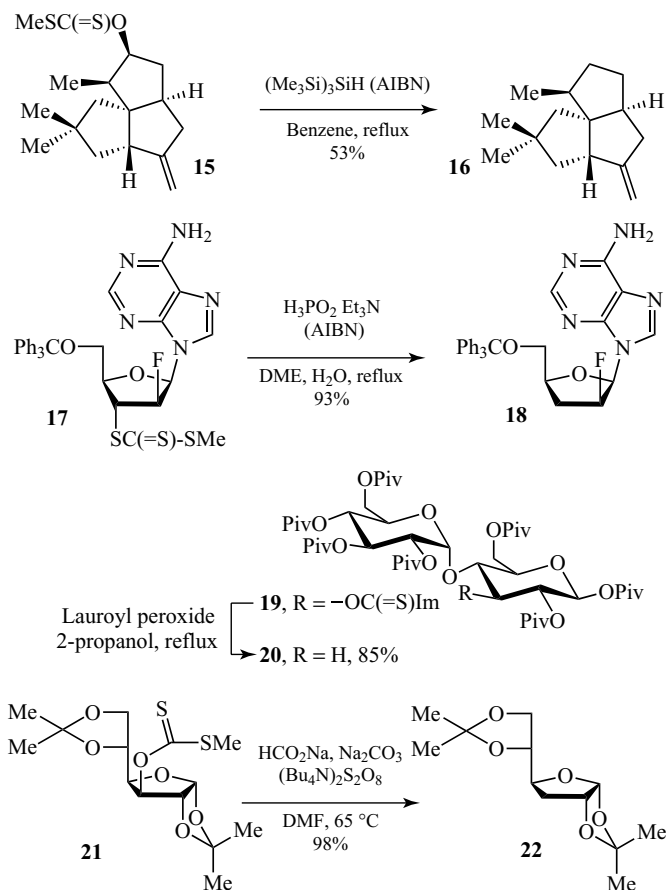
The considerable difficulty often encountered in removing tin residues and the toxicity of organotin derivatives (see **Tin Hydrides and Functional Group Transformations**), which complicates possible biological testing of the products, has encouraged the development of catalytic systems as well as completely tin-free radical processes. The combination of poly(methylhydrosiloxane) with a small amount of hexabutyltin oxide, reported initially by Grady and Kuivila,³⁵ has been applied to Barton–McCombie type deoxygenations.³⁶ A number of silanes have



Scheme 3 Some examples of Barton–McCombie deoxygenations.

been examined as alternative reducing agents; the most promising are arylsilanes^{37,38} and tris(trimethylsilyl)silane (see **Silanes as Reducing Reagents in Radical Chemistry**).^{39–41} The latter has proven to be especially versatile, even though it is still too expensive to be considered

for large-scale deoxygenations. For instance, tris(trimethylsilyl)silane cleanly reduced xanthate **15**, providing a pure sample of ventricosene **16** (Scheme 4), in contrast to tributylstannane which furnished contaminated material that could not be purified.⁴² Recently, Studer and Walton

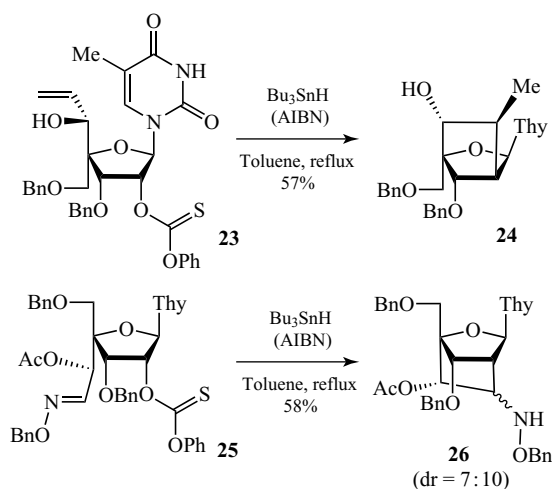


Scheme 4 Tin-free Barton–McCombie deoxygenations.

described the use of silylated cyclohexadienes for accomplishing Barton–McCombie deoxygenations under ecologically acceptable conditions.⁴³

As a result of the seminal efforts by Barton and his coworkers,^{44,45} hypophosphorus acid, its salts, and related derivatives have emerged as practical, cheap, and ecologically benign alternative reducing agents to stannanes.^{46–50} The conversion of xanthate **17** into protected lodenosine **18** is not only efficient but could be performed successfully on multikilogram scale.^{51,52} Phosphine–borane complexes^{53,54} and, more recently, *N*-heterocyclic borane complexes have been proposed as hydrogen atom donors for the deoxygenation.^{55–57} Their use has so far been limited, but could increase if specific practical advantages are eventually identified. The same applies for a mechanistically intriguing method

involving a combination of water and a Lewis acid such as boron trifluoride etherate or titanium complexes.^{58,59} A combination of lauroyl peroxide and 2-propanol has also been found to mediate the Barton–McCombie deoxygenation, as illustrated by the reduction of maltose-derived thio-cabonyl imidazolidine **19** into deoxy-maltose heptapi-valate **20**.^{60,61} Incidentally, this method was also applied to the lodenosine problem with equal success.⁶² A more recent and conceptually related procedure involves the use of peroxydisulfate and sodium formate in dimethylformamide (DMF).⁶³ One application pictured in Scheme 4 is the deoxygenation of isopropylidene xanthate **21** to give protected deoxyglucose **22** in high yield. The last two methods are both economical and scaleable.



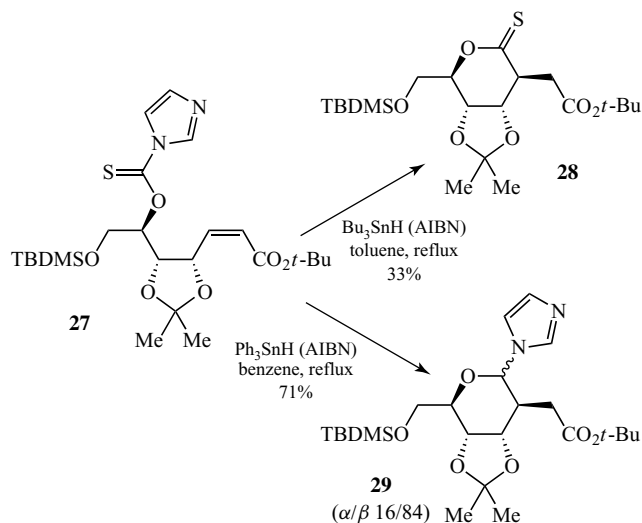
Scheme 5 Radical cyclizations starting from thionocarbonates.

4 SYNTHETIC VARIATIONS OF THE BARTON–McCOMBIE REACTION

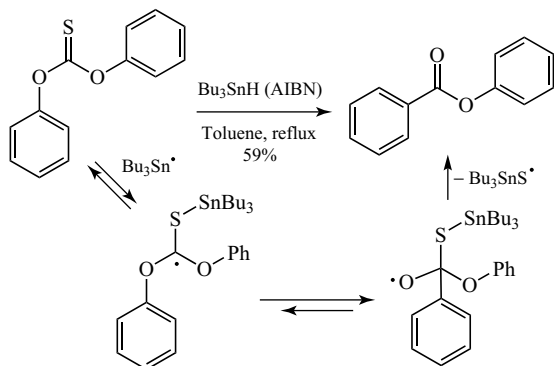
While the Barton–McCombie reaction has mostly been exploited for simple deoxygenations, it represents in fact a very convenient method for generating radicals from alcohols. These radicals can be readily intercepted by internal or, but more rarely, external traps. Two carbohydrate examples of

cyclization, among very many others, are depicted in Scheme 5. Thus, treatment of thionocarbonate **23** with stannane results in the formation of bicyclic product **24** in moderate yield.⁶⁴ The second transformation, taken from work by the same research group, illustrates the trapping of the carbon radical derived from thionocarbonate **25** by an internal oxime to give bicyclic hydroxylamine **26**.⁶⁵ Indeed, the association of the Barton–McCombie reaction with a radical ring closure has proven to be a very convenient and powerful strategy for converting carbohydrates into highly substituted, optically pure carbocycles.⁶⁶

Much less common are instances where the intermediate adduct radical **2** (Scheme 2) is intercepted before the occurrence of the fragmentation step.^{67–71} In a recent study, RajanBabu and co-workers found that the intermediate derived from thiocarbonyl imidazolides may be effectively captured by an internal electrophilic alkene (or even by an oxime), as shown by the reactions presented in Scheme 6.⁷² Interestingly, when compound **27** was treated with *tributyltin* hydride, a modest yield of thiolactone **28** was obtained; in contrast, reaction with *triphenyltin* hydride furnished imidazolidine **29** in good yield. This raises intriguing mechanistic questions, in particular concerning the species that is actually being trapped in each case. For instance, could an alkoxythiocarbonyl radical **6** be involved in the formation of **28**?



Scheme 6 Capture of the intermediate in the Barton–McCombie reaction.

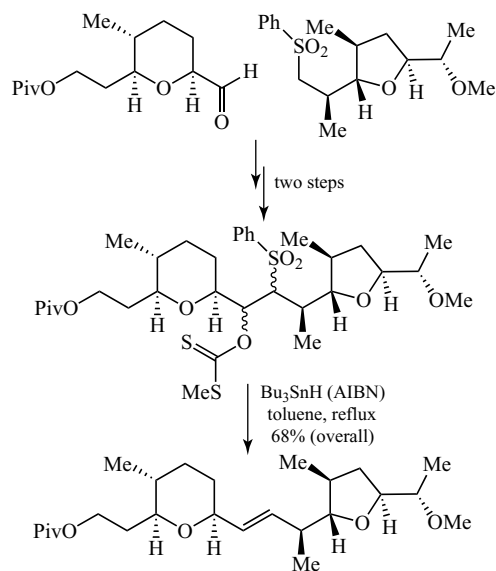


Scheme 7 Neophilic rearrangement of a Barton–McCombie intermediate.

The Barton–McCombie reaction may also be diverted from its normal course by involving intermediate **2** in a neophilic rearrangement (see **Radical Arylations and Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**). This represents a neat radical-Smiles-based strategy that allows the ultimate replacement of the C–O bond in phenols with a C–C bond. A typical example is reproduced in Scheme 7.⁷³

The Barton–McCombie deoxygenation has been used in a radical modification of the Julia olefination to create alkenes from vicinal hydroxysulfones. The carbon radical resulting from the cleavage of the C–O bond induces the β -fragmentation of the sulfone and expulsion of a sulfonyl radical.^{74–77} One illustrative application is the key step in the total synthesis of tetronasin displayed in Scheme 8.⁷⁷ The elimination produces selectively the desired *E*-alkene.

Practically all the above transformations are in fact in competition with an underlying background reaction, which has not been discussed so far, namely the addition of the intermediate carbon radical to the thiocarbonyl group of the xanthate or related thionocarbonyl precursors. As indicated in Scheme 9, this addition, leading to intermediate **30**, is *reversible* and does not alter the system if it is not followed by the slow but *irreversible* rupture of the C–O bond to give isomeric dithiocarbonate **31**. With most substrates, this radical O $\rightarrow$ S isomerization is too slow under the normal conditions of the Barton–McCombie deoxygenation, and does not therefore interfere. However, when this

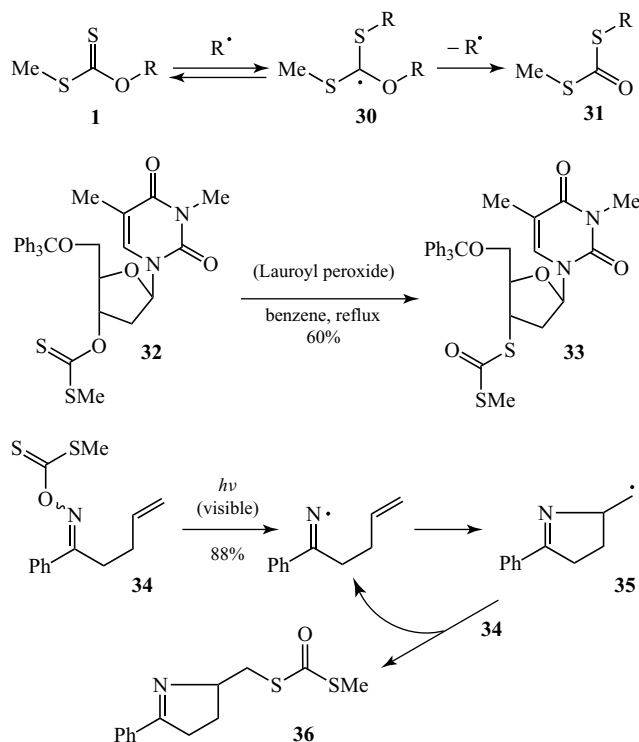


Scheme 8 Formation of an alkene by a modification of the Barton–McCombie deoxygenation.

isomerization does indeed take place, it is most often overlooked because dithiocarbonate **31** and starting xanthate **1** have almost identical polarities and cannot be distinguished easily by simple thin-layer chromatography. Since dithiocarbonates **31** are poor substrates for the deoxygenation, the only hint that the isomerization has in fact occurred is the unusually sluggish reduction and the ultimate inordinate excess of reducing agent needed to observe the disappearance of what looks like the “starting material.”

Nevertheless, this radical O $\rightarrow$ S isomerization is of some synthetic interest, for it allows the conversion of alcohols into thiols under very mild conditions. By operating in a concentrated medium *in the absence of a hydrogen atom donor* and by using lauroyl peroxide as the initiator, the isomerization becomes the major pathway, as shown by the conversion of xanthate **32** into dithiocarbonate **33**, with the expected retention of configuration in this case.⁶⁰

A similar reaction can be observed with ketoxime xanthates, where the weakness of the N–O bond facilitates the rearrangement process considerably. The reaction involves the intermediacy of iminyl radicals, which can be captured readily, as shown by the example in the lower part of Scheme 9. Thus, irradiation with visible light of ketoxime



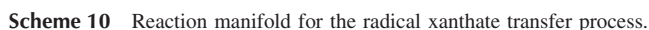
Scheme 9 Radical isomerization of xanthates and generation and capture of iminyl radicals.

xanthate **34** results in the formation of pyrrolenine **36**, through reaction of cyclized radical **35** with the starting xanthate.⁷⁸ Ketoxime xanthates are thermally unstable, and irradiation turns out to be the simplest and most efficient way to trigger the chain process.

5 DEGENERATIVE TRANSFER OF XANTHATES: MECHANISTIC CONSIDERATIONS

A completely different reaction manifold may be obtained by switching the nature of the groups on the starting xanthates so that cleaving the C–S bond becomes the dominant path. A degenerative addition–transfer of the xanthate to an alkene can now be envisaged, as depicted in Scheme 10.^{79–85} Thus, following a chemical or photochemical initiation step, radical $R^\bullet$ arising from rupture of the C–S bond in xanthate **37** is rapidly captured by the starting xanthate to give adduct **38** (path **A**). This radical cannot easily undergo β -scission of the C–O bond, which in

this case would lead to symmetrical dithiocarbonate **39** and a high-energy ethyl radical (Path **B**). Cleavage of the C–S bond is much easier, but only returns the system to its original state, that is, back to $R^\bullet$ and the starting xanthate (Path **C**). The very fast addition–fragmentation is therefore a degenerate process that does not cause any macroscopic change in the system, but the constant regeneration of $R^\bullet$ means that its effective lifetime in the medium is increased dramatically. This “persistence” allows it to participate in various radical transformations, even ones with relatively slow kinetics. For example, addition to an olefin **40** leads to adduct radical **41**; this is followed by a rapid, reversible addition–fragmentation sequence to give finally a new xanthate **43** and radical $R^\bullet$, which can thus propagate the chain. The ethyl on the oxygen atom may be replaced by other groups as long as the corresponding radical is of similar (but preferably of lower) stability as compared to $R^\bullet$. For most applications, a primary substituent is sufficient (methyl, ethyl, neopentyl “*neoPn*,” etc.). *O*-Ethyl xanthates have by far been the most popular, simply



The unique properties and numerous subtleties of the system may be appreciated by examining more carefully the reaction manifold in Scheme 10. There is strong evidence to suggest that adduct radicals such as **38** and **42** are fairly persistent species. Their reaction with radicals of their kind or with other

Some of the far-reaching consequences of these observations are the following: (i) The *absolute* concentrations of the “active” radicals ($R^{\bullet}$ and **41**, and any radicals derived from the initiator) are considerably decreased, causing a very significant diminution in the importance of the termination steps. (ii) It is now possible to operate under very concentrated conditions, not only because the degenerate nature of the reaction of the initial radical $R^{\bullet}$ with its xanthate precursor means that this step does not compete with the desired addition to the olefinic trap **40**, but also because an increase in the concentration favors more the *bimolecular* formation of the “dormant” species in comparison to the *unimolecular* scission leading to the “active” radicals. The process is therefore self-regulating, in terms of keeping the concentration of the “active” radicals low, and thus quite forgiving with respect to modifications in the experimental

setup. (iii) Another consequence is that the *relative* concentrations of all the “active” radicals in the medium are controlled. To a first approximation, and neglecting polar factors, the rate of collapse of the “dormant” intermediates is greater when it leads to more stabilized radicals. Hence, the concentration of the thermodynamically more stable radicals will be higher than that of the less stabilized ones. For instance, a mere 2 kcal mol⁻¹ difference in relative stability between two “active” radicals will result in about 100-fold difference in their relative concentration. So, while the *absolute* steady-state concentrations of all the “active” radicals remain very low, their *relative* concentrations can still differ by several orders of magnitude.

This last property constitutes a key element for controlling the radical addition–transfer process. With the caveat noted above concerning polar factors, the components of the reaction must be selected such that the initial radical R[•] is more “stable” than the adduct radical **41**. In this manner, the fragmentation of the “dormant” intermediate **42** will be biased toward the former, and the steady-state concentration of R[•] will remain much higher than that of radical **41**. The desired addition thus stays favored over the unwanted oligomerization, which occurs by further addition of radical **41** to olefin **40**. Indeed, the greater the difference in stability between R[•] and **41**, the easier it is to control the process. These are crucial factors that have to be kept constantly in mind, especially when dealing with the more challenging *intermolecular* reactions.

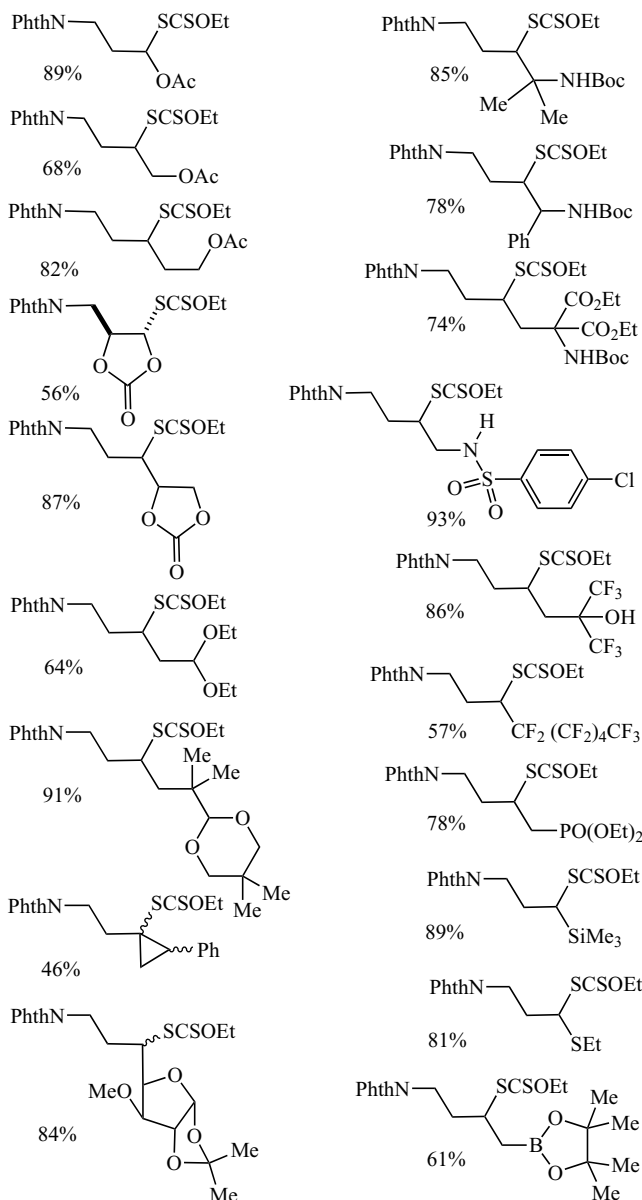
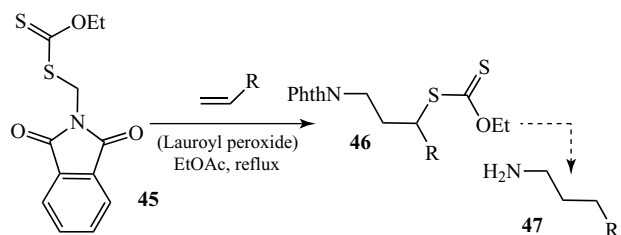
There are many advantages, practical and otherwise, attached to the use of the reversible addition–fragmentation of dithiocarbonyl derivatives: (i) The reagents are readily available, cheap, stable, and generally very easy to handle. (ii) The radical additions can be run under high concentrations, typically 1–2 M, and sometimes even without solvent (reduced waste). (iii) The reactions are atom-economical, since all the starting components end up in the product, and highly convergent in the case of the intermolecular variants. (iv) While numerous solvents can be used, including water, the environmentally benign and industrially acceptable ethyl acetate was found to be appropriate for most reactions. (v) No heavy metals are involved. (vi) The processes are self-regulating, safe, and easily scalable. (vii) Although peroxides are usually the preferred initiators for triggering the chain reaction, other initiators such as diazo derivatives, a

combination of triethylborane and oxygen, or irradiation with UV or even visible light, can be used in some cases. (viii) Numerous types of radicals may be directly generated and captured in an inter- or intramolecular fashion; these include not only functionalized alkyl radicals, but also acyl, alkoxy-carbonyl, alkoxythiocarbonyl, nitrogen-centered, and even tin-centered radicals. (ix) The product, being also a xanthate, can act as the starting point for another radical transformation or converted into a myriad derivatives using the exceedingly rich chemistry of sulfur. (x) One final, very important feature is that a classical chain process is not strictly necessary. If the adduct radical **41** (or, more generally, any intermediate radical involved in the actual process in hand) is electron-rich, it can often be oxidized by the peroxide into cation **44**, causing a crossover from a radical to a polar manifold. This oxidation is slow compared to the various radical steps, but it becomes of some importance when dealing with aromatic and heteroaromatic derivatives. In these situations, the peroxide behaves both as an initiator and as an oxidant, and therefore needs to be used in stoichiometric amounts.

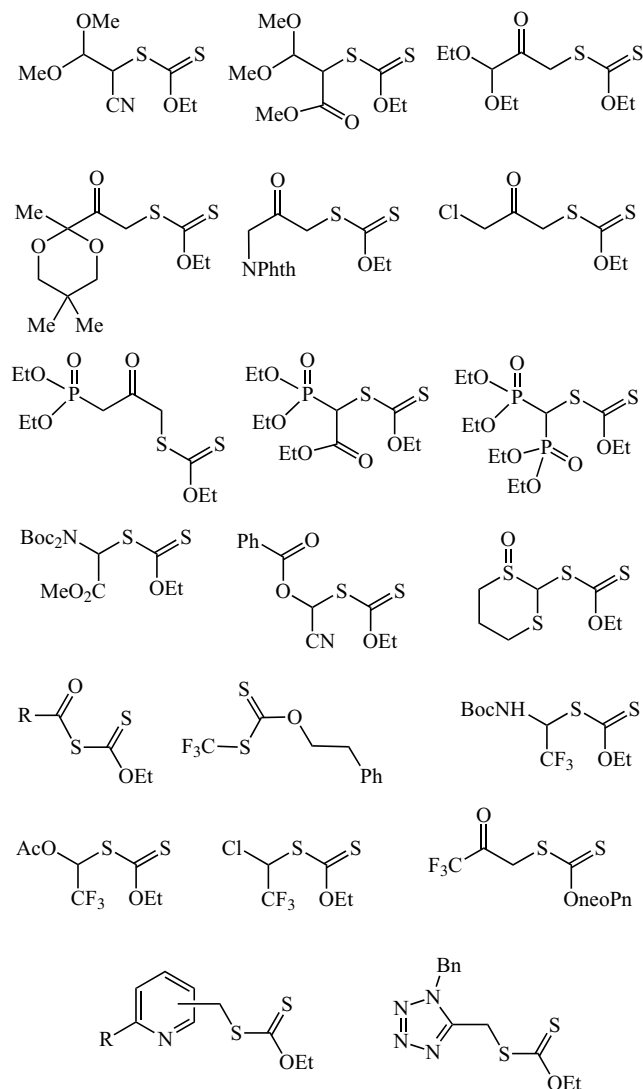
6 SOME EXAMPLES OF THE XANTHATE TRANSFER PROCESS

One of the key synthetic features of the xanthate transfer process is its ability to accomplish radical additions to unactivated alkenes and various other typically sluggish radical transformations that are not readily feasible by other methods. The additions of phthalimidomethyl xanthate **45** to various olefins pictured in Scheme 11 are representative.^{86–89} These transformations may be construed as the synthetic equivalent of an aminomethylation process, since reductive removal of the xanthate in the adduct **46** and deprotection would give amine **47**. It is worth pointing out that the phthalimido group exerts a stabilizing effect on intermediate primary radical PhthNCH₂[•], so that the condition for success detailed in point (iii) above is met.

Numerous functional groups are tolerated, both in the xanthate and in the alkene partner, allowing an almost infinite number of possible combinations. Indeed, more than 100 different xanthates have been examined and about 2000 additions performed since the discovery of the reaction in 1988.⁹⁰ Some



Scheme 11 Aminomethylation of alkenes.



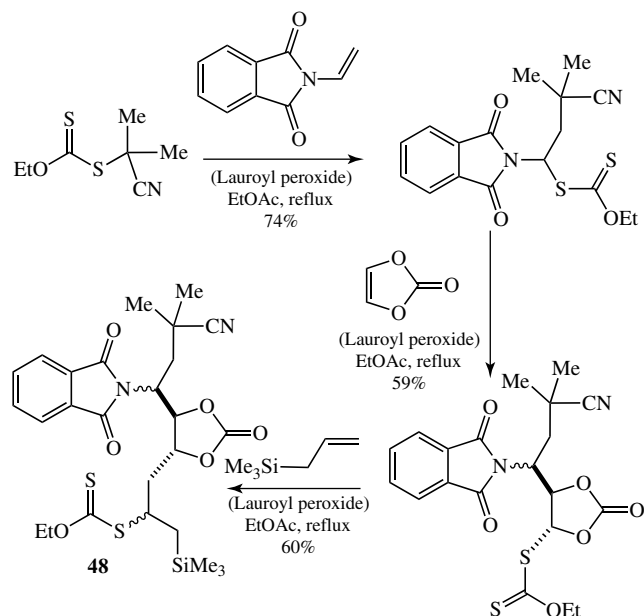
Scheme 12 Examples of xanthates that undergo addition to alkenes.

of the synthetically more interesting xanthates are compiled in Scheme 12.^{79–85}

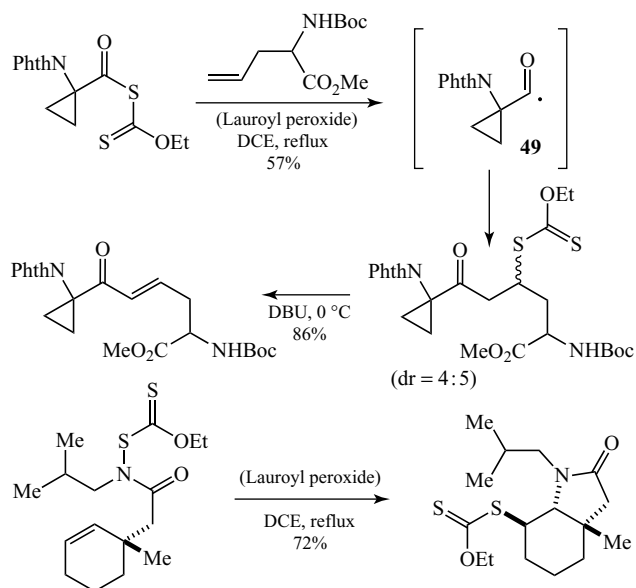
A particularly attractive feature of the system is that the product is also a xanthate, so a second, and sometimes a third, addition can be performed in succession, as long as the initial radical involved is more stabilized than the adduct radical (point (iii) above). This is illustrated by the sequence in Scheme 13, where successive additions to three different alkenes furnish a rather complex protected amine **48**.⁸⁸

Examples concerning the formation and capture of acyl and amidyl radicals are portrayed in Scheme 14. The case of cyclopropylacyl radical **49** is especially interesting, since no decarbonylation or ring opening of the cyclopropyl ring apparently takes place.⁹¹ In the case of nitrogen-centered radicals, only intramolecular reactions have so far been accomplished.⁹²

Ring formation is another area where the xanthate transfer proves useful. In addition to easily formed five-membered rings, it is often possible to construct



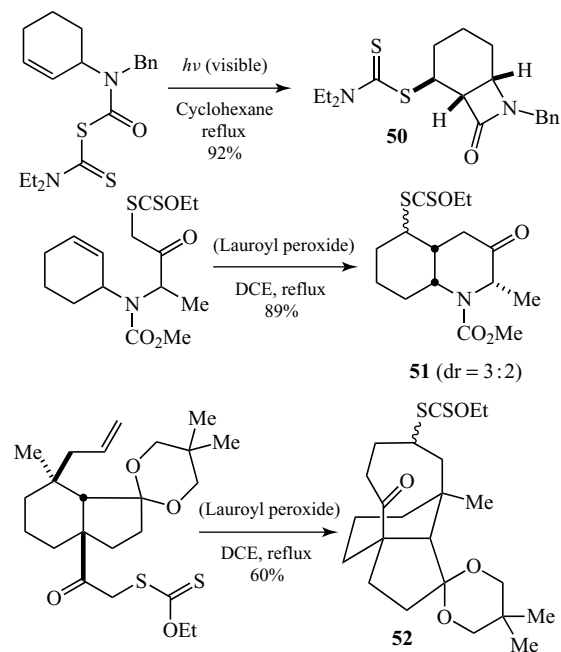
Scheme 13 Example of successive additions to three different olefins.



Scheme 14 Examples of generation and capture of cyclopropylacyl and amidyl radicals.

four-, six-, seven-, and even eight-membered rings by direct cyclization. The transformations assembled in Scheme 15 are illustrative. The formation of azetidinone **50** involves ring closure of a carbamoyl

radical, and for these an *S*-acyl dithiocarbamate precursor proved superior to the corresponding xanthate.⁹³ The cyclization leading to piperidinone **51** is a key step in a formal synthesis of lepadin B,⁹⁴



Scheme 15 Examples of formation of four-, six-, and eight-membered rings.

whereas the formation of the eight-membered ring in **52** allows the swift construction of the pleuromutilin skeleton.⁹⁵

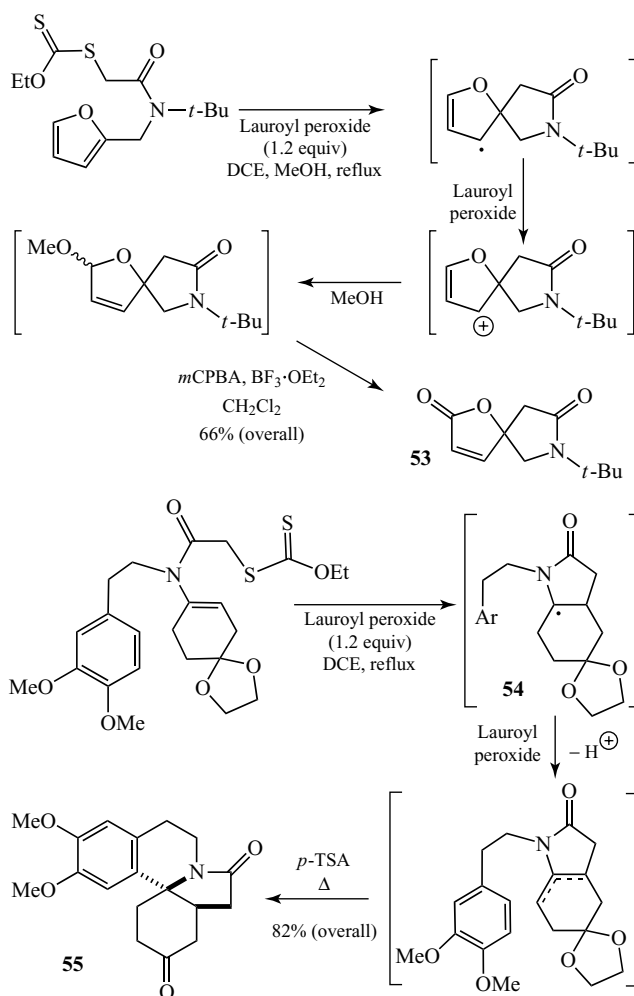
The fact that a peroxide may be used both as an initiator and an oxidant, discussed in point (x) above, allows a crossover into a cationic manifold and expands considerably the scope of this technology. The first transformation in Scheme 16 illustrates an ipso reaction on a furan ring, leading ultimately, after further oxidation, to a spirolactone structure **53**.⁹⁶ The second example concerns a difficult 5-*endo* ring closure to give an easily oxidized radical **54**. The final product is a mixture of two isomeric cyclic enamides, which is readily converted into tetracycle **55** possessing the erythrina skeleton.⁹⁷ The lauroyl peroxide in both examples needs to be used in stoichiometric amounts.

More interesting, perhaps, is the possibility of constructing polycyclic aromatic molecules by a direct ring closure on aromatic and heteroaromatic rings. The sequence in Scheme 17 showcases the synthesis of indolines and the multiple uses of chloroacetyl xanthate **56**.⁹⁸ Thus, intermolecular addition followed by cyclization onto the aromatic ring furnishes indoline **57**, which can be readily

converted into a new xanthate **58** by nucleophilic displacement of the chlorine with potassium *O*-ethyl xanthate. This allows a second intermolecular addition, this time to vinyl pivalate, leading to adduct **59**, where the carbon bearing the xanthate and the pivalate groups is in fact a latent aldehyde. Heating this compound with cyclopropylamine in the presence of acid gives rise to pyrrole **60** by a variation on the classical Paal–Knorr synthesis.⁹⁹

The possibility of constructing six-membered rings by direct cyclization onto an aromatic ring may be exploited for the synthesis of tetralones. Two examples are depicted in Scheme 18.¹⁰⁰ The first is a short synthesis of (±)-shinanolone **63**, whereas the second leading to tetralone **64** underscores the complexity that can be rapidly attained and the mildness of the experimental conditions. Two key carbon–carbon bonds are thus created in succession without the epoxide ring being affected. Both these examples are also noteworthy because substrate **61** is a naked phenol. The hydrogen bonding decreases the rate of abstraction of the phenolic hydrogen and freezes the side chain in a conformation that is propitious for ring closure. The result is a significant increase in yield at the cyclization step. Another interesting aspect is that tetralones such as **62** are readily converted into naphthols by simple heating with *p*-TsOH in toluene.¹⁰¹ Indeed, this approach is highly flexible and provides a practical and versatile access to naphthalenes and naphthols with almost any substitution pattern.

Numerous aromatic derivatives to which five-, six-, and sometimes even seven-membered rings are fused can be accessed in a simple, straightforward manner. The same approach can be extended to encompass heteroaromatic structures of interest to medicinal chemists (see Refs 79–85 for a more extensive overview). The case of pyridines is especially important. This heteroaromatic ring is a recalcitrant partner in Friedel–Crafts reactions, and the pool of halogenated and other pyridine derivatives capable of participating in organometallic couplings is comparatively limited in comparison with the benzene series. The xanthate transfer technology is therefore especially attractive since radicals add more readily to the pyridine nucleus than to a benzene ring, and the addition is less reversible. A typical approach providing a 6-azaindoline and a 6-azaindole is outlined in Scheme 20.^{102,103}

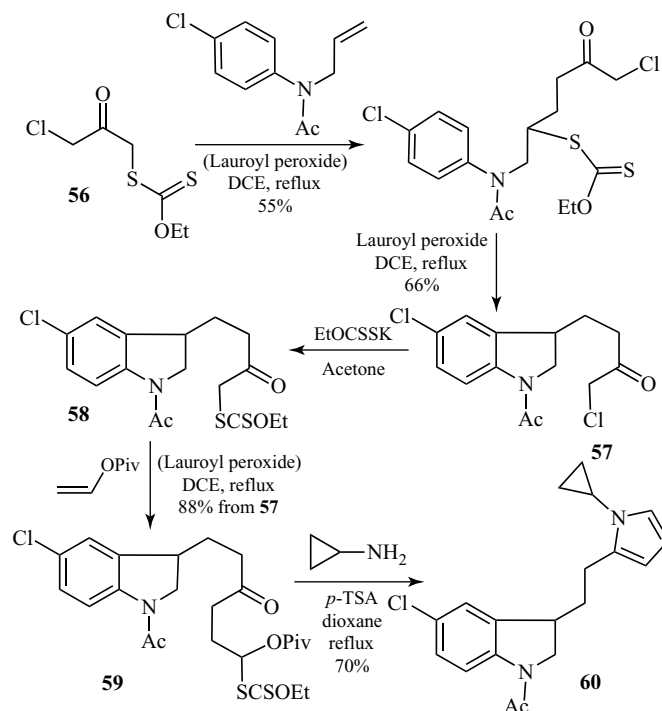


Scheme 16 Examples of radical–polar crossover reactions.

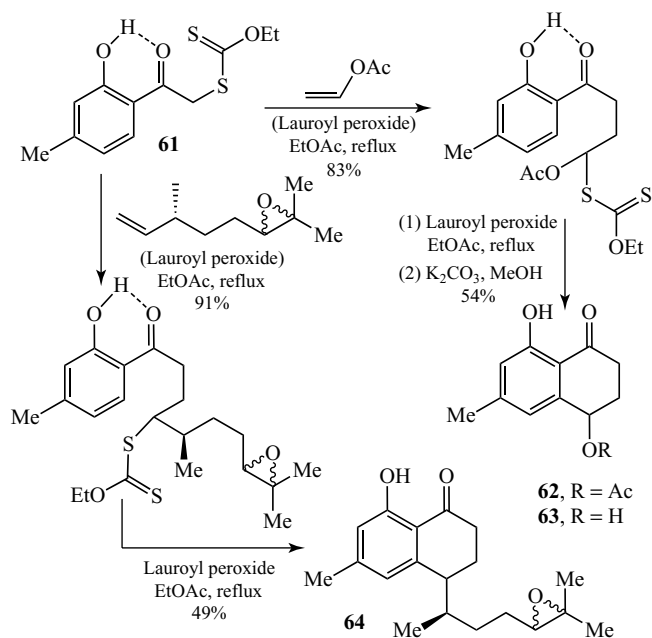
In many of these synthesis, the intermolecular addition and the ring closure onto the aromatic can be performed in one pot. With the more reactive heteroaromatic derivatives, such as indoles, the ring closure may in fact be difficult to avoid. An addition–cyclization process was used in a short, formal synthesis of mersicarpine, an alkaloid with an interesting tetracyclic structure (Scheme 19).¹⁰⁴ Because of the presence of the electron-withdrawing ester group, it proved necessary to complete the aromatization process by addition of manganese dioxide. Indole rings are sufficiently reactive to allow *intermolecular* additions to proceed in some cases. The one-step

synthesis of azetidinone derivative **65** is illustrative.¹⁰⁵ Other heteroaromatic rings, such as pyrroles, furans, and thiophenes, may sometimes be cleanly substituted.^{106–108}

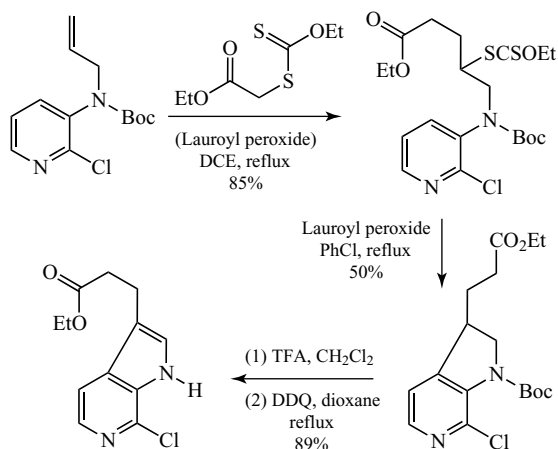
One interesting, and quite unusual, transformation involves a radical addition *on the nitrogen atom* of certain pyridine and pyrimidine derivatives.^{109,110} The reaction ultimately leads to pyridones and pyrimidones, once the intermediate adduct radical is oxidized by the peroxide. One such sequence involving a pyrimidine substrate is presented in Scheme 21.¹⁰⁹ New and richly substituted heterocyclic scaffolds such as **66** can thus be cobbled together very simply, for example by selecting



Scheme 17 Synthesis of an indoline by a radical cyclization onto an aromatic ring.



Scheme 18 Synthesis of hydroxytetralones.



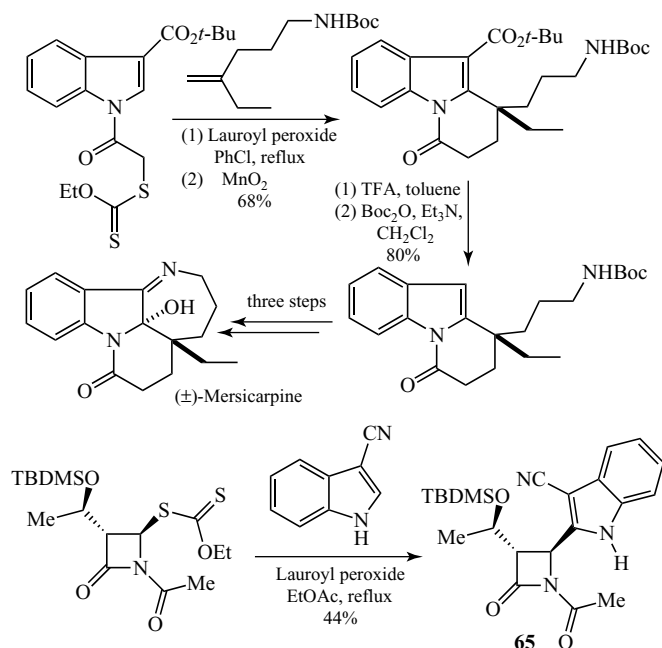
Scheme 19 Synthesis of 6-azaindoles and 6-azaindoles.

various xanthate partners from the assortment displayed in Scheme 12.

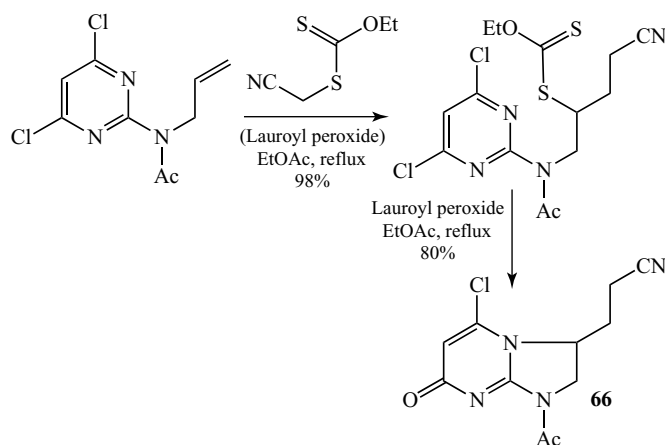
Some of the examples above have illustrated how the xanthate group in the adduct may be exploited in further radical processes. There are in fact many more radical-based transformations that could be of synthetic interest. The xanthate group may be simply removed by applying any

of the reagents used for the Barton–McCombie deoxygenation.^{79–85} Indeed, because it is the weaker C–S bond that needs to be broken instead of the strong C–O bond, these reductions are invariably faster and more efficient.¹¹¹ The xanthate group may be exchanged with a sulfide,¹¹² a bromine atom,¹¹³ or an azide.^{114–119} New carbon–carbon bonds may be created by exposing the xanthates to various radical traps bearing suitable leaving groups, such as a tributylstannyl,¹²⁰ an alkylsulfone,^{121–126} a diphenylphosphine oxide,¹²⁷ or an epoxide.¹²⁸ In the last case, a combination of triethylborane and oxygen has to be used to mediate the reaction. Four assorted examples are collected in Scheme 22.

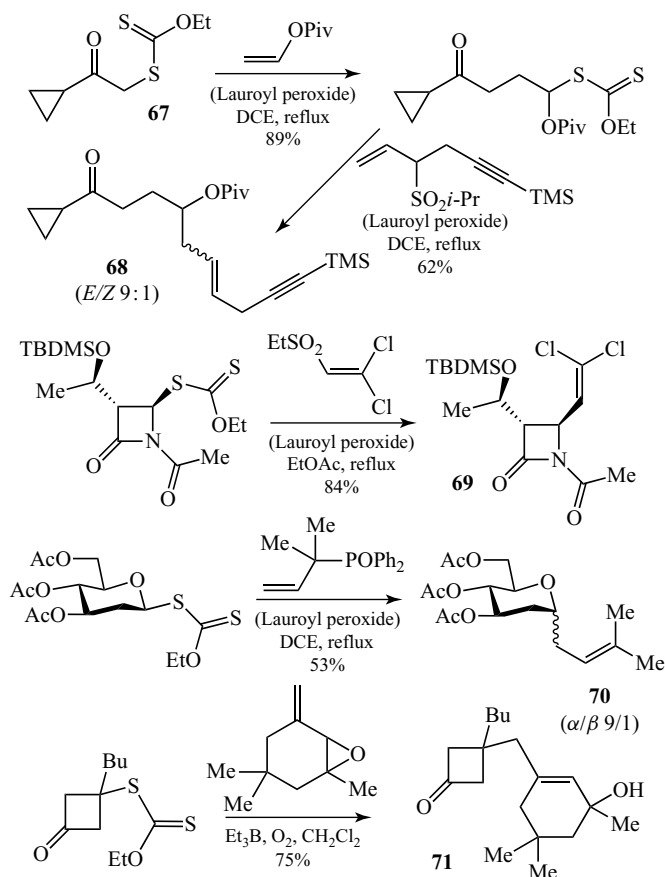
The first underscores yet again the potential of xanthates for rapidly building up complexity, since xanthate **67** can initially be added to vinyl pivalate, and the adduct then subjected to an allylation reaction to give skipped enyne **68** in good yield.¹²¹ The second example also uses a sulfone reagent to introduce a dichlorovinyl group on the β -lactam ring.¹²² Compound **69** is thus obtained stereoselectively and in high yield. The use of a phosphine oxide as a prenylating agent is illustrated by the third transformation leading to deoxyglucose derivative



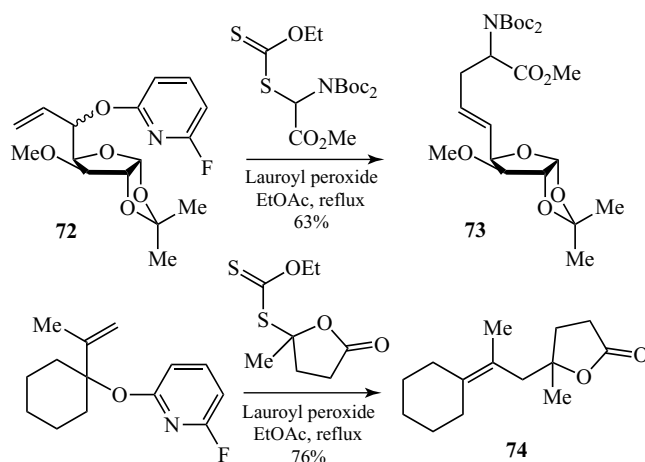
Scheme 20 Reaction of xanthates with indoles.



Scheme 21 Synthesis of dihydro-imidazopyrimidinones.



Scheme 22 Examples of radical allylations and vinylation of xanthates.



Scheme 23 Allyl alcohol derivatives as radical allylating agents.

70.¹²⁷ Finally, the efficient formation of allylic alcohol **71** through the triethylborane/oxygen-mediated addition of a xanthate to a vinyl epoxide highlights the easy creation of a quaternary center on a cyclobutanone.¹²⁸

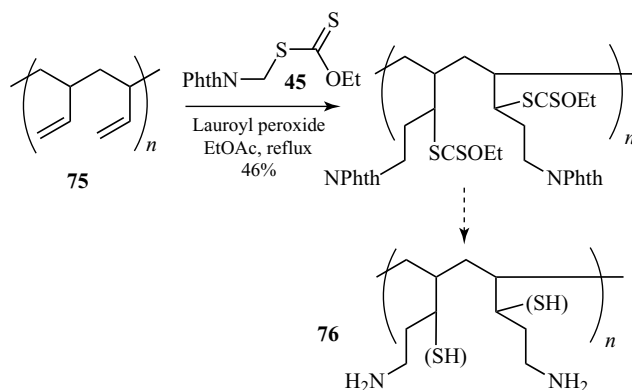
Except for epoxides, it is generally not easy to cleave homolytically a normal C–O bond. Recently, it was found that the fluoropyridinyloxy group indeed undergoes homolysis of the C–O bond and can therefore act as a leaving group in a radical sense.¹²⁹ Two examples are shown in Scheme 23. The first corresponds to the synthesis of a protected carbohydrate amino acid **73** starting with activated derivative **72**, whereas the second illustrates the formation of a tetrasubstituted alkene **74**. Since the precursor allylic alcohols are themselves usually made by addition of a vinyl metal to a ketone or an aldehyde, the overall process may be construed as a synthetic equivalent of the Wittig olefination. One of the advantages of this approach is that tetra-substituted and otherwise crowded alkenes, such as **74**, that are not easily accessible by a direct Wittig condensation, can be readily obtained by the present addition–elimination of a xanthate.

7 OUTLOOK AND PERSPECTIVES

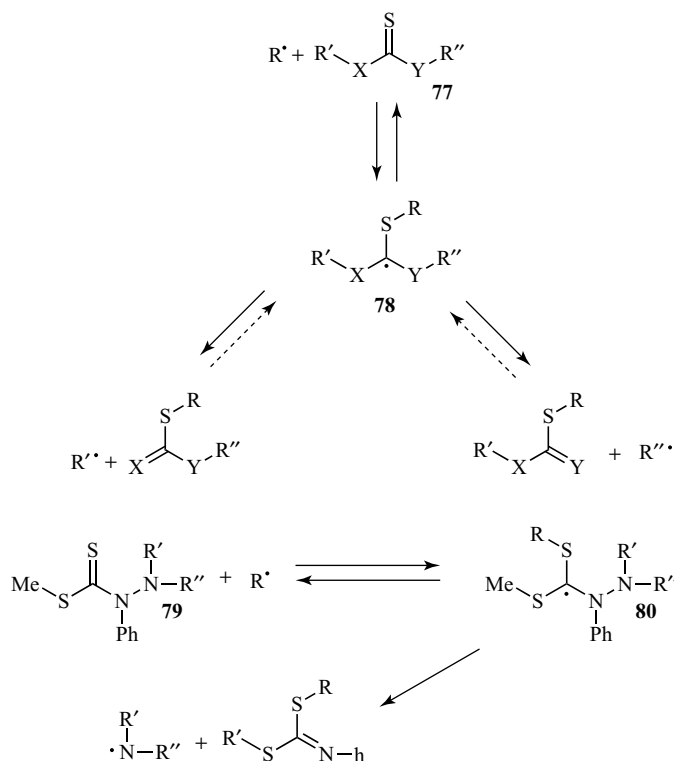
It is a true wonder that a modest looking functional group such as a xanthate could harbor such a rich and varied radical chemistry. The

Barton–McCombie deoxygenation is still unparalleled in its potency as a method for generating radicals from alcohols. The degenerative xanthate transfer represents a good solution to a long-standing problem in organic synthesis, namely the *intermolecular* formation of carbon–carbon bonds starting with unactivated alkenes. The possibility of iterating the addition of xanthates and related compounds of general structure (RSC(=S)Z) to polymerizable alkenes (monomers) constitutes the basis of the very powerful RAFT-MADIX controlled polymerization technology. This has become a topic of intense research and is discussed in detail elsewhere in this encyclopedia (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**). It is nonetheless worthwhile pointing out that, in addition to the construction of block polymers of almost any architecture, the xanthate transfer can be employed to modify existing polymers. Thus, addition of xanthate **45** to commercial 1,2-polybutadiene **75** shown in Scheme 24 is a representative example; it could in principle be exploited to provide a long-chain polyamine **76** with or without sulfur residues.⁸⁶ The reaction is in practice trivial to conduct, and many functional groups besides amines can be introduced in this manner.

The radical chemistry of xanthates is just a particular case of a broader reaction pattern that can be envisaged for thiocarbonyl derivatives of general formula **77** (Scheme 25). Their reaction with a given radical R[•] (not necessarily carbon-centered)



Scheme 24 Modification of 1,2-polybutadiene.



Scheme 25 General reaction manifold for thiocarbonyl derivatives.

is in principle reversible and leads to a key intermediate **78**. This species can collapse in two ways depending on the nature of X and Y and, to a first approximation (i.e., neglecting polar factors), the relative stabilities of R' and R''. This generic scheme encompasses, for instance, the Barton–McCombie deoxygenation with all the

variations on the precursors, the reversible addition–fragmentation transfer of xanthates and other thiocarbonylthio derivatives (dithioesters, dithiocarbamates, trithiocarbonates), and the Barton decarboxylation involving thiohydroxamic esters (Barton esters). By modifying the substituents in **77**, numerous other useful radical processes can be conceived.

One illustration is the behavior of thiosemicarbazide **79**, which gives intermediate **80** upon radical addition. The comparative weakness of the N–N bond now directs the fragmentation toward the formation of a nitrogen radical. Indeed, thiosemicarbazides and kindred derivatives have emerged as perhaps the best precursors for nitrogen radicals, especially iminyls and amidyls.^{130–133}

Hopefully, the present brief overview will give an idea of the scope and synthetic potential of the radical chemistry associated with xanthates and their relatives. Notwithstanding the variety of transformations described herein, some of which may indeed be viewed as solutions waiting for a problem, this area of research is still in its infancy and much remains to be explored and discovered.

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Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions

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1 INTRODUCTION

A promising approach to radical generation is constituted by Lewis acidic activation of and electron transfer to the heterocycle by a low valent metal complex that can potentially act as a catalyst. A first example of an epoxide opening of this type was published by the group of Kochi. They deoxygenated cyclohexene oxide with Cr(II) reagents.¹

In 1988 Nugent and RajanBabu^{2–5} introduced Cp₂Ti(III)Cl as a reagent for epoxide opening through electron transfer. The opening of the epoxide by titanium can be regarded as analogous to the opening of the cyclopropylcarbinyl radical (Scheme 1).^{6–13}

Cp₂Ti(III)Cl is still the most useful reagent for epoxide opening because of its high selectivity and the broad range of consecutive reactions. With titanocene(III) reagents, the typical radical reactions, such as hydrogen atom abstraction,² intermolecular additions to activated olefins,³ and cyclizations of the β -titanoxy radicals formed after ring opening⁴ can be exploited. However, epoxide deoxygenations have also been developed and these reactions are discussed first.

2 EPOXIDE DEOXYGENATION

Usually, epoxide deoxygenations are not highly attractive because epoxides are normally prepared from olefins.

This changes when epoxides are readily available from compounds that are already highly oxidized, such as carbohydrates and their derivatives, or when the resulting olefins are different from the epoxide substrates. The deoxygenation of epoxides was applied in useful transformations of highly functionalized substrates like **1**.

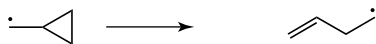
The preparation of **2**⁵ that is rather unstable in 66% yield, which failed by other routes, is remarkable (Scheme 2).¹⁴

Anhydrovinblastine, an important intermediate for the anticancer drug navelbine, was prepared from leurosine, an abundant alkaloid, in 70% yield by using Cp₂TiCl.^{15,16} Stereospecific deoxygenations in the cryptophycin family of natural products from Nostocaceae were also reported.¹⁷

A deoxygenation using enantiomerically pure **3** to give the enantiomerically pure **4** was described (Scheme 3).¹⁸ This approach circumvented Sharpless' kinetic resolution, which implies a maximum yield of 50%.^{19,20}

The competition between radical trapping leading to deoxygenation and mixed disproportionation, a hydrogen atom abstraction on the carbon adjacent to a radical by another radical, has been discussed recently (Scheme 4).²¹

The conversion of 1,3-diepoxydes to 2-ene-1,4-diols has been reported in the context of the synthesis of dihydrotaxoid derivatives.²²



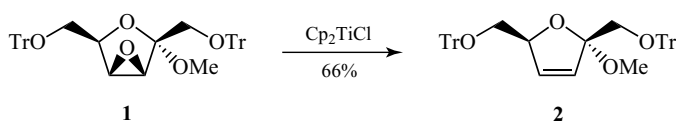
3 REDUCTIVE EPOXIDE OPENING TO ALCOHOLS



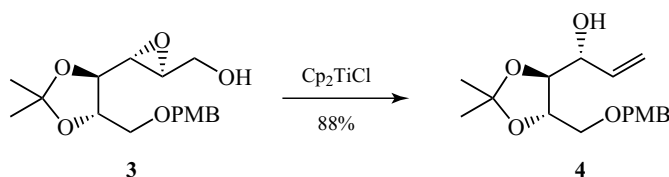
3.1 Introductory Remarks

Scheme 1 Synthesis of β -titanoxy radicals from epoxides by the strategy of Nugent and RajanBabu.

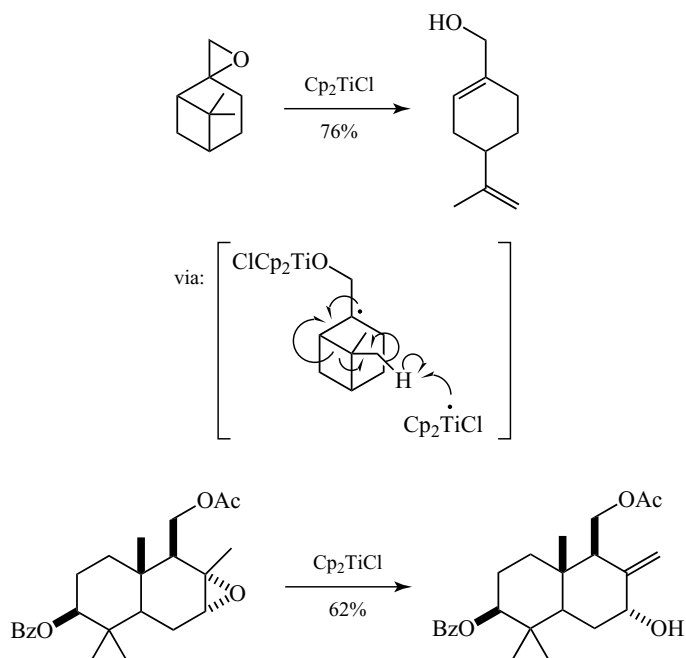
So far, $\text{Cp}_2\text{TiCl}^{2,5}$ constitutes the only efficient reagent reported for carrying out this reductive



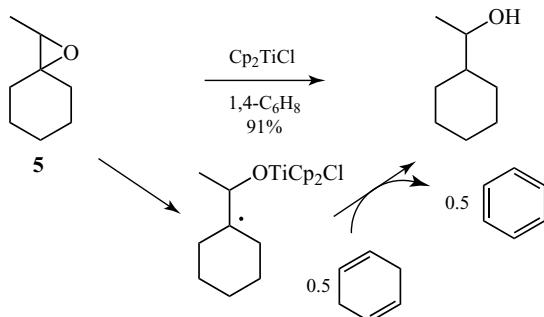
Scheme 2 Titanocene-mediated deoxygenation of highly functionalized epoxides.



Scheme 3 Deoxygenation of β -hydroxyepoxides leading to enantiomerically pure allylic alcohols.



Scheme 4 Mixed disproportionation of epoxides through hydrogen atom abstraction.



Scheme 5 Mechanism of titanocene-mediated reductive epoxide opening.

epoxide opening. The β -titanoxy radicals were initially reduced by hydrogen atom donors, for example, 1,4-cyclohexadiene or *tert*-butyl thiol. The highly regioselective opening of unsymmetrical epoxides such as **5** (Scheme 5) to give the less substituted alcohols is especially important.

In the case of monosubstituted epoxides up to 33% of deoxygenation and a lower regioselectivity (90:10) in favor of the primary alcohol were observed.⁵ Therefore, the method complements the typical opening of epoxides with hydrides²³ via S_N2 and is much more chemoselective.

3.2 Structure of the Reagent and Mechanism of Ring Opening

Daasbjerg and Skrydstrup have disclosed electrochemical studies on the structure of titanocene(III) reagents in solution.²⁴ It was established that the reduction of Cp_2TiCl_2 with either Mn or Zn leads to the same redox active intermediate. Most likely, the active species in ring opening was not Cp_2TiCl , which is in equilibrium with its dimer²⁵, but the, half-open dimer. Also, the effect of counterions on the reagents' structures was examined.

The transition structures and intermediates were studied by DFT methods.^{26,27} All epoxide openings were exothermic and, in agreement with the experiments, the higher substituted radicals were predicted to be formed preferentially. The regioselectivity of epoxide opening was correctly predicted for the case of propene oxide (9:1). The reasons for the formation of the higher substituted radical are mainly of steric nature because in the early transition structure, the spin density on the developing radical center is low.

3.3 Synthetic Applications

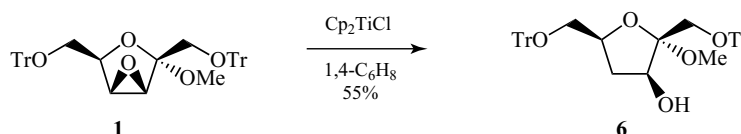
High regioselectivity of ring opening is not confined to unsymmetrical substitution patterns of the epoxide. In 1,2-disubstituted epoxides, excellent results could be therefore observed in many cases,²⁸ for example, exclusive formation of **6** from **1** (Scheme 6).⁵ Most likely, this is also due to steric reasons.

Sharpless epoxides²⁹ and their derivatives are especially valuable substrates in this respect. From these compounds, Nugent and RajanBabu were the first to reduce these radicals to prepare 1,3-diols.⁵ The regioselectivity of epoxide opening was excellent (94:6). Other, more elaborate 1,3-diols could also be obtained.^{30–32} Various 2-methyl-1,3-diol frameworks were synthesized (Scheme 7) and tetrahydrofuran (THF) was proposed as hydrogen donor even though this seems less likely.³³

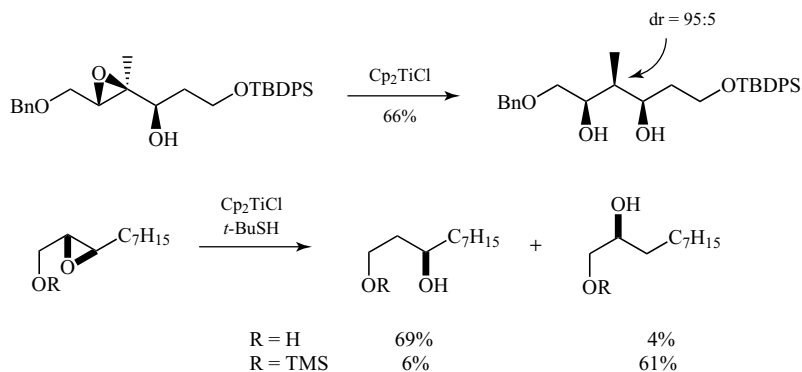
The ring opening to 1,2-diols was first obtained when the hydroxy group was converted into the trimethylsilyl ether.

Both methods compared very well with the established nucleophilic conditions for regioselective epoxide opening using hydride reagents.³⁴

Also, α,β -epoxy ketones could be opened with Cp_2TiCl in good to excellent yields³⁵ and performed even better than SmI_2 .^{36–43}



Scheme 6 Regioselective opening of 1,2-disubstituted epoxides by RajanBabu and Nugent.



Scheme 7 Regioselective epoxide opening in the formation of 1,3- and 1,2-diols.

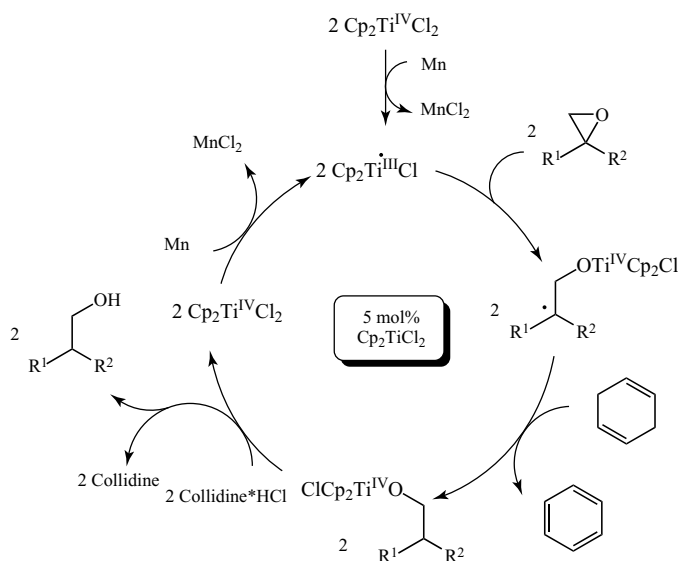
3.4 Titanocene-Catalyzed Reductive Epoxide Opening

In general, the use of the titanocenes in catalytic amounts is attractive especially for reagent-controlled radical reactions.^{44–48} The solution of the conceptually similar problem of achieving catalytic turnover^{49,50} in McMurry couplings,⁵¹ Nozaki–Hiyama reactions,^{52,53} and pinacol couplings^{54,55} had been reported by Fürstner and by Hirao by *in situ* silylation of titanium, vanadium, and chromium oxo species with Me_3SiCl . In the case of the epoxide openings, Me_3SiCl was not an

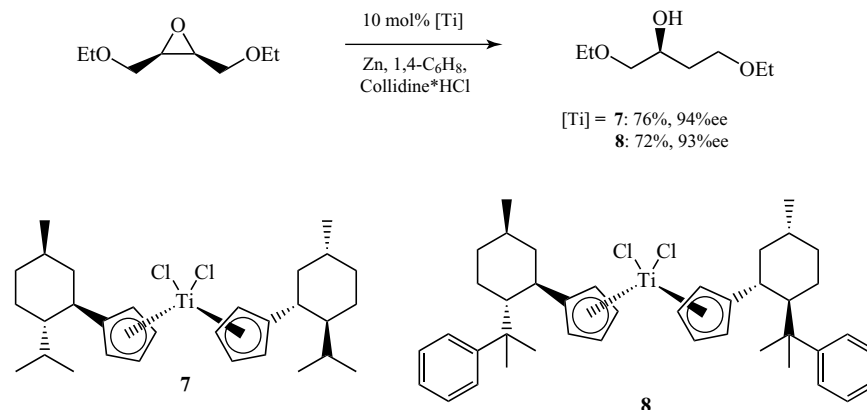
appropriate reagent for the cleavage of a titanium alkoxide because of the high Lewis acidity of silicon that lead to undesired epoxide opening.

Substituted pyridine hydrochlorides^{56–63} emerged as excellent mediators for catalysis. Lutidine and especially collidine hydrochloride performed best in the presence of manganese dust as stoichiometric reductant. The resulting catalytic cycle preserving all attractive features of the stoichiometric reaction is shown in Scheme 8.

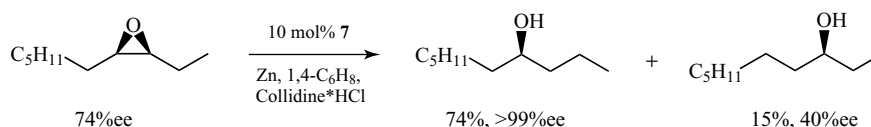
The catalytic conditions proved valuable in the enantioselective opening of *meso*-epoxides through electron transfer with preferential cleavage



Scheme 8 Mechanism of the titanocene-catalyzed reductive epoxide opening.



Scheme 9 Enantioselective reductive opening of *meso*-epoxides.



Scheme 10 Regioselective epoxide opening (REO) of 1,2-disubstituted epoxides.

of one of the enantiotopic C–O bonds of the epoxide.^{64–66} Surprisingly, complex **7** possessing the substitution pattern of menthol was as efficient as the phenylmenthol-derived catalyst **8** (Scheme 9).⁶⁷

This concept could be extended to the regiodivergent opening of racemic and enantiomerically enriched epoxides (Scheme 10).^{68,69} In these substrates, the C–O bonds are diastereotopic and can be cleaved with a high degree of catalyst control. The products obtained are interesting for applications in the synthesis of biologically active substances.

3.5 Sustainable Hydrogen Atom Donors

A disadvantage of the reduction of the β -titanoxy radicals by large excesses of 1,4-cyclohexadiene or γ -terpinene is constituted by the generation of stoichiometric amounts of waste, which in the case of benzene is highly toxic.

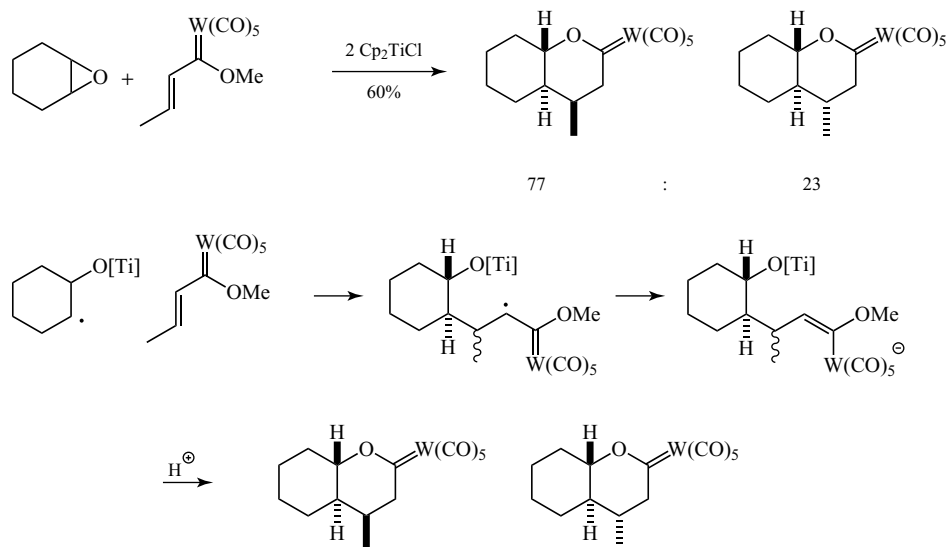
It has been demonstrated that titanocene(III) reagents activate water and methanol toward hydrogen atom transfer by substantially lowering the bond dissociation energy (BDE) of the OH-bond.^{70,71} Gratifyingly, this most remarkable reagent combination is also chemically more efficient than the

cyclohexadienes and environmentally more benign. Additionally, D₂O can be used to deuterate the radicals formed.⁷² In the presence of collidinium hydrochloride, the reaction can also be performed catalytically in titanocene.

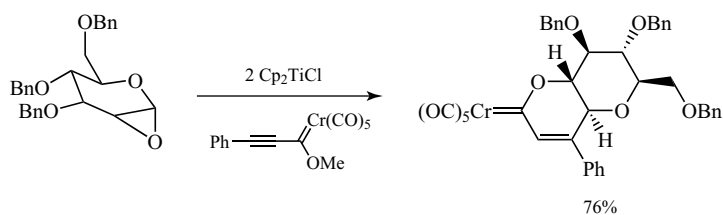
Another attractive hydrogen atom donor is H₂. It has recently been demonstrated that hydrogen atoms can be transferred from classical hydrogenation catalysts to β -titanoxy radicals in a system comprised of two coupled catalytic cycles.^{73,74} It turned out that Wilkinson's catalyst performed very well in this respect, whereas heterogeneous catalysts were not suitable. It remains to be seen if these novel HAT systems can also be employed in enantioselective radical reductions.

4 INTERMOLECULAR ADDITION REACTIONS TO ACTIVATED ALKENES

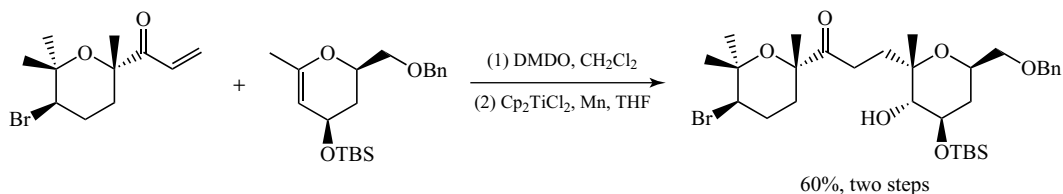
Epoxide-derived radicals generated under the very mild reaction conditions of titanocene-mediated and -catalyzed electron transfer are excellent intermediates for intermolecular C–C bond forming reactions.^{3,5} The resulting products, δ -hydroxy



Scheme 11 Synthesis of functionalized tungsten carbenes by Merlic *et al.*



Scheme 12 The first use of glycol epoxides as radical precursors by Dötz and Gomes da Silva.



Scheme 13 Intermolecular addition of β -titanoxy radicals onto activated alkenes in the synthesis of thysiferol.

esters, nitriles, amides, and δ -lactones constitute valuable building blocks.

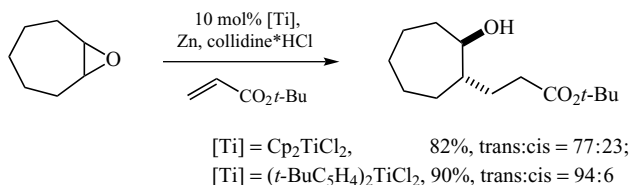
The efficient addition of epoxide-derived radicals to α,β -unsaturated chromium and tungsten carbene complexes as reactive radical acceptors (Scheme 11) highlights the mildness of the conditions.^{75,76}

Extensions of this concept by using sugar-derived carbenes as radical acceptors and by adding radicals derived from the rather sensitive glycol epoxides to α,β -unsaturated carbenes were also investigated

(Scheme 12).⁷⁷ The products obtained are of interest for the synthesis of biologically active substances.

The same system for the addition of carbohydrate-derived radicals was applied with simple organic acceptors with the same selectivities as above.⁷⁸ The same procedure was used in a remarkable approach toward thysiferol (Scheme 13).

The catalytic conditions were well suited for the preparation of δ -hydroxyesters, lactones, and δ -hydroxynitriles.⁶⁰ In this case, alkyl substituted



Scheme 14 Reagent-controlled diastereoselectivity in the addition to acrylates.

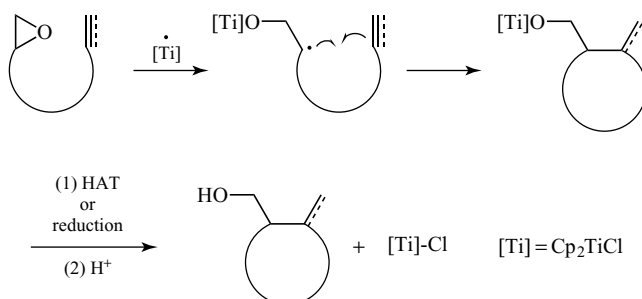
titanocenes constituted more efficient catalysts for the often highly diastereoselective addition of radicals to α,β -unsaturated carbonyl compounds (Scheme 14).⁶⁶

The preferential formation of the trans isomers was explained by the shielding of the radicals by the bulky ligands.

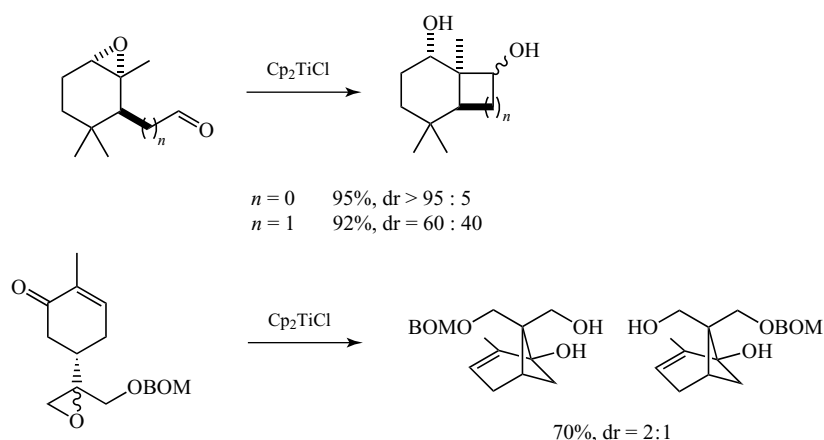
Finally, epoxides derived from vinylsilanes have been added to activated olefins, such as acrylonitrile, to obtain synthons for the preparation of functionalized 1,2-diols.⁷⁹

5 TITANOCENE-MEDIATED AND -CATALYZED CYCLIZATIONS

Cyclization reactions,⁸⁰ especially 5-exo cyclizations,⁸¹ have been of outstanding importance to radical chemistry mechanistically and synthetically. Titanocene-mediated and -catalyzed cyclizations have been demonstrated as very attractive in this respect. A schematic mechanism of such cyclizations is depicted in Scheme 15.



Scheme 15 Schematic mechanism of the titanocene-mediated cyclization of unsaturated epoxides.



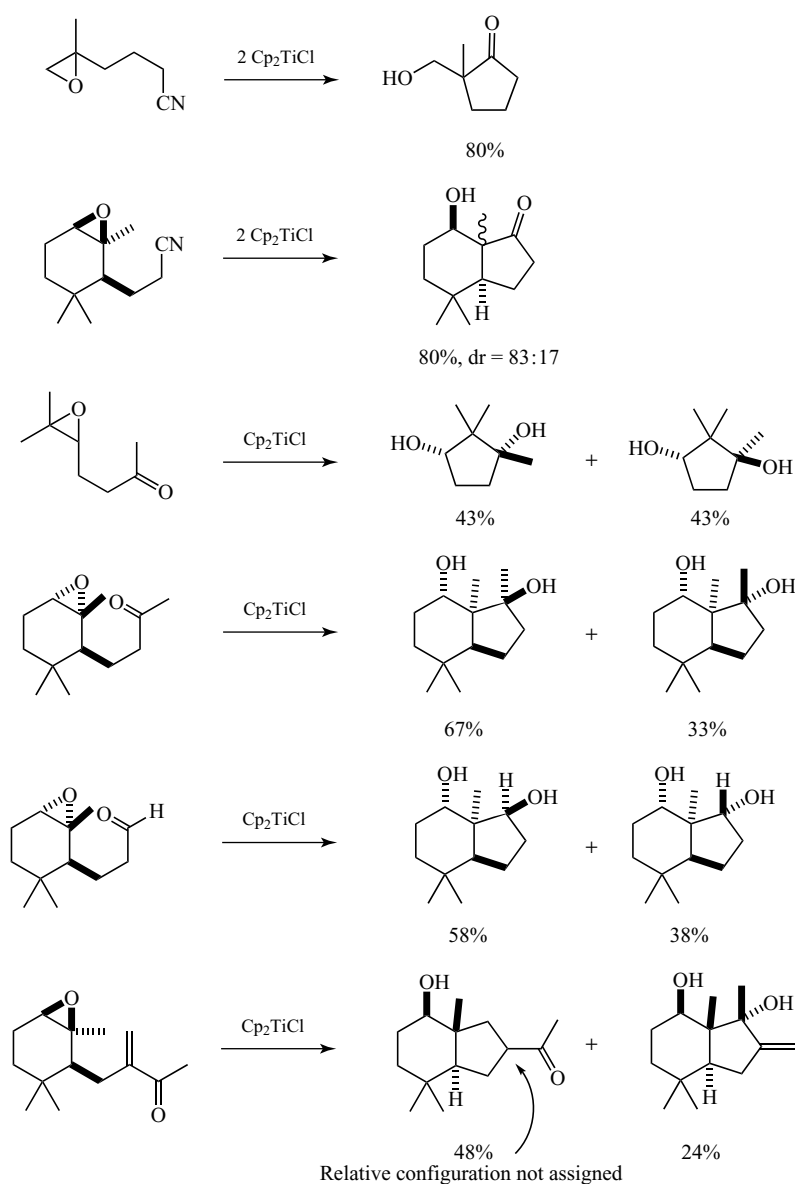
Scheme 16 3-exo and 4-exo Cyclizations by intramolecular addition to aldehydes and ketones.

5.1 3-exo and 4-exo Cyclizations

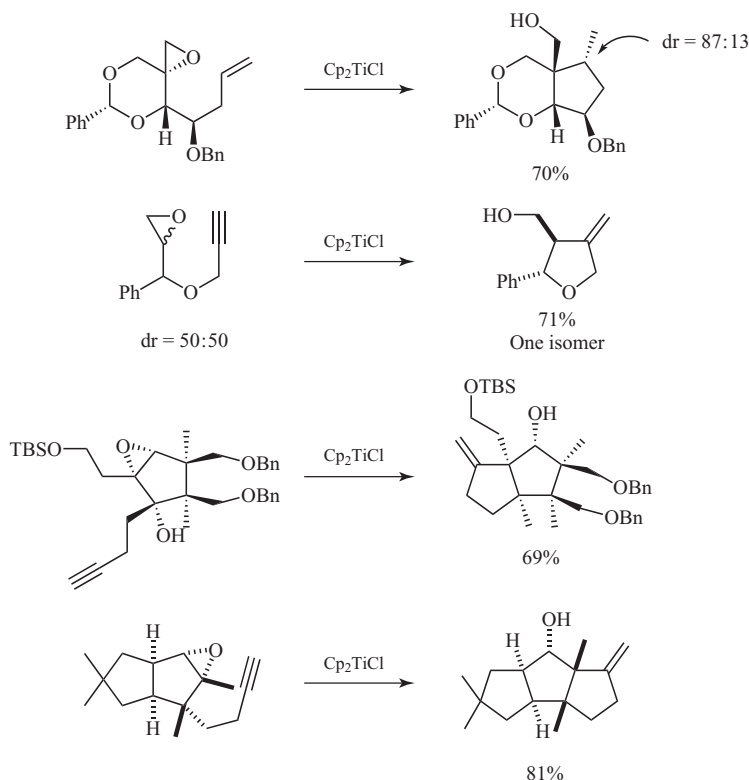
The synthesis of small rings via 3-exo and 4-exo cyclizations is considered difficult owing to the high strain of cyclopropanes and cyclobutanes. As a consequence, cyclopropyl- and cyclobutylcarbinyl radicals usually give the ring opening butenyl and pentenyl radicals. With the aid of titanocene complexes, it has been demonstrated in recent years

that this problem can be circumvented by a selective trapping of electrophilic radicals generated through cyclization of nucleophilic radicals.⁸² This has been first exploited in the synthesis of cyclopropanols and cyclobutanols by intramolecular radical addition to aldehydes and ketones as shown in Scheme 16.^{83,84}

Cyclobutanones can be prepared with nitriles as radical traps either stoichiometrically⁸⁵ or catalytically.⁸⁶ Cyclopropanes and cyclobutanes can be



Scheme 17 Titanocene-mediated 5-exo cyclizations.



Scheme 17 (continued)

obtained with α , β -unsaturated carbonyl compounds as radical acceptors.^{82,87–90} Remarkably, even the easily reduced enones are suitable acceptors.

5.2 5-exo Cyclizations

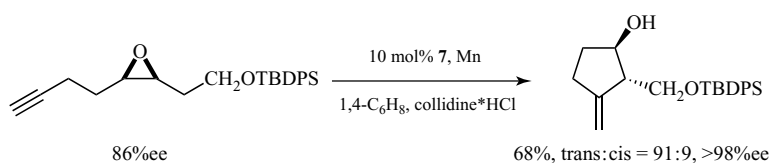
Since the initial report by Nugent and RajanBabu⁴ and the development of the catalytic conditions,^{56–63} many examples of 5-exo cyclization have been reported. The cyclizations are especially powerful in the generation of radicals from highly functionalized epoxides with groups that were typically not tolerated under the conditions of other organometallic

or cationic reactions. Some of the many impressive examples are shown in Scheme 17.^{5,83,85,91–95}

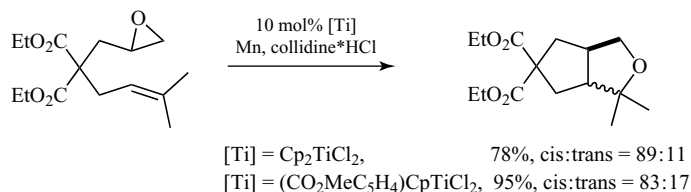
The reaction of epoxy formates with titanocene leads to the synthesis of useful hydroxy lactols.⁹⁶

Titanocene-catalyzed 5-exo cyclizations can be combined with intermolecular addition reactions to tandem sequences for the highly diastereoselective synthesis of tri- and tetrasubstituted olefins.⁹⁷

Finally, first examples of enantioselective 5-exo cyclizations have been reported that rely on the regiodivergent epoxide opening of racemic or enantiomerically enriched Sharpless epoxides (Scheme 18).⁹⁸



Scheme 18 Enantioselective 5-exo cyclizations after regiodivergent epoxide opening of Sharpless epoxides.



Scheme 19 Tetrahydrofuran synthesis featuring homolytic C–O bond cleavage and formation.

5.3 Tandem Sequences Featuring C–O Bond Formation and Cleavage

The titanocene-mediated epoxide opening proceeds with low exothermicity. In the absence of the release of the epoxide ring strain, the cleavage of C–O bonds by titanocenes is endothermic. Thus, the attack of a radical on a Ti(IV)–O bond should result in the formation of a C–O bond and the titanocene(III) reagent. Tandem sequences of this type (Scheme 19) were realized for the synthesis of THFs.^{99,100}

The ring substitution of the titanocene has a marked influence, with electron deficient complexes leading to almost quantitative yields in many cases.¹⁰¹

It should be noted that many furanolignanes were prepared with stoichiometric amounts of Cp_2TiCl in a similar manner.^{102,103} However, it was claimed that iodine had to be added to cleave the Ti–C bonds formed during the course of the reaction. While this seems unlikely to be necessary, the synthetic value of the approach to the lignanes is beyond doubt.

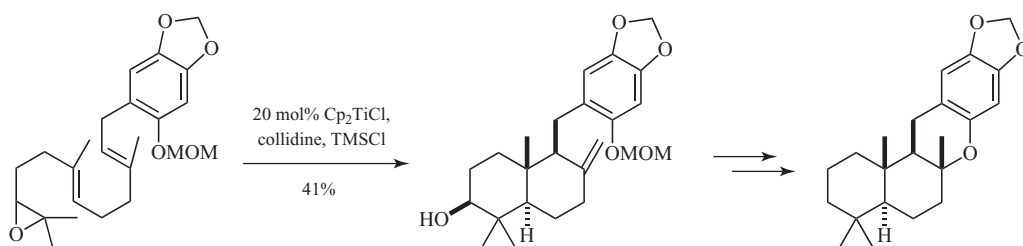
5.4 6-endo Cyclizations and Epoxypolyene Cyclizations

The synthesis of substituted cyclohexanes via 6-endo cyclizations is usually less efficient than the

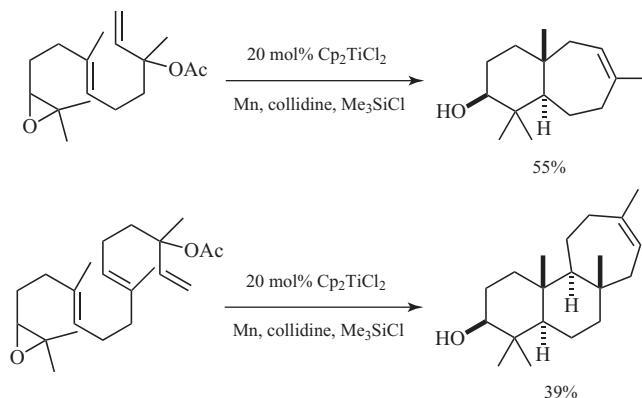
5-exo cyclization for stereoelectronic reasons. However, with a suitable substitution pattern, the regioselectivity of the addition can be reversed. This is especially interesting for the synthesis of terpenes and for epoxypolyene cyclizations with radicals.¹⁰⁴ It has been demonstrated that the combination of collidine and Me_3SiCl is especially attractive in this sequence. The termination of the cyclizations cascade by a hydrogen atom abstraction that results in the formation of an exo-cyclic olefin in the products makes the radical epoxypolyene cyclization complementary to the cationic reactions where the more substituted olefins are formed during the termination of the sequence. It is therefore not surprising that many natural product syntheses using this protocol have been described.^{105–108} An example is shown in Scheme 20.

An especially important aspect of these reactions is that 7-endo cyclizations can also be included in the tandem sequences.¹⁰⁹ This has resulted in some exceptionally short synthesis of natural products (Scheme 21).

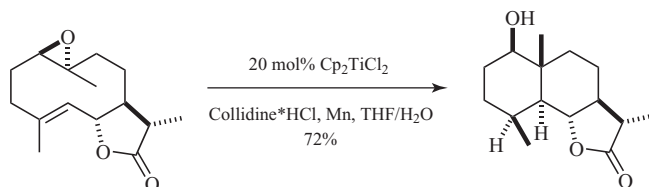
The Coll* Me_3SiCl -mediated catalytic conditions have also been used in transannular cyclizations. The very short semisynthesis of the eudesmanolides from germacranes (Scheme 22) highlights both the power and the mildness of this method in the synthesis of natural products.¹¹⁰



Scheme 20 Epoxypolyene cyclization in the formal synthesis of 8-*epi*-puupehedione.



Scheme 21 7-endo Cyclizations in the synthesis of natural products.



Scheme 22 Titanocene-catalyzed semisynthesis of eudesmanolide from germacrane.

6 SUMMARY AND OUTLOOK

Since the discovery of Cp_2TiCl as a useful reagent for the epoxide opening via ET by Nugent and RajanBabu and the development of the catalytic conditions, many fascinating applications of these protocols have been described and many novel reactions have been developed that unite the advantages of radical chemistry and catalysis. For the future, we expect the use of processes described above in large-scale applications and in the synthesis of ever more complex natural products and, perhaps most importantly, the invention of novel reactions addressing issues of stereoselectivity and sustainability.

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Transition Metals and Radicals

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1 INTRODUCTION

Oxidative addition of an organic halide to a low-valent transition-metal complex is an important elementary reaction in organometallic chemistry. The mechanisms of oxidative addition heavily depend on the type of organic halides. Although oxidative additions of aryl and alkenyl halides occur by concerted pathways, many oxidative additions of alkyl halides occur by radical pathways.^{1,2} However, radical oxidative additions are generally difficult to control because of the high reactivity and short lifetime of the radical intermediates. This difficulty therefore had held back the development of transition-metal-catalyzed reactions of alkyl halides. Recently, the use of alkyl halides as substrates under transition-metal catalysis has been actively investigated.^{3–8} Notably, the investigations have realized intriguing transformations by taking advantage of both radical and transition-metal-catalyzed reactions.

This article begins with two brief summaries about transition-metal-induced Kharasch-type radical reactions and about simple yet intriguing radical initiators, which accompany neither the formation nor cleavage of a carbon–metal bond. The following sections deal with recent studies on sophisticated radical reactions that are well controlled by a transition metal and are hence useful in modern organic synthesis. Radical reactions mediated by samarium diiodide and trivalent titanium complexes are discussed elsewhere (see **Organic Synthesis Using Samarium Diiodide and Epox-**

ides in Titanocene-Mediated and -Catalyzed Radical Reactions). Transition-metal-mediated oxidative radical processes (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**) and application of transition-metal-controlled radical reactions to polymerization^{9–11} (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications and Fundamentals of Controlled/Living Radical Polymerization**) are presented in other articles of this encyclopedia.

2 TRANSITION-METAL-CATALYZED KHARASCH-TYPE RADICAL REACTIONS

The Kharasch addition reaction, which is the addition of polyhalogenated methanes to alkenes, proceeds in the presence of transition-metal complexes as well as conventional radical initiators such as azobis(isobutyronitrile) (AIBN) and benzoyl peroxide (BPO). Although the transition-metal-mediated additions of polyhalogenated methanes are historically important,^{12–15} they are not really useful from the viewpoint of modern organic synthesis. Inter- and intramolecular radical additions of α -halo carbonyl compounds have attracted more attention in organic synthesis because of the ubiquity and importance of carbonyl compounds. Copper,^{16–18} ruthenium,^{19–21} and palladium^{22,23} salts and/or complexes are frequently employed as mediators. Equations (1)²⁴ and (2)²¹

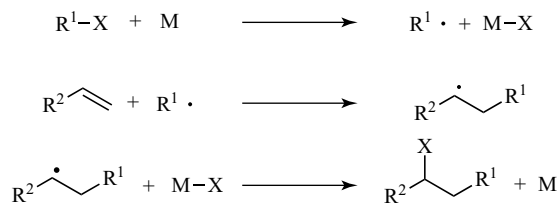
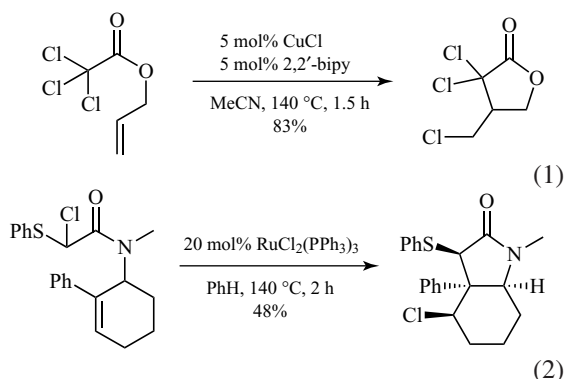


Figure 1 Transition-metal-mediated chain propagation in atom-transfer radical reaction.

illustrate representative examples of the synthesis of biologically interesting lactone and lactam.

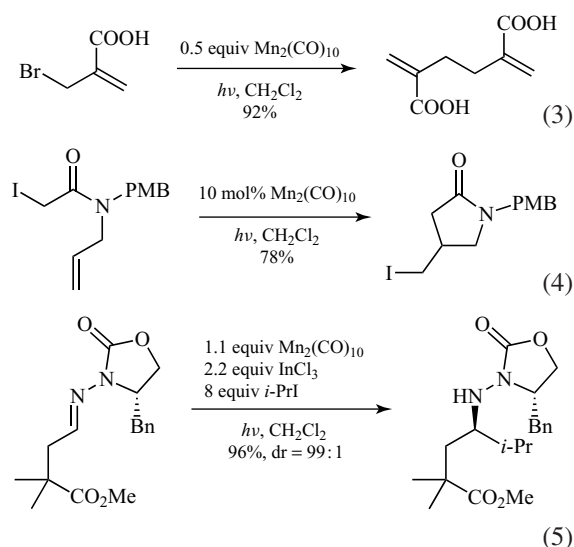


The exact role of the transition-metal complexes in the Kharasch-type atom-transfer radical reactions is still under discussion.²³ Some complexes can simply behave as radical initiators by abstracting a halogen at the initial stage and stay unreactive during chain propagation. Others can serve as a source of halogen via a metal halide in chain propagation, as described in Figure 1.²⁰

3 TRANSITION-METAL COMPLEXES AS CHARACTERISTIC RADICAL INITIATORS

Bis(pentacarbonylmanganese) consists of two pentacarbonylmanganese units connected by a Mn–Mn bond. The Mn–Mn bond is weak enough to undergo homolytic cleavage upon irradiation or heating (see **Overview of Radical Initiation**).^{25–27} The resulting pentacarbonylmanganese radical can abstract iodine atom from alkyl iodides and bromine and chlorine from polyhalogenated alkanes. Advantageously, the byproduct pentacarbonyl-halomanganese is readily removable by using a 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) workup

in purifying the products. Although its rhenium analog behaves similarly,²⁷ it is inferior in terms of the cost and ubiquity. Bis(pentacarbonylmanganese) is effective upon irradiation to induce debrominative homocoupling of allylic bromide (3),²⁸ atom-transfer radical additions (4),²⁹ and deiodinative addition of alkyl iodides to imines (5).^{30–32}



Movassaghi reported that $\text{CoCl}(\text{PPh}_3)_3$ mediates efficient dimerization of benzylic bromides for the elegant synthesis of hexahydropyrroloindole alkaloids (Figure 2).^{33–35} The cobalt complex is much more effective without irradiation than photoactivated hexabutyliditin or bis(pentacarbonylmanganese). The superiority of the cobalt complex would be due to its high reactivity to achieve a high concentration of the corresponding benzylic radical for the dimerization which is of second order with respect to the radical.

4 RECENT RADICAL REACTIONS CONTROLLED BY TRANSITION-METAL COMPLEXES

4.1 Palladium Catalysis

Oxidative additions of alkyl iodides to palladium often proceed by radical processes.³⁶ Suzuki and Miyaura reported that a radical oxidative addition mechanism operates in the palladium-catalyzed cross-coupling reactions of alkyl iodides

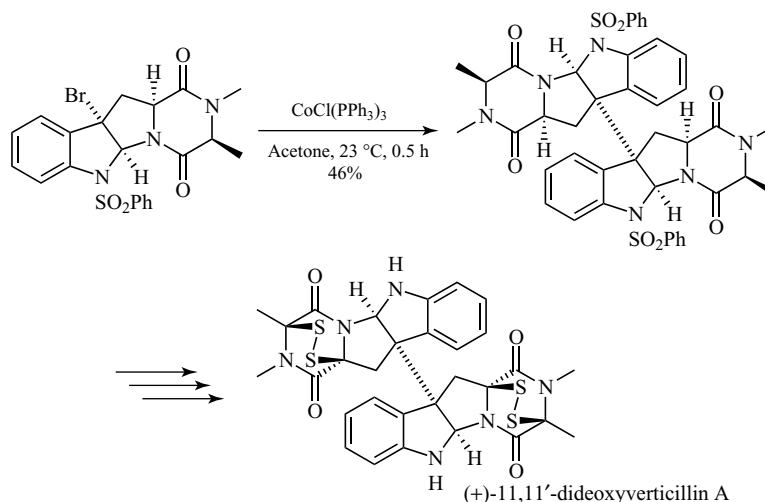
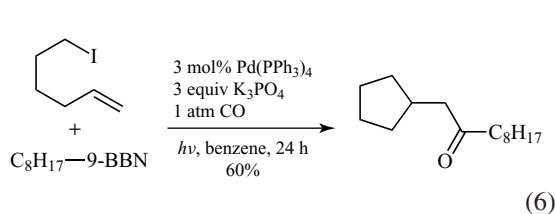


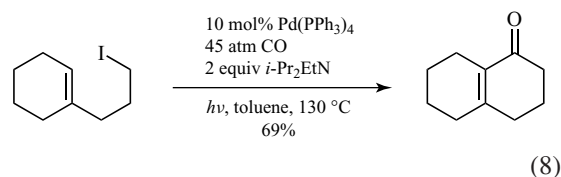
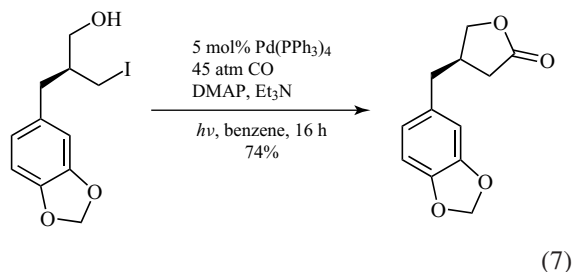
Figure 2 Cobalt-mediated efficient dimerization of benzylic bromides for the synthesis of (+)-11,11'-dideoxyverticillin A.

with 9-alkyl-9-borabicyclo[3.3.1]nonanes (9-alkyl-9-BBN).³⁷ Notably, light accelerates the palladium-catalyzed carbonylative cross-coupling (6).^{38,39}



Ryu developed palladium-catalyzed carbonylative cyclization reactions of 5-iodo-1-pentene derivatives under UV irradiation (Figure 3).^{40,41} The reactions provide a variety of (2-oxocyclopentyl)acetates in good yields. They proposed a *radical/palladium hybrid* mechanism. Initial iodine abstraction would take place with the aid of zero-valent palladium under irradiation. Radical carbonylation followed by intramolecular cyclization would afford a 2-oxocyclopentylmethyl radical. Another radical carbonylation would yield the corresponding acyl radical, which would be trapped by palladium(I) iodide to form an acylpalladium intermediate. The reaction of alcohol with the acylpalladium should furnish the product. The intermediary radicals are supposed to be in equilibrium with the corresponding organopalladium species by reversible formation/cleavage of carbon–palladium bonds. The same group^{42–44} and Bloome and Alexanian⁴⁵ also developed several carbonylation

reactions of alkyl iodides based on the concept of the radical/palladium hybrid (7 and 8).



Knochel reported that palladium complexes catalyze the cyclization of 6-iodo-1-hexene derivatives in the presence of diethylzinc to afford cyclopentylmethylzinc iodides (9).⁴⁶ The resulting zinc reagents can react with a variety of electrophiles such as activated organic halides and Michael acceptors after transmetalation with CuCN·2LiCl. The reaction mechanism should include oxidative addition by a radical process to generate cyclopentylmethylpalladium and the following transmetalation with diethylzinc.

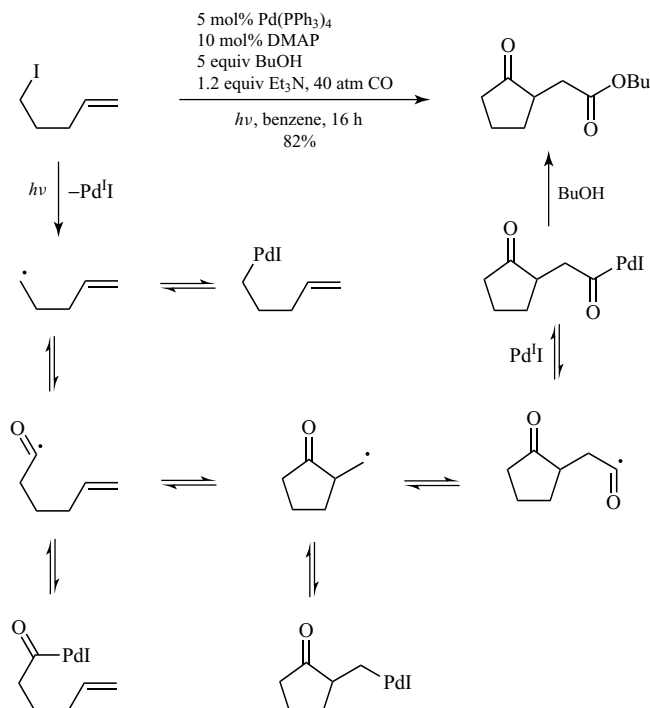
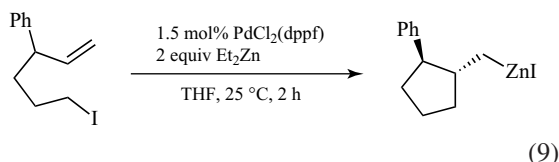


Figure 3 Radical/palladium hybrid for efficient carbonylative cyclization.

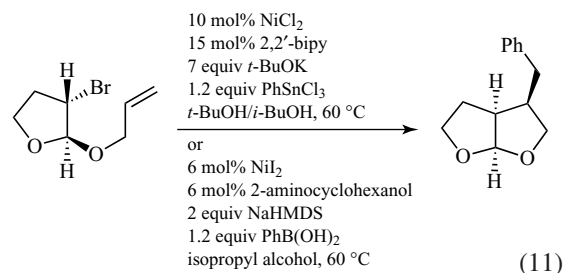
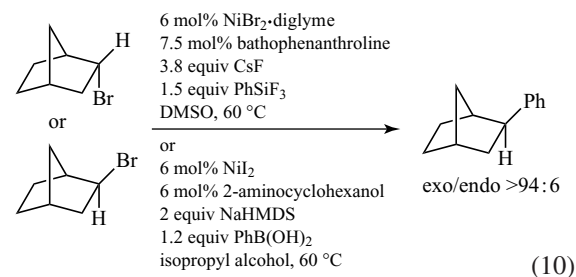


involvement of a radical oxidative addition process. Cárdenas also reported similar nickel-catalyzed radical cyclization/cross-coupling reactions of 6-iodo-1-hexene derivatives with alkylzinc reagents.⁵²

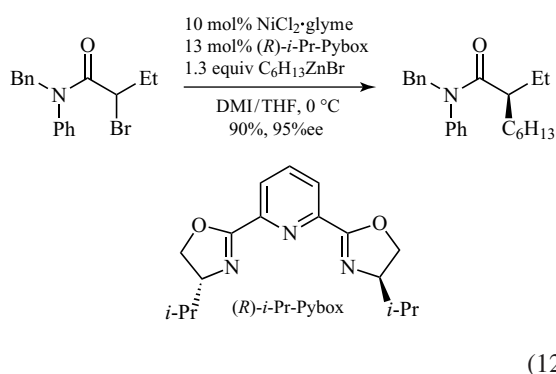
4.2 Nickel Catalysis

Nickel catalysis is used more frequently than palladium catalysis in the cross-coupling reactions of alkyl halides.^{47,48} Oxidative addition to nickel is believed to proceed by radical mechanisms in most cases.

Fu reported nickel-catalyzed reactions of alkyl bromides with organosilicon⁴⁹ or organoboron⁵⁰ reagents. The cross-coupling reactions of both *exo*- and *endo*-2-bromonorbornane afforded the corresponding *exo* coupling products exclusively (10), which suggests that the reactions would proceed via the same radical intermediate, 2-norbornyl radical, bearing no original stereochemical information. Arylative cyclization of 6-bromo-4-oxa-1-hexene derivatives with trichlorophenyltin⁵¹ or phenylboronic acid⁵⁰ (11) also strongly supports the

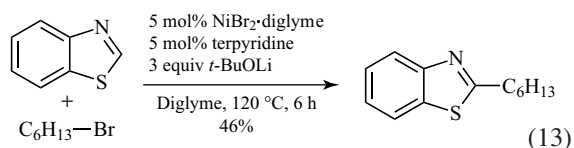


Fu subsequently presented asymmetric nickel-catalyzed cross-coupling reactions of racemic secondary alkyl halides (12).^{53–57} The asymmetric transformations proceed with stereoconvergence, which indicates the generation of planar radical intermediates from both enantiomers.



Hirano and Miura found nickel-catalyzed direct alkylation of benzothiazole with alkyl bromides albeit with moderate efficiency (13).⁵⁸ They proposed a radical oxidative addition mechanism since cyclopentylmethylation and 3-butenylation

took place upon treatment with 6-bromo-1-hexene and cyclopropylmethyl bromide, respectively.



In most cases, pyridine-based ligands are efficient for the nickel-catalyzed reactions. Vicic investigated the role of terpyridine as the ligand to elegantly reveal that a (terpyridine)nickel(0) complex does not react with organic halides by oxidative addition (Figure 4).^{59,60} Instead, a (terpyridine)Ni(I)R complex should be generated by a comproportionation reaction between a (terpyridine)Ni(II)R₂ complex and the (terpyridine)nickel(0) complex, and would be responsible for oxidative addition. The (terpyridine)Ni(I)R complex can be best described as a nickel(II)R cation bound to the radical anion of terpyridine. The single unpaired electron is localized mostly on the ligand, and the (terpyridine)Ni(I)R complex effects single-electron transfer

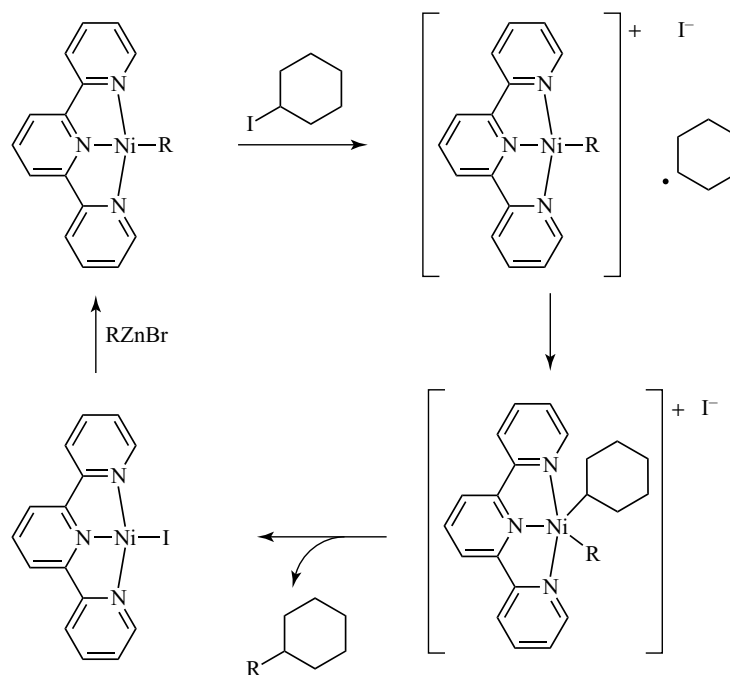


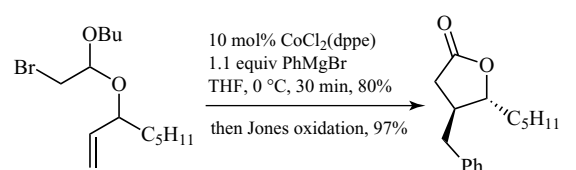
Figure 4 Ni(I)/Ni(III) catalytic cycle for alkyl-alkyl Negishi coupling.

from the ligand to alkyl halide RX to realize a radical oxidative addition mechanism. The catalytic cycle is hence concluded to be a $Ni(I)/Ni(III)$ cycle. Phillips performed density functional theory calculations to provide further evidence for Vicic's mechanism, showing the conventional two-electron oxidative addition is energetically unfavorable.⁶¹ Cárdenas also supported Vicic's mechanism on experimental as well as theoretical basis.⁵²

4.3 Cobalt Catalysis

In 2001, Oshima reported cobalt-catalyzed tandem radical cyclization/cross-coupling arylation reactions of 6-halo-1-hexene derivatives with aryl Grignard reagents (14),^{62,63} which represent the breakthrough in the recent rapid development of transition-metal-controlled radical reactions in organic synthesis. A possible mechanism is illustrated as Figure 5. The reaction of $CoCl_2(dppe)$ with 4 equiv of $PhMgBr$ would afford a zero-valent cobaltate $[Co(0)Ph_2(dppe)](MgBr)_2$ with concomitant formation of biphenyl. The electron-rich ate complex would be responsible for single-electron transfer to a substrate to realize oxidative addition by a radical mechanism. It is fundamental knowledge that oxidative addition of organic halide to

metal can proceed by a radical mechanism.^{1,2} However, little attention had been paid to its application to organic synthesis. This cobalt-catalyzed reaction had shed light on the importance of radical species in cross-coupling reactions of alkyl halides.⁶⁴



(14)

Cobalt catalysis also allows cross-coupling allylation and benzylation of alkyl halides.^{65,66} Notably, tertiary alkyl bromides as well as primary and secondary ones can participate in the allylation, which was not possible by using palladium and nickel catalysis (15). Tandem radical cyclization/allylation justifies the intermediacy of radical species (16). A cobalt (–)-chiraphos complex can catalyze enantioselective allylation of a racemic tertiary alkyl bromide (17). Although the enantioselectivity was very low, the reaction is important as the first trial for the transition-metal-catalyzed enantioselective cross-coupling of racemic alkyl halides, which Fu had been actively developing.^{53–57}

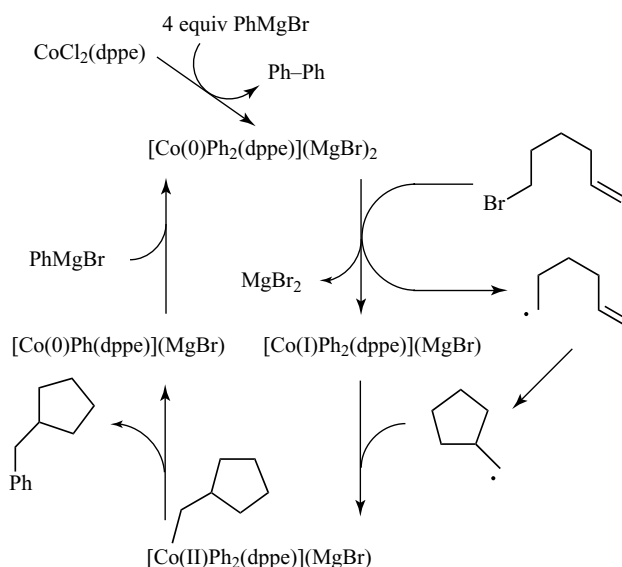
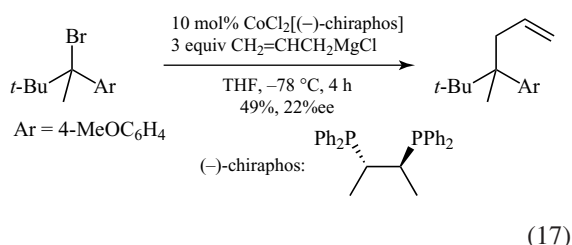
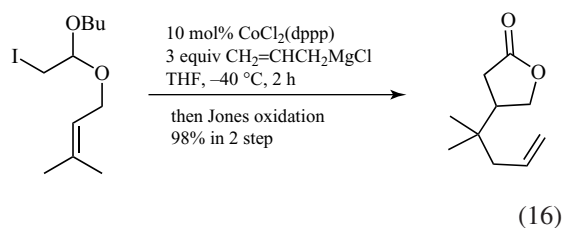
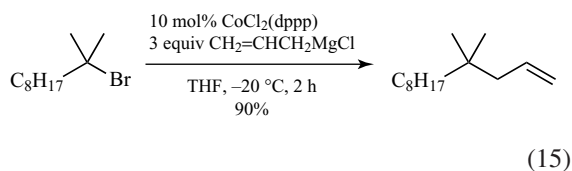


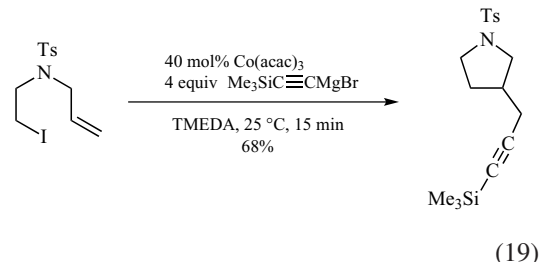
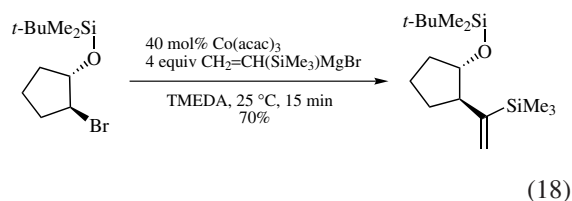
Figure 5 Plausible mechanism of cobalt-catalyzed arylation cyclization.



The scope of the arylation catalyzed by the cobalt–diphosphine complexes is limited to primary alkyl halides.^{62,63} Later, *N,N,N',N'*-tetramethyl-1,2-cyclohexanediamine (TMCHDA) was found to be a superior ligand for cobalt, realizing the use of secondary alkyl halides as coupling partners.⁶⁷ The arylation is highly efficient to go to completion within 15 minutes at room temperature. The intermediacy of planar carbon-centered radicals allows diastereoselective phenylation of chiral bromo acetals, which leads to a variety of phenylated tetrahydrofuran (THF) derivatives

(Figure 6). Combined with a radical cyclization reaction, the cobalt-catalyzed arylation provides an efficient access to a synthetic prostaglandin AH13205 (Figure 7).

N,N,N',N'-Tetramethylethylenediamine (TMEDA) is a suitable solvent for cobalt-catalyzed cross-coupling reactions of alkyl halides with 1-trimethylsilyl-2-ethynyl and trimethylsilyl-2-ethynyl Grignard reagents (18 and 19).⁶⁸



N-Heterocyclic carbene ligands are effective in cobalt-catalyzed sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives with 1-alkynyl and trialkylsilylmethyl Grignard reagents (20 and 21), in which bidentate diphosphine and diamine ligands were completely ineffective.^{69,70}

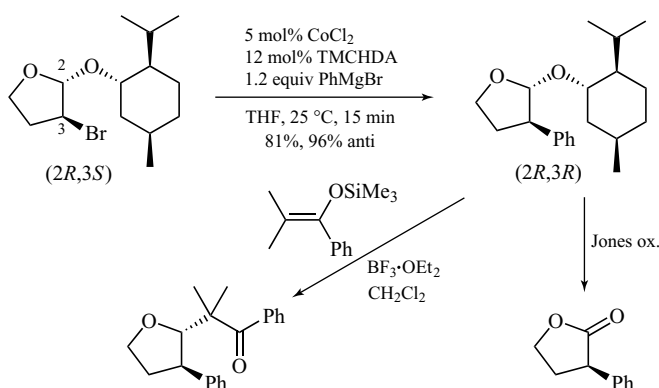


Figure 6 Cobalt-catalyzed phenylation of chiral bromo acetal.

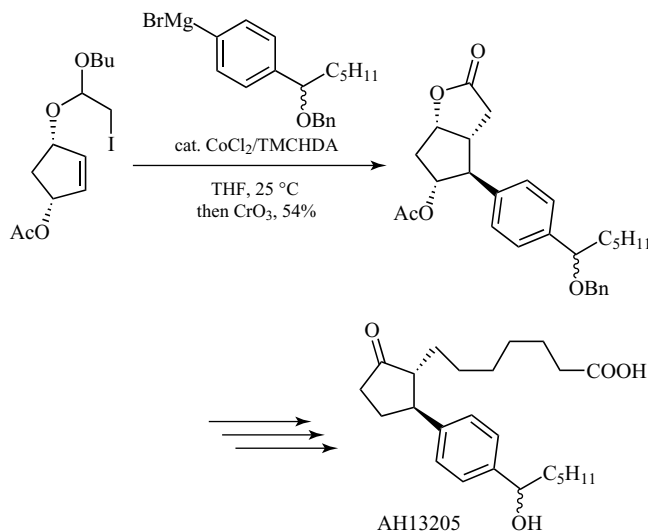
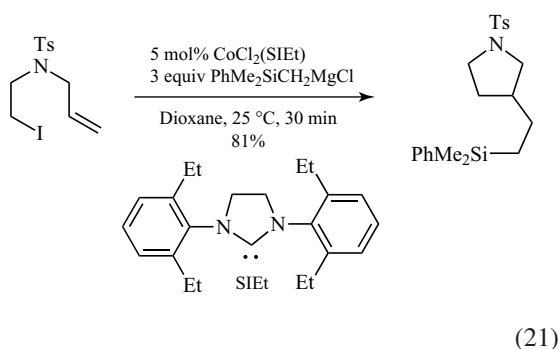
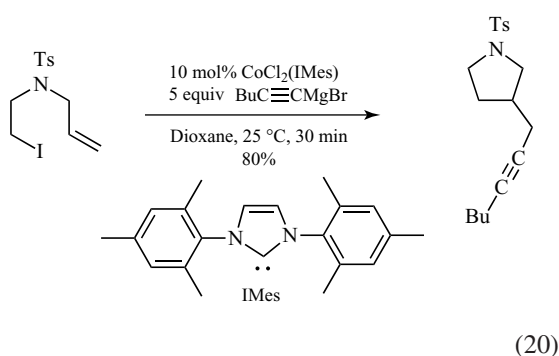
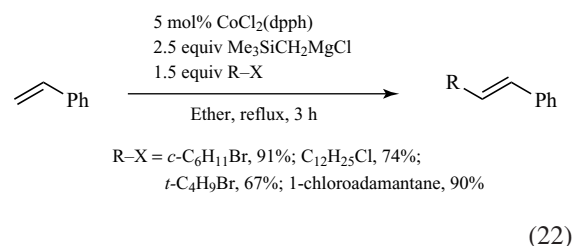


Figure 7 Synthesis of AH13205.



The major limitation of the conventional Mizoroki–Heck reaction is that one cannot use alkyl halides as substrates mainly because the alkylpalladium intermediates suffer from β -hydride elimination, which always dominates over the insertion of alkene. A combination of $\text{CoCl}_2(\text{dppe})$ ($\text{dppe} = 1,1'$ -

6-bis(diphenylphosphino)hexane) and trimethylsilylmethylmagnesium chloride offers a complementary method that allows the alkylation of styrenes.^{71,72} Primary, secondary, and tertiary alkyl halides all participate in the alkylation (22). Notably, less reactive alkyl chlorides are also good alkyl sources. The use of trimethylsilylmethylmagnesium chloride is quite important, and other Grignard reagents are completely ineffective. In addition, the Grignard reagent has modest reactivity, thereby allowing various functionalities such as ester to survive (23). A catalytic cycle should begin with single-electron transfer to alkyl halide. Radical addition of the resulting alkyl radical to styrene would yield the corresponding benzylic radical (Figure 8). A cobalt complex captures the benzylic radical, and the resulting benzylic cobalt undergoes β -hydride elimination to afford alkylated styrene. Investigation by using typical radical clocks supports the intermediacy of radical species (24 and 25). The cobalt-catalyzed system is also applicable to intramolecular reactions (26).^{72,73}



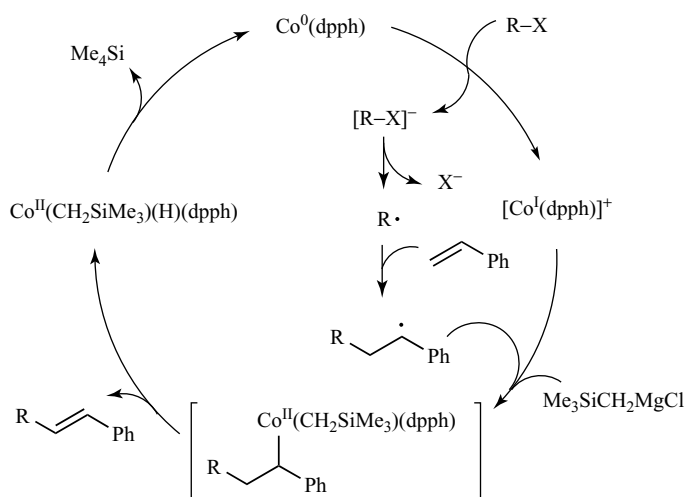
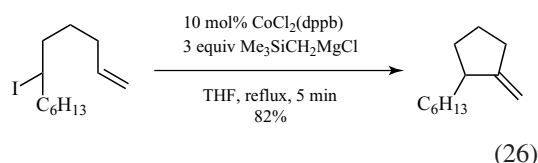
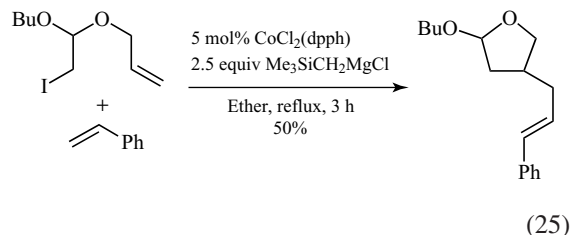
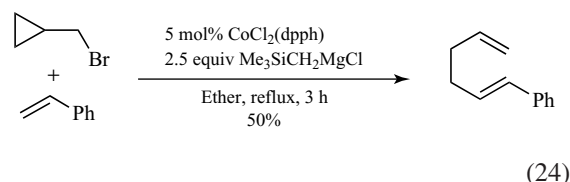
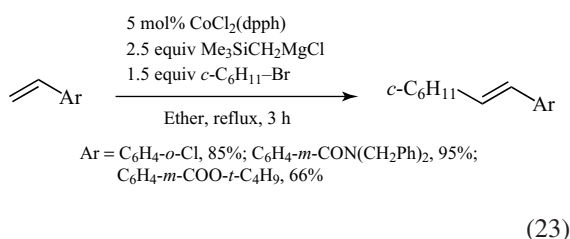
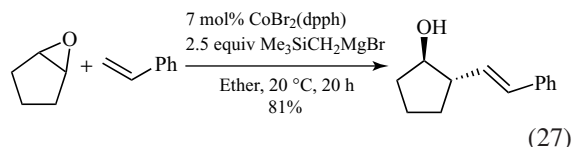


Figure 8 Catalytic cycle of cobalt-catalyzed alkylation of styrene.



Cobalt-catalyzed Mizoroki–Heck-type reactions of epoxides with styrene take place under similar reaction conditions (27).⁷⁴ Magnesium

bromide-mediated ring-opening of epoxides would afford the corresponding magnesium 2-bromoalkoxides, which are the actual substrates for the reaction.



Conjugated 1,3-dienes are good radical acceptors. Treatment of 1,3-dienes under similar cobalt-catalyzed conditions does not yield the Mizoroki–Heck-type product but results in three-component coupling to afford homoallylic silanes (Figure 9).⁷⁵ Reductive elimination from the allylic cobalt species dominates over β -hydride elimination. Chromium⁷⁶ and nickel⁷⁷ were reported to catalyze similar three-component coupling reactions of 1,3-dienes as radical acceptors.

A combination of a cobalt/IMes catalyst and dimethylphenylsilylmethylmagnesium chloride promotes highly regioselective dehydrohalogenation of alkyl halides (28).⁷⁸ The elimination reaction consists of oxidative addition by a radical mechanism and the following β -hydride elimination from the corresponding alkylcobalt intermediate. The reaction mechanism offers intriguing regioselectivity. For instance, 1-iodo-2-phenylcyclohexane is not converted to conjugated 1-phenylcyclohexene but to unconjugated 3-phenylcyclohexene (29).

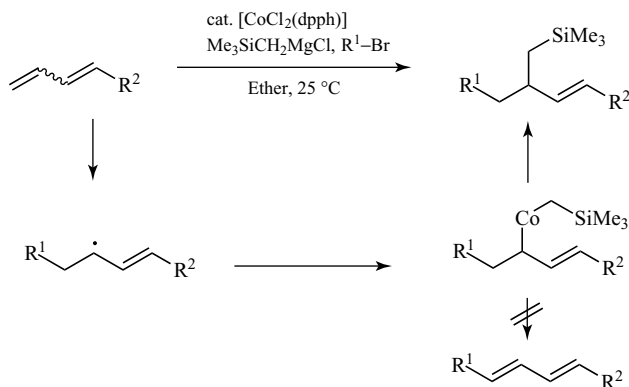
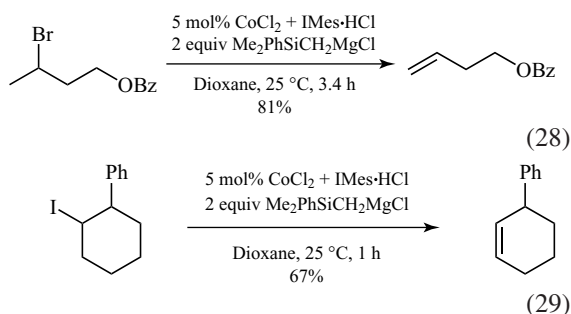


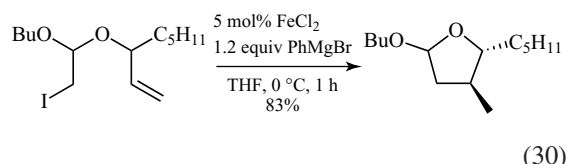
Figure 9 Three-component coupling of alkyl halide, 1,3-diene, and trimethylsilylmethyl Grignard reagent.



4.4 Iron Catalysis

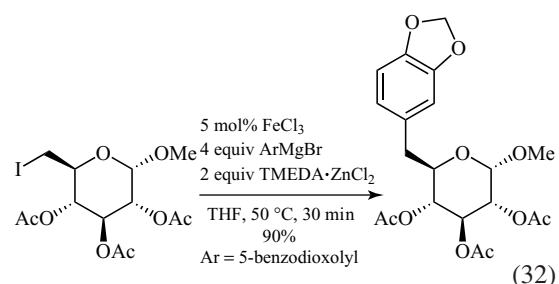
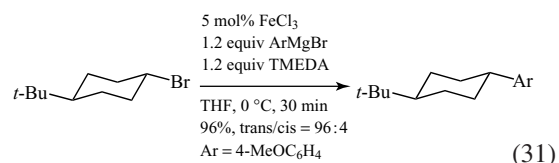
Iron is cheap, ubiquitous, and environmentally benign, and hence is an ideal transition metal for catalysis. Like cobalt, iron has been attracting increasing attention in the cross-coupling reactions of alkyl halides.

Oshima developed iron-catalyzed reductive radical cyclization of 6-halo-1-hexene derivatives with phenylmagnesium bromide (30),⁷⁹ wherein single-electron transfer from electron-rich iron-ate species occurs to initiate the radical cyclization and no phenylation takes place.



Nakamura *et al.*,⁸⁰ Nagano and Hayashi,⁸¹ and Martin and Fürstner⁸² independently reported in 2004 iron-catalyzed Kumada–Tamao–Corriu coupling arylation of primary and secondary alkyl

halides (31)⁸⁰ and (32).⁸³ Following these results, a number of reports on iron-catalyzed cross-coupling reactions of alkyl halides with organometallic reagents have appeared, which are summarized in excellent reviews^{5,84–86} and have been extensively cited in a very recent paper.⁸⁷ In most cases, aryl and alkenyl metal reagents are available for use.



The exact reaction mechanism of the iron-catalyzed cross-coupling reactions of alkyl halides is not clear. However, there is sufficient data to suggest oxidative addition by single-electron transfer from electron-rich iron complexes. Like the cobalt-catalyzed processes, strong support of the radical oxidative addition is the loss of the initial stereochemistry of a chiral halogenated carbon (33)^{82,83,88} as well as the following typical radical clock reactions (34).^{82,83,88–92} A representative, plausible mechanism proposed by Nakamura and Nagashima is shown in Figure 10.⁹³

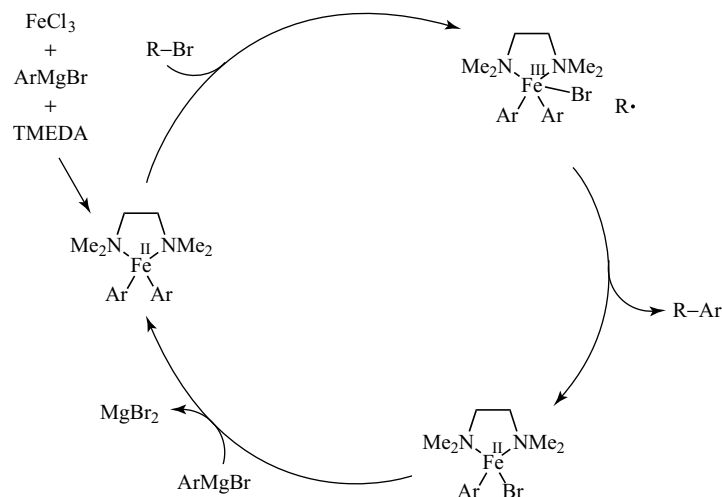
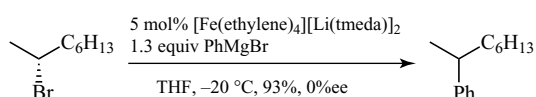
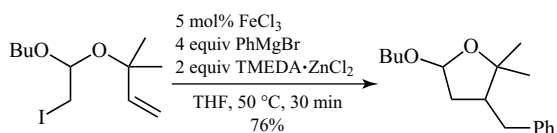


Figure 10 A proposed catalytic cycle for iron-catalyzed cross-coupling.



(33)



(34)

Yoshikai and Nakamura developed iron-catalyzed arylation of *N*-(2-iodobenzyl)-substituted aliphatic amines at the α position with organomagnesium or

organozinc reagents (Figure 11).⁹⁴ They proposed that the reaction mechanism involves the generation of the corresponding aryl radical, which then undergoes 1,5-hydrogen transfer to afford an α -aminoalkyl radical.

Charette reported iron-catalyzed direct arylation of benzene with aryl iodides in the presence of potassium *t*-butoxide (35).⁹⁵ A large amount of benzene solvent is essential to achieve the reaction. A plausible mechanistic pathway involves the formation of an aryl radical from aryl iodide by single-electron transfer followed by intermolecular radical addition to benzene (see **Intramolecular Homolytic Substitutions in Synthesis**). It

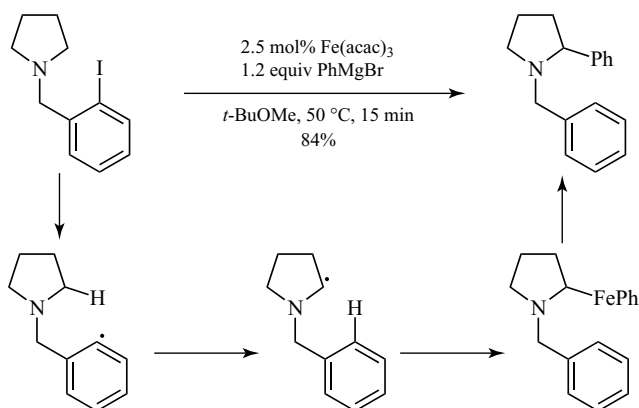
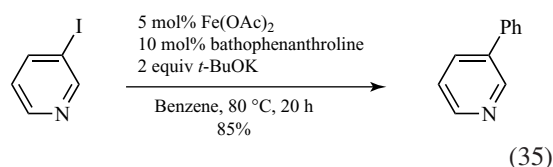


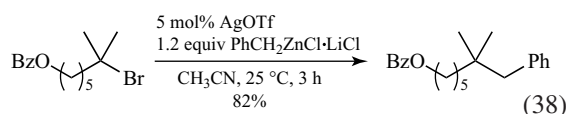
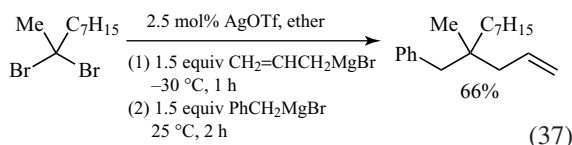
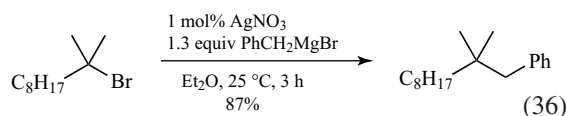
Figure 11 Iron-catalyzed arylation at α position of aliphatic amines protected by 2-iodobenzyl group.

should be pointed out that different groups have reported alkali *t*-butoxide-mediated direct arylation of benzene with aryl iodides in the absence of any transition-metal catalysts.^{96–98}



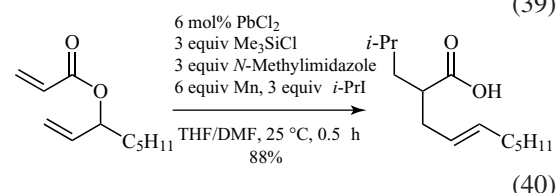
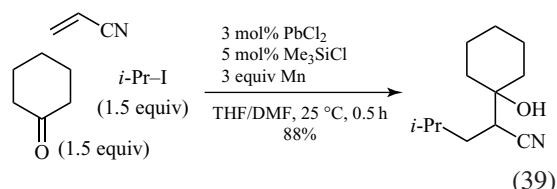
4.5 Silver Catalysis

Silver catalysis has proved to be more robust than the cobalt catalysis^{65,66} for benzylation and allylation of alkyl halides.^{99–101} The reaction procedure is quite simple: a Grignard reagent is added to a mixture of alkyl bromide and a catalytic amount of silver nitrate in ether at room temperature (36). A radical clock experiment as well as stereoconvergent benzylation reactions of *exo*- and *endo*-2-bromonorbornane verify the intermediacy of carbon-centered radicals. Intriguingly, *gem*-dibromoalkanes undergo sequential carbon–carbon bond formation with two different Grignard reagents to create a chiral quaternary carbon center (37). Allylic and benzylic zinc reagents of milder reactivity are also effective under similar conditions (38). Indenyllithium reacts under silver catalysis to yield sterically crowded alkylated indene derivatives.¹⁰² Aryl Grignard reagents can couple with secondary and tertiary alkyl bromides albeit with low efficiency.¹⁰³ Mechanistically, low-valent silver-ate complexes are proposed to be responsible for oxidative addition by a radical mechanism.

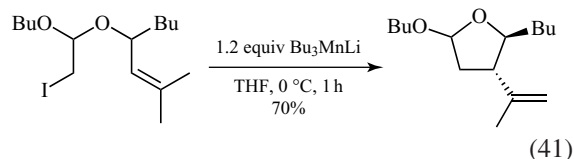


4.6 Manganese-Mediated Processes

Activated manganese metal can transfer one electron to alkyl halides. Takai developed three-component coupling of alkyl iodides, electron-deficient alkenes, and carbonyl compounds by using manganese powder activated by catalytic amounts of PbCl₂ and chlorotrimethylsilane (39).¹⁰⁴ Sequential 1,4-addition/Ireland–Claisen rearrangement is also promoted under similar conditions (40).¹⁰⁵ Reduction of alkyl iodide with manganese would generate the corresponding alkyl radical, which then undergoes radical addition to electron-deficient alkene. The adduct would accept another electron to form a stable carbanion, which is responsible for the Aldol-type reaction or the rearrangement.



Manganese-ate complexes are efficient electron donors that promote radical cyclization of 6-halo-1-hexene derivatives (41).^{106–108} Highly active manganese powder, prepared from Li₂MnCl₄ and magnesium, can also promote similar transformations.^{109,110}



4.7 Titanium Catalysis

Styrenes react with alkyl halides in the presence of butylmagnesium chloride and a catalytic amount of titanocene dichloride to afford Mizoroki–Heck-type products (42).¹¹¹ The mechanism would be similar to the cobalt-catalyzed reaction.^{71,72} The functional group compatibility is unsatisfactory because of the high reactivity of the Grignard reagent.

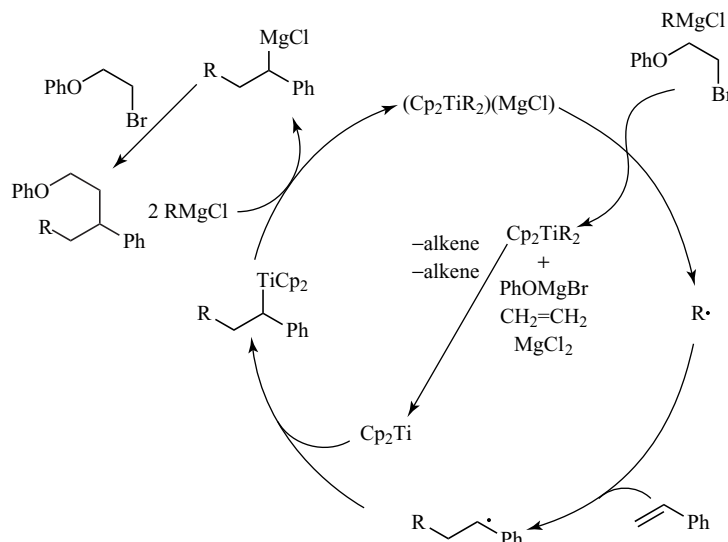
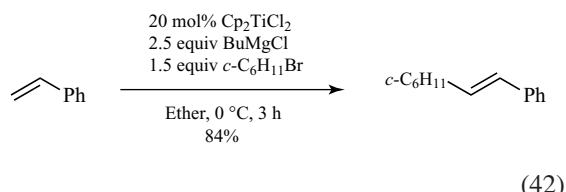
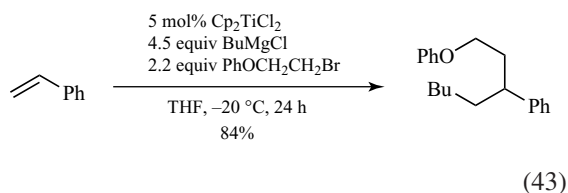


Figure 12 Proposed mechanism of titanocene-catalyzed double alkylation of styrene.

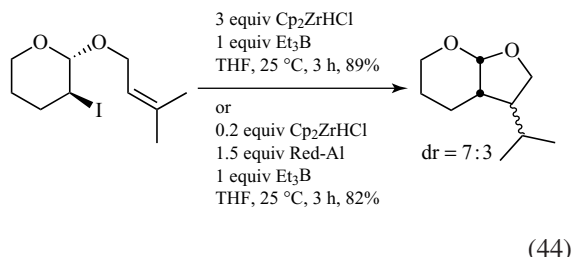


When alkyl bromides having a heteroatom at the β -position are subjected to the titanocene-catalyzed reaction, regioselective double alkylation of styrene takes place (43).¹¹² Mechanistic experiments have revealed the reaction pathway, as shown in Figure 12. Cp_2TiCl_2 would be reduced with alkyl Grignard reagent to generate dialkyltitanate(III) $\text{Cp}_2\text{TiR}_2(\text{MgCl})$. Oxidation of the titanate by β -bromoethyl ether leads to extrusion of alkyl radical $\text{R}^\bullet$. Addition to styrene followed by the capture by a titanocene complex affords the corresponding benzyl titanocene. Subsequent transmetalation with the alkyl Grignard reagent would afford the benzylic Grignard reagent, which finally reacts with β -bromoethyl ether to form the product.



4.8 Zirconium-Mediated Processes

Schwartz reagent is a promising alternative to tributyltin hydride in radical reaction (44).^{113,114} Alkyl chlorides as well as iodides and bromides are reduced smoothly in the presence of triethylborane. Reduction of aryl iodide is also very efficient. Functional groups such as ether and ester can survive under the reaction conditions. Schwartz reagent can be generated *in situ* from zirconocene dichloride by means of an aluminum hydride reagent Red-Al. The amount of zirconocene dichloride can be reduced to catalytic levels.



Allylic zirconocenes are effective for radical allylation of α -halo carbonyl compounds and tandem radical addition/allylation of acrylate esters with alkyl iodides, serving as allyltin surrogates ((45), Figure 13).¹¹⁵

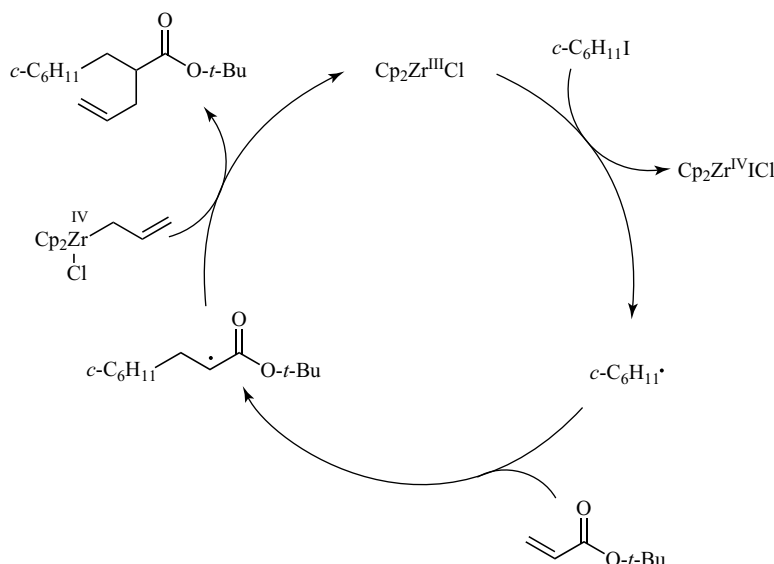
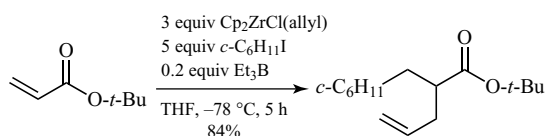
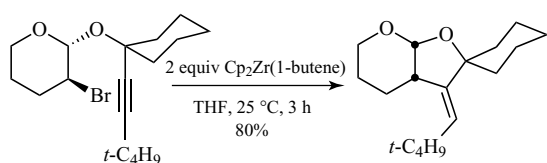


Figure 13 Tandem radical addition/allylation with allylic zirconocene.



(45)

Negishi reagent, a zirconocene(II)-alkene complex, serves as a single-electron transfer agent to induce radical reactions (46).^{114,116,117} In most cases, the Negishi reagent serves as a reducing agent like samarium diiodide. Radical propagation would not operate, and a plausible hydrogen donor is THF.



(46)

5 CONCLUSION

The elementary radical reactions are limited in number and complexity. Combinations of radical reactions with transition-metal-catalyzed ones have provided a wider variety of transformations than

with independent use of standard radical or catalytic technology. Such combinations will continue to significantly expand the scope of radical reactions in organic synthesis.

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Radicals and Carbohydrates

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1 INTRODUCTION

Radical reactions in carbohydrate chemistry have been a matter of intense research activity during the last years. These synthetic and mechanistic studies have not only decisively contributed to a better understanding of radical reactions but have also played a major role in the transference of these methodologies to the synthetic chemistry community. Of particular note is the contribution of carbohydrate chemistry in evaluating the importance of steric, stereoelectronic, and conformational effects on the reactivity and stereoselectivity of radical reactions. One important aspect of free-radical chemistry at the anomeric center is the predictable stereoselectivity of hexopyranosyl radicals, which makes them valuable intermediates for the stereoselective synthesis of C-glycosides and C-disaccharides.

The application of radical methods in carbohydrate chemistry has been thoroughly reviewed covering the literature up to 1999.¹ Since then, a number of reviews, dealing with specific areas, have been published.^{2–7} Although some earlier work is mentioned, this article reviews progress in the area with special attention to new developments published during the past decade. Because of the great number of publications in this field, an exhaustive review of the literature is not possible. However, an attempt has been made to highlight the most synthetically valuable processes. The major focus is on inter- and intramolecular carbon–carbon bond-forming radical

reactions, with emphasis placed on the preparation of C-glycosides, C-ketosides, C-disaccharides, and branched-chain sugars, as well as on the synthesis of polyfunctionalized carbocycles by radical cyclization of acyclic carbohydrate derivatives. The next two sections describe methods for the formation of carbon–hydrogen bonds and synthesis in which a heteroatom-centered radical plays a clear role in the carbon–heteroatom bond formation. Finally, a few selected examples of alkoxyl radical β -fragmentation reactions, carried out under oxidative or reductive conditions, are included to illustrate their potential in the synthesis of chiral synthons.

2 INTERMOLECULAR CARBON–CARBON BOND-FORMING PROCESSES

Free-radical chemistry at the anomeric center has attracted a great deal of attention owing to the unusual diastereoselectivity (see **Stereoselective Radical Reactions**) of glycopyranosyl radical reactions. These radicals react with electrophilic acceptors to give axial-substituted adducts preferentially, in contrast to cyclohexyl radicals which react principally in the equatorial mode.^{8,9} The reactivity strongly depends on two main stereoelectronic stabilizing effects: the anomeric effect (interaction between the singly occupied molecular p orbital (SOMO) and the adjacent highest occupied molecular orbital (HOMO) of the pyran oxygen lone pair) and the β -oxygen effect

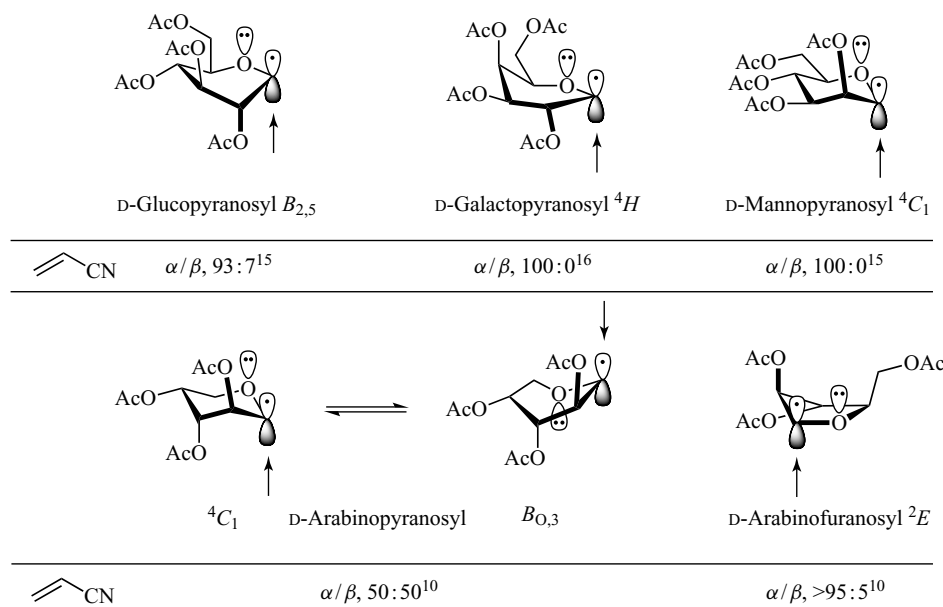


Figure 1 Stereoelectronic effects and conformation of glycosyl radicals. The preferred addition to acrylonitrile is shown by arrows.

(interaction between the SOMO and the σ^* -lowest unoccupied molecular orbital (LUMO) of the coplanar β -C–OR bond).¹⁰ A combination of both effects, the so-called quasi-homo-anomeric effect, has been used by Giese to explain the stereoselectivity of a variety of carbohydrate radical reactions (Figure 1).^{11–13} This quasi-homo-anomeric effect may also induce conformational changes in the glycopyranosyl radical with respect to the original carbohydrate in order to maximize orbital interactions. For instance, the electron paramagnetic resonance (EPR) (see **Analysis of Radicals by EPR**) data for D-glucopyranosyl and D-galactopyranosyl radicals have been interpreted by Giese in terms of a slightly twisted $B_{2,5}$ boat and a 4H half-chair conformations, respectively, instead of the original 4C_1 shape of D-glucose and D-galactose.¹⁴ In contrast, the D-mannopyranosyl radical remains in the 4C_1 chair conformation of the D-mannose. As the configuration at C-2–C-4 in xylose and lyxose is identical to those of glucose and mannose, respectively, similar conformations for D-xylopyranosyl ($B_{2,5}$) and D-lyxopyranosyl (1C_4) radicals were observed by EPR.¹² The much more flexible D-arabinopyranosyl radical exists as an equilibrium between the 4C_1 and $B_{0,3}$ conformation, and their reactions with alkenes are

unselective. However, D-arabinofuranosyl radicals adopt a 2E conformation and react with high diastereoselectivity. The diastereoselective ratios and preferential acrylonitrile attack on the anomeric radicals maintaining the stabilizing interaction with the lone pair of the ring oxygen are shown in Figure 1.^{15,16}

2.1 Synthesis of C-Glycosides

Since its introduction by Keck and Yates¹⁷ in 1982, allyltributylstannane has frequently been used for the synthesis of C-glycosyl compounds. The radical chain reaction (see **The History of Free Radical Chemistry**) is initiated by thermolysis of azobisisobutyronitrile (AIBN) or irradiation, and the mechanism is depicted in Figure 2. The glycosyl radical **I** is generated from the precursor by X (halide, xanthate, thioether, or selenide) abstraction of the stannyl radical. The formed adduct radical **II** undergoes a rapid β -fragmentation of the C–Sn bond to give the allylated compound and the chain propagation tin radical **III**.¹⁸

The reaction has been applied to pyranose,^{19–22} furanose **1**,^{19,23} and N-acetylneuraminic acid **2** derivatives^{24–26} (Scheme 1). As a consequence

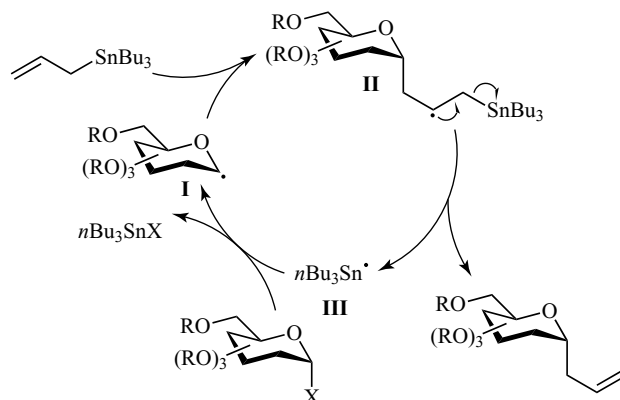
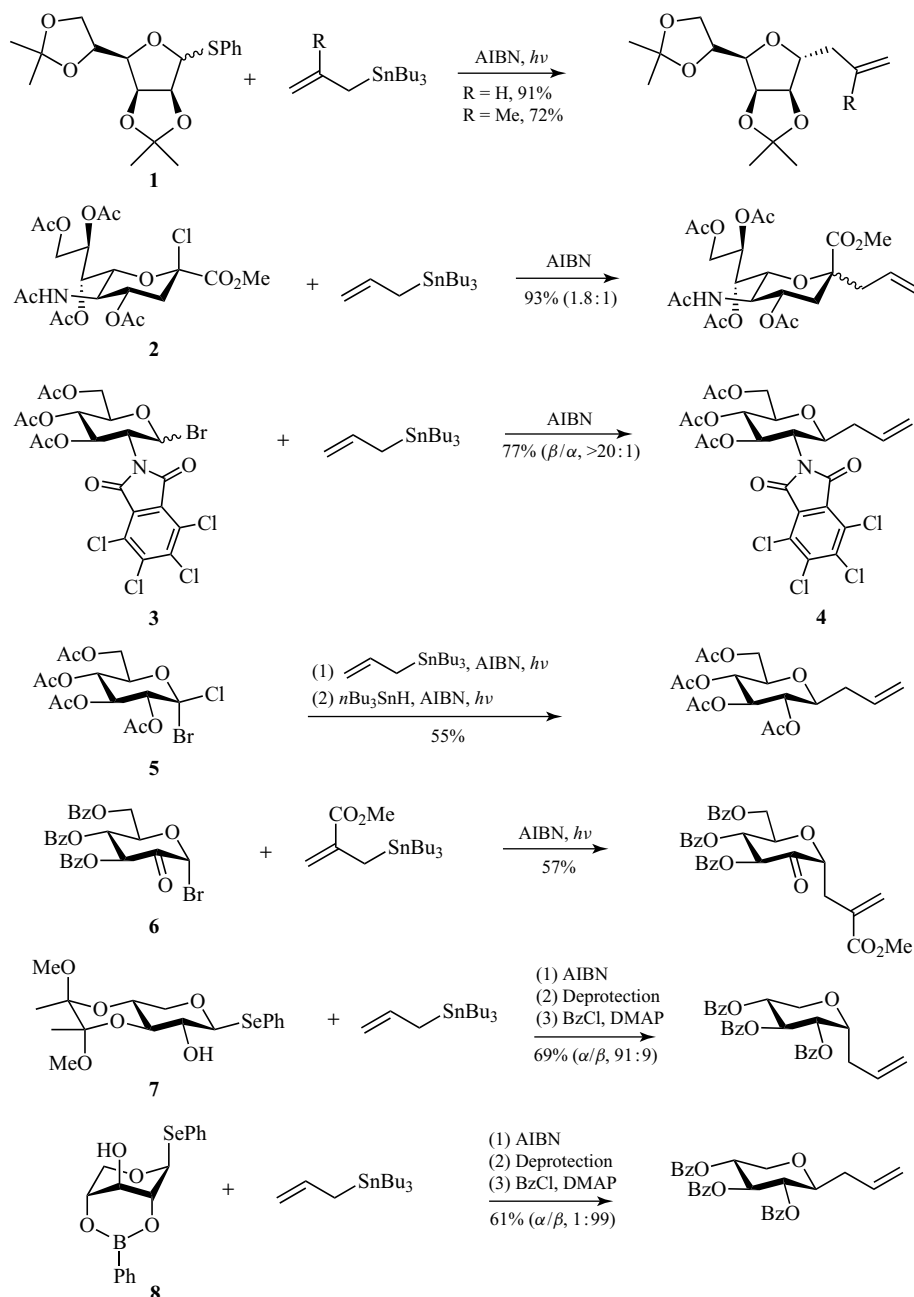


Figure 2 Radical chain reaction mechanism of Keck allylation. X: halide, xanthate, thioether, or selenide.

of the α -axial quenching of D-glycopyranosyl radicals,^{10,14} 3-C-(α -D-glycopyranosyl)-1-propene derivatives are formed predominantly. Notwithstanding, the presence of a bulky substituent at C-2 (*N*-phthalimido,²¹ *N*-tetrachlorophthalimido **3**²²) reverses the stereochemical outcome to form β -C-glycosides **4**. A novel approach to the synthesis of 3-C-(β -D-glycopyranosyl)-1-propene derivatives has been reported by Praly *et al.*²⁷ in a one-pot, two-step sequence involving allylation and reductive dehalogenation of 1-bromo- β -D-glycopyranosyl chloride **5**. The reaction may be effected even with electrophilic glycosyl radicals; α -D-arabino-hexopyranosyl-2-ulose bromide **6** reacts with methyl 2-(tributylstannylmethyl)acrylate albeit in moderate yield.²⁸ A study of the conformation–anomeric effect–stereoselectivity relationship in the anomeric radical reaction of pentopyranoses has been reported. Selectivity was increased by conformational restriction of the pentopyranose ring in 4C_1 -chair **7** and completely inverted by flipping the conformation from the 4C_1 - into the 1C_4 -chair **8**, because of the kinetic anomeric effect.²⁹ Allylthio compounds are also effective anomeric radical-trapping agents for the synthesis of C-allyl glycosides. Thus, the ultraviolet (UV) irradiation of α -D-galactopyranosyl bromide with allylic sulfides and sulfones in the presence of hexabutyltin gave the corresponding 3-C-(α -D-galactopyranosyl)-1-propene derivatives with excellent diastereoselectivity.³⁰

D-Gluco-1-yl radicals can also be generated by reaction of D-glucosyl iodide **9** with 1-ethylpiperidine hypophosphite (EHPH) (Scheme 2).

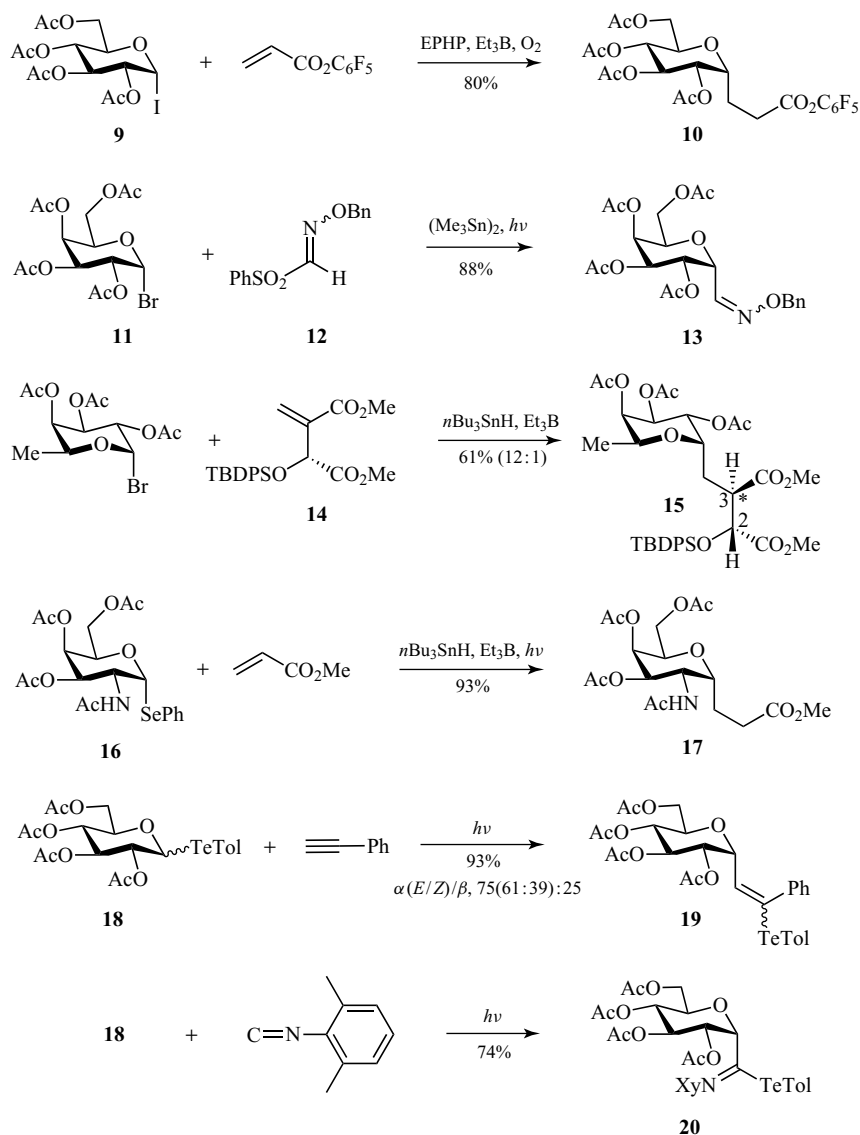
The anomeric radicals add efficiently to pentafluorophenyl acrylate as electron-deficient olefin to give C-glycoside **10**.³¹ EPHP is a mild alternative to tin reagents in radical chemistry. The chemoselective radical reduction of the iodine atom in a series of 1-deoxy-1-halo-1-iodo-alditols and the addition of the intermediate radicals to acrylonitrile has been described.³² One-carbon extended C-glycosylation to glycopyranosides **13** can be achieved by radical acylation of peracetylated gluco- and galacto-pyranosyl bromide **11** with phenylsulfonyl oxime ether **12** in the presence of hexamethyldiastannane under photochemically initiated conditions.³³ The reaction may also be applicable to the preparation of C-branched sugars (see **71** in Scheme 8). In the addition of L-fucosyl radical to α,β -unsaturated ester **14**, two 1,3-distant stereocenters are created with high diastereoselectivity: the first one results from a totally selective α -C-glycosylation under stereoelectronic control and the second by a hydrogen-atom transfer (HAT) reaction which proceeded preferentially to the 2,3-syn isomer **15**.³⁴ Some limitations associated with the use of glycosyl bromides of 2-amido sugar as radical precursors, which in some cases led only to the corresponding oxazoline, prompted Gallagher^{35,36} to examine alternative radical precursors in these compounds. The anomeric selenides derived from D-GlcNAc, D-ManNAc, and D-GalNAc **16** underwent smooth C–Se homolysis and the resulting radicals were trapped with electron-deficient olefins to give C-glycosides **17**. Since the pioneering work on the synthesis of showdomycin by Barton in 1990,³⁷



Scheme 1 Synthesis of C-allyl glycosides by intermolecular trapping of glycosyl radicals with allylstannanes.

some attention has been paid to the preparation of glycosyl tellurides as a source of 1-glycosyl radicals. Yamago and Yoshida³⁸ have shown that anomeric radicals generated photochemically or thermally from glycosyl tellurides such as **18**

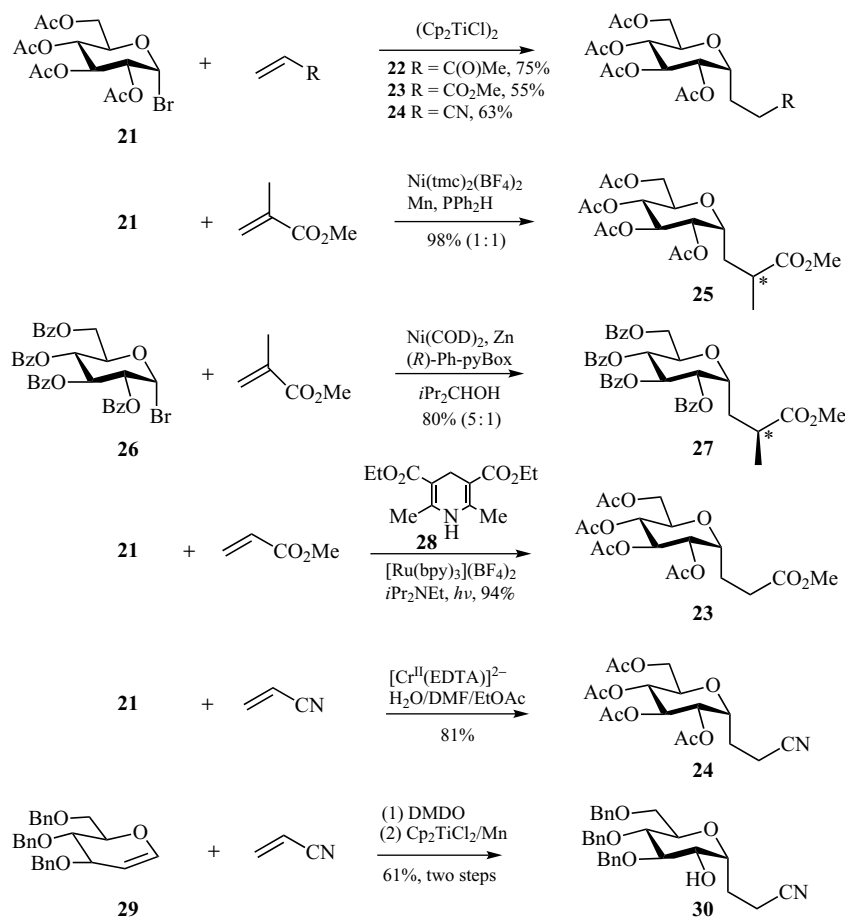
add to alkynes to give vinyl C-glycosides **19** in good yield as a mixture of anomers (α/β , 75:25) (see **Halogen and Chalcogen Transfer Chemistry and Sb, Bi, Te, and I-Transfer Polymerization and Applications**). Interestingly, under



Scheme 2 Synthesis of C-glycosides by intermolecular addition of glycosyl radicals to unsaturated compounds. EPHP, 1-ethylpiperidine hypophosphite.

these conditions the reactivity of electron-deficient and electron-rich alkynes is similar, which is surprising given that glycosyl radicals behave as nucleophilic species. This Japanese group also studied the imidoxylation of these organotellurium compounds with isonitriles; the reaction of **18** with 2,6-xylylisonitrile under photochemical conditions afforded imine **20** in good yield and high α-selectivity.³⁹ The known steric influence of

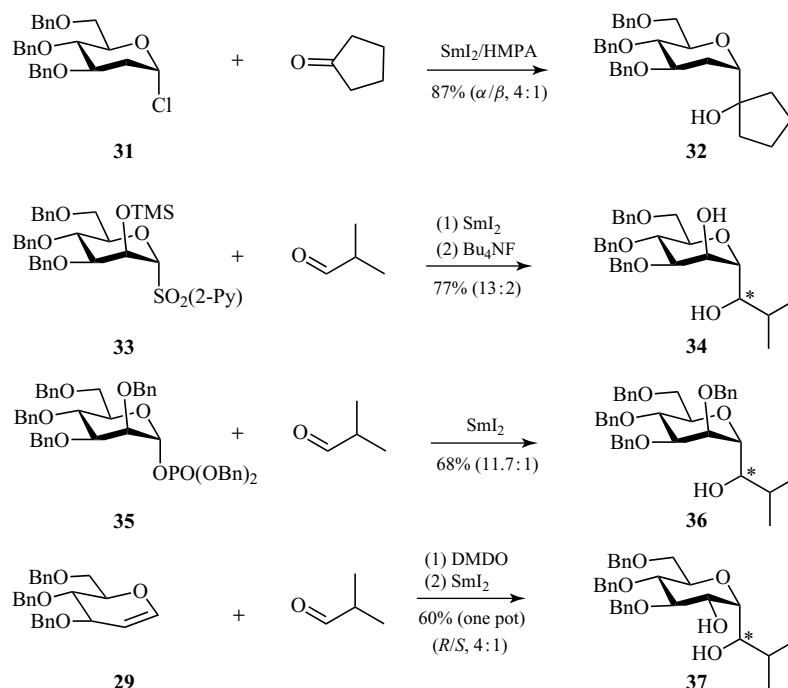
the C-2 substituent has also been observed in this imidoxylation reaction; a bulky *N*-phthalimido group at this position reverses the stereochemical outcome to form β-C-glycosides exclusively. The reaction of pentopyranosyl and hexopyranosyl tellurides with electron-deficient heteroaromatic bases has been studied by Togo and Yokoyama and C-nucleoside analogs have been synthesized in moderate yields.⁴⁰



Scheme 3 Synthesis of C-glycosides by intermolecular trapping of glycosyl radicals with unsaturated compounds using transition-metal reagents. tmc, tetramethylcyclam; COD, 1,5-cyclooctadiene; bpy, 2,2'-bipyridyl; DMDO, dimethyl dioxirane.

Several coordination complexes and salts of the transition metals such as Ti(III) (see **Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**), Ni(II), Ru(II), Cr(II), and Sm(III) (see **Organic Synthesis Using Samarium Diiodide**) have been used in the formation of anomeric radicals from glycosyl halides, and some examples are outlined in Scheme 3. Spencer and Schwartz have demonstrated that titanocene(III) chloride, a mild, nontoxic, and relatively inexpensive reducing reagent, is effective in the diastereoselective conversion of glucosyl bromide **21** into C-glycosides.^{41,42} The anomeric radical rather than an intermediate organotitanium species seems to be involved. In case of hexopyranosyl halides, when methyl vinyl ketone, methyl acrylate,

and acrylonitrile are used as radical traps, exclusive α -selectivity has been observed in the addition products **22–24**. 1-Gluco-, 1-manno-, and 1-galacto-pyranosyl radicals can also be generated from the corresponding bromides using nickel(II) salts as catalysts. For example, the reaction of glucosyl bromide **21** with Ni(tetramethylcyclam)₂(BF₄)₂ (20 mol%) and an excess of manganese dust with methyl methacrylate as an electron-deficient radical acceptor gave α -C-glycoside **25** in excellent yield.⁴³ Gagné have reported another stereoselective method for the Ni-catalyzed synthesis of α -C-alkylglycosides.^{44,45} The reaction of benzoyl glucosyl bromide **26** with methyl methacrylate using catalytic Ni(COD)₂ complex as precursor, (R)-Ph-pyBox as ligand, Zn dust as terminal



Scheme 4 Synthesis of *C*-glycosides via glycosyl-1-yl samarium intermediates.

reductant, and *i*Pr₂CHOH as proton source afforded α -*C*-glycoside **27** in high yield and diastereoselectivity. The same authors recently reported that irradiation of glucosyl bromide **21** with visible light in the presence of an excess of Hantzsch ester **28** and catalytic amounts of Ru(bpy)₃(BF₄)₂ generated glucopyranosyl radicals that reacted intermolecularly with electron-deficient olefins to provide α -*C*-glycosides **23**.⁴⁶ Several hydrolytically sensitive glycosyl halides of hexopyranose and pentopyranose series of carbohydrates have been transformed into *C*-glycosides with [Cr^{II}(EDTA)]²⁻ and electron-deficient alkenes under mild aqueous reaction conditions. For example, the two-phase reaction of an aqueous solution of the chromium complex and the glucosyl bromide **21** and acrylonitrile in ethyl acetate afforded the *D*-glycero-*L*-gulo-nonononitrile derivative **24**.⁴⁷ The anomeric radical produced by the reductive ring-opening of 1,2-anhydro sugars with titanocene(III) chloride can be trapped with electrophilic olefins to give exclusively α -*C*-glycosides such as **30**, with the free hydroxyl group at C-2 available for further elaboration.⁴⁸ The reaction proceeded in two steps from the corresponding

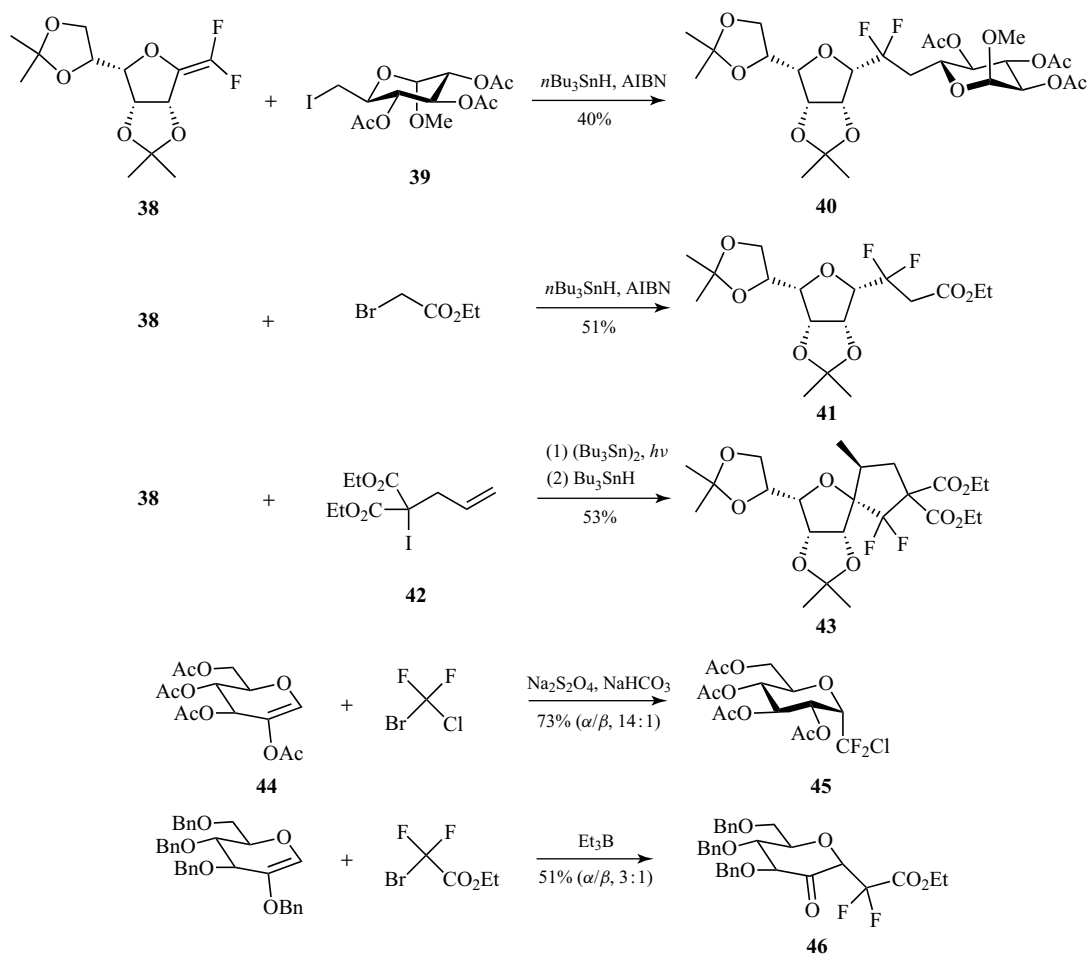
glycal **29** by preliminary epoxidation with dimethyl dioxirane (DMDO).

Sinaÿ in 1993 reported that reductive samarium of 2-deoxy- α -D-*arabino*-hexopyranosyl chloride **31** by the SmI₂/hexamethylphosphoramide (HMPA) system in the presence of cyclopentanone provided the corresponding α -*C*-glucoside **32** in high yield (Scheme 4).⁴⁹ They also found that under these conditions α -D-glucopyranosyl phenyl sulfones and bromides gave mainly 1,2-elimination products. In the absence of carbonyl compounds 1,2-elimination occurs exclusively and glucals are formed in synthetically useful yields.⁵⁰ Subsequently, Beau and Skrydstrup have thoroughly studied the samarium diiodide reduction of glycosyl pyridyl sulfones with aldehydes or ketones for the stereospecific formation of 1,2-*trans*-*C*-glycosides.^{51,52} Mannosylpyridyl sulfones such as **33** gave α -*C*-glycosides **34** in good yield, while glucosyl and galactosyl pyridyl sulfones gave β -*C*-glycosides only in moderate to low yields. In this last case, the major by-product was the corresponding glucal and the reaction needed to be catalyzed with NiI₂ to prevent the 1,2-elimination drawback.⁵³ Similarly, Hung and Wong⁵⁴ used samarium of

mannosyl phosphate **35** with simple aldehydes to give α -C-mannoside **36**. The two-step/one-pot DMDO oxidation– $\text{SmI}_2/\text{NiI}_2$ intermolecular reductive coupling sequence of glycals, such as **29**, with carbonyl compounds developed by Chiara and Sesmilo⁵⁵ provides a new methodology for the synthesis of 2-hydroxy C-glycosides **37**. The stereoselectivity, which can be significantly modified by the addition of a proton source, was also very sensitive to steric effects. With aldehydes, α -C-glycosides were predominantly or exclusively obtained, whereas ketones gave the corresponding β -isomers as major products.

Motherwell⁵⁶ has prepared difluoromethylene-linked C-glycosides and C-disaccharides by addition of electrophilic and nucleophilic radicals

to *gem*-difluoro-*exo*-glycals. The reaction of gulofuranose derivative **38** with 6-deoxy-6-iodo-glucopyranose **39**, under the tin hydride system, to give *gem*-difluoro-C-disaccharide **40** is representative of the addition to nucleophilic radicals (Scheme 5). The use of electrophilic radicals gave somewhat better results; thus the reaction of **38** with ethyl bromoacetate afforded α -C-glycoside **41** in 51% yield. As an interesting extension of this approach, the authors have reported the addition and concomitant 5-*exo*-trig ring closure of allyl iodomalonate **42** to *exo*-glycal **38** to afford the 1-oxaspiro[4.4]nonane bicycle derivative **43** in a one-pot, two-step sequence. Two new routes to α - CF_2 -glycosides by the addition of difluoromethyl radicals to 2-*O*-alkoxy glycals have been described.



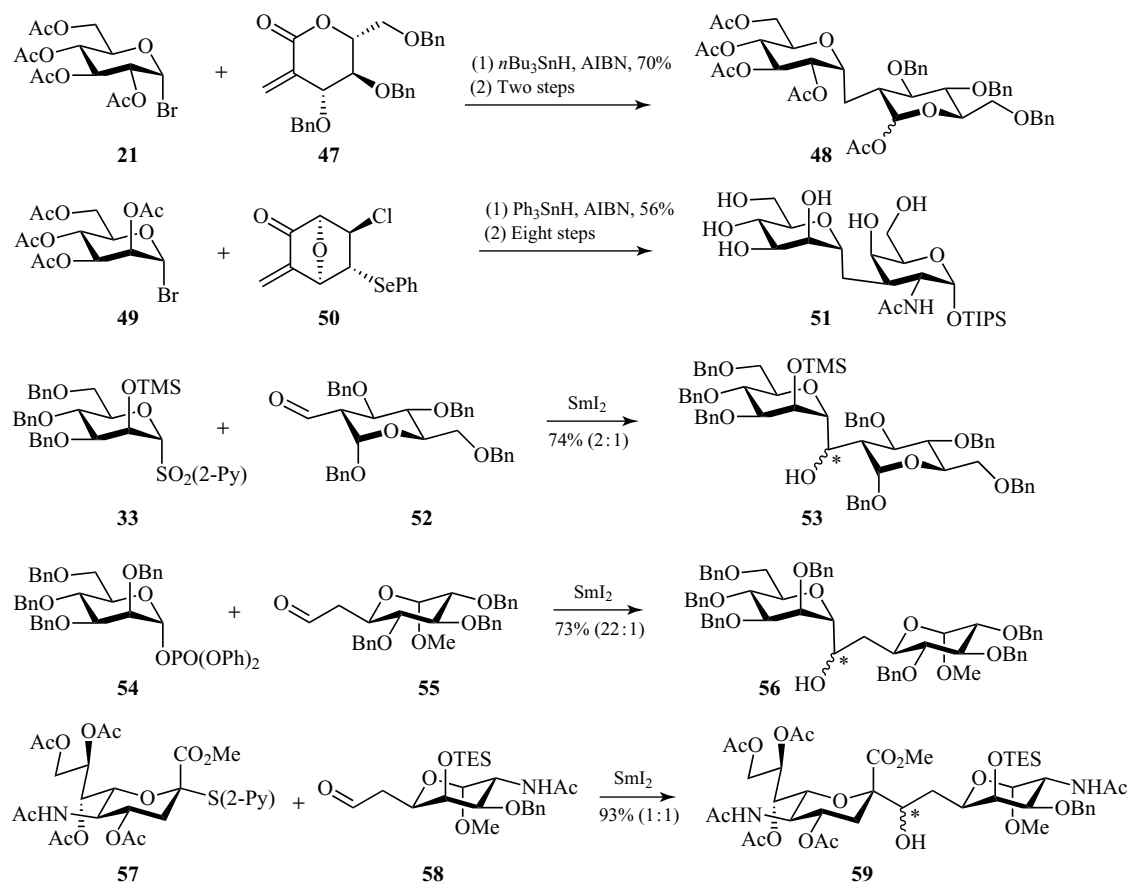
Scheme 5 Synthesis of C-glycosides by intermolecular addition of alkyl radicals to unsaturated carbohydrate acceptors.

Miethchen⁵⁷ prepared 1,1-difluoroheptitol **45** by reaction of 2-*O*-acetyl-1,5-anhydrohex-1-enitol **44** with bromochlorodifluoromethane in the presence of sodium dithionite, which acts as radical initiator but also as reducing agent. In the other approach, the triethylborane-mediated reaction of ethyl bromodifluoroacetate with 2-*O*-benzyl glycols to give 2,2-difluoro-4-ulosonic ester **46** has been developed by Leclerc.⁵⁸

2.2 Synthesis of C-Disaccharides

Since Giese and Witzel published their seminal work in 1986,⁵⁹ radical chemistry has been transformed into a useful alternative for the synthesis of *C*-disaccharides, which are important nonhydrolyzable *O*-disaccharide mimetics with

potential activity as enzymatic inhibitors. The utility of Giese *C*-glycosylation is exemplified by the synthesis of the analog of kojibiose α -D-Glcp-(1 $\rightarrow$ 2a)-2a-carba- α -D-Glcp **48** by reaction of the α -methylene lactone **47** with glucosyl bromide **21** (Scheme 6). The intermolecular radical addition occurs in 70% yield with high diastereoselectivity.⁶⁰ Vogel has used this tin-based methodology to add a number of glycosyl halides to enone **50**, a versatile chiral synthon prepared from a “naked sugar”.⁶¹ The radical addition products were subsequently and conveniently transformed into *C*-disaccharides by a multistep sequence. For example, the reaction with mannosyl bromide **49** afforded α -D-Manp-(1 $\rightarrow$ 3a)-3a-carba-D-GalpNAc **51**, while a slight modification of the synthetic procedure permitted the *C*-2 isomer α -D-Manp-(1 $\rightarrow$ 3a)-3a-carba-D-TalpNAc to be prepared. Another example of the



Scheme 6 Intermolecular synthesis of *C*-disaccharides.

Table 1 Synthesis of *C*-disaccharides by intermolecular samarium.

Entry	<i>C</i> -Disaccharide	Yield (%)	Reference
1	α -D-Manp-(1 $\rightarrow$ 2a)-2a-carba- α -D-Glcp	74	51, 52
2	α -D-Manp-(1 $\rightarrow$ 2a)-2a-carba- α -D-Manp	73–85	63
3	α -D-Manp-(1 $\rightarrow$ 3a)-3a-carba- α -D-Manp	23 ^a	64
4	α -D-Manp-(1 $\rightarrow$ 4a)-4a-carba- α -D-Manp	55	65
5	α -D-Manp-(1 $\rightarrow$ 4a)-4a-carba- α -D-Glcp	42	73
6	α -D-GlcpNAc-(1 $\rightarrow$ 6a)-6a-carba- α -D-Glcp	60 ^b	66
7	β -D-Glcp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Manp	83 ^c	53, 67
8	β -D-Galp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Manp	85 ^c	53
9	α -D-Manp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Manp	88 ^c	53, 64
10	β -L-Fucp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Manp	89 ^c	53
11	α -D-Manp-(1 $\rightarrow$ 3a)-3a-carba-[α -D-Manp-(1 $\rightarrow$ 6a)-6a-carba]- α -D-Manp	46 ^a	64
12	α -D-Manp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Glcp	73	54
13	α -Neup5Ac-(2 $\rightarrow$ 6a)-6a-carba- α -D-Galp	82	68, 69
14	α -Neup5Ac-(2 $\rightarrow$ 6a)-6a-carba- α -D-Manp	80	68, 69
15	α -Neup5Ac-(2 $\rightarrow$ 6a)-6a-carba- α -D-GalpNAc	93	69, 70
16	α -Neup5Ac-(2 $\rightarrow$ 3a)-3a-carba- α -D-Galp	88	71
17	α -Kdop-(2 $\rightarrow$ 6a)-6a-carba- α -D-Galp	77	72

^a Three-step overall yield, including the radical deoxygenation of the interglycosidic alcohol.^b dr α/β , 4:1.^c A catalytic amount of NiI₂ was added.

utility of unsaturated ketones as acceptors and the tin hydride method is the reaction of 2,6-anhydro-1-deoxy-1-iodo-D-*glycero*-D-*gulo*-heptitol with levoglucosenone to give β -D-Glcp-(1 $\rightarrow$ 4a)-4a-carba-3-deoxy-D-Glcp due to Witczak *et al.*⁶²

Over the past several years, Beau and Skrydstrup^{51–53,63–70} have conducted a detailed study on the samarium diiodide reduction of glycosyl pyridyl sulfones with carbohydrate aldehydes under Barbier conditions which led to the intermolecular formation of *C*-disaccharides in a highly efficient and stereoselective manner. With regard to the samarium mechanism, the reduction of the glycosyl sulfone is believed to proceed through two consecutive one-electron processes. The resulting anomeric organosamarium species subsequently adds to the carbonyl compound. The reaction proceeds efficiently in the manno series to give 1,2-*trans*-*C*-disaccharides in high yield and excellent diastereoselectivity. In the gluco and especially in the galacto series, the presence of NiI₂ as a catalyst is necessary; otherwise, significant amounts of 1,2-eliminated products (glycals) are obtained.⁵³ As a representative example, the samarium of 2-pyridyl sulfone **33** in the presence of aldehyde **52** to give *C*-disaccharide **53** in good yield is shown in Scheme 6.^{51,52} The use of a glycosyl phosphate group **54** as an

acceptor in the initial electron-transfer reaction and subsequent addition to aldehyde **55** to give the α -D-Manp-(1 $\rightarrow$ 6a)-6a-carba- α -D-Glcp derivative **56** has been proposed by Hung and Wong.⁵⁴ *C*-Disaccharides with the four possible linkages (1 $\rightarrow$ 2a), (1 $\rightarrow$ 3a), (1 $\rightarrow$ 4a), and (1 $\rightarrow$ 6a) have been prepared using this methodology, and the structures and yields are summarized in Table 1 (Entries 1–12). Of special interest are the samarium of D-GlcpNAc which gave a *C*-disaccharide with an anomalous 1,2-*cis* disposition preferentially, attributable to strong complexation between the *N*-acetamido group and the samarium ion (Entry 6), the Ni(II)-catalyzed reactions (Entries 7–10), and the synthesis of a *C*-trisaccharide in a single step from a 3,6-diformylmanno derivative (Entry 11). Since the first synthesis of an α -*C*-disaccharide of *N*-acetylneuraminic acid by Linhardt in 1997,⁷¹ a number of these compounds have been prepared, which are given in Table 1 (Entries 13–17). In a recent example, the 2-pyridyl sulfide of the Neup5Ac derivative **57** reacts with aldehyde **58** in a type of samarium-Reformatsky process to give stereoselectively **59** (Scheme 6).^{69,70} The procedure worked equally well with anomeric pyridyl sulfones of 3-deoxy-D-manno-2-octulosonic acid as donor using 6-formylgalactopyranoside as acceptor to give the α -*C*-disaccharide

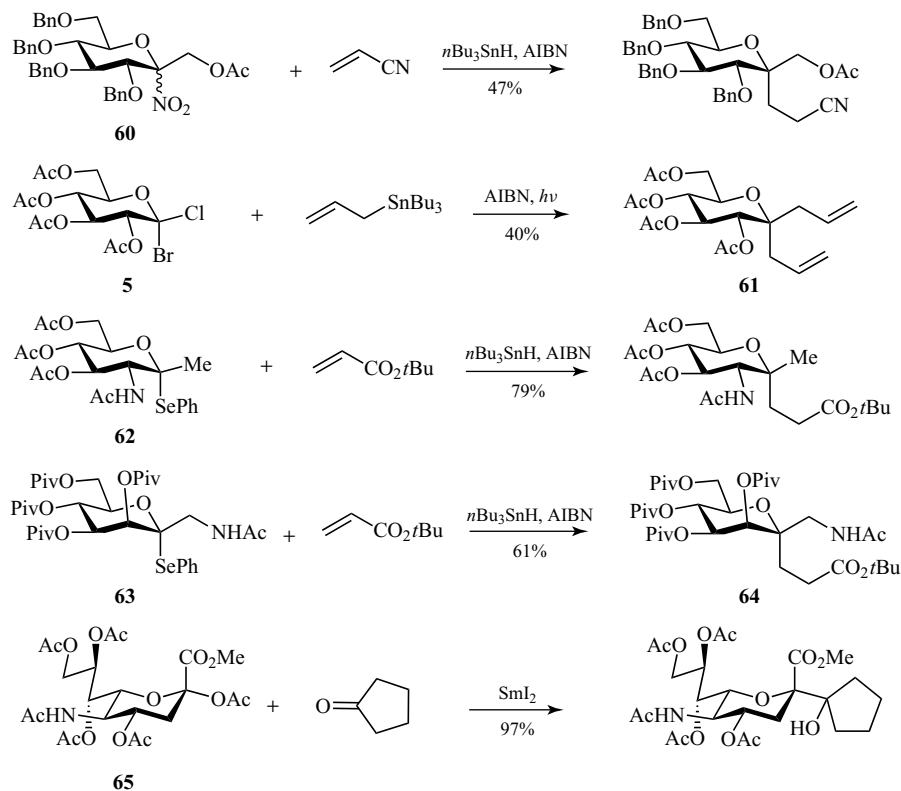
of KDO [α -Kdop-(2 $\rightarrow$ 6a)-6a-carba- α -D-Galp] (Entry 17).⁷²

2.3 Synthesis of C-Ketosides

C-Ketosides (bis-C,C-glycosides) are a class of carbohydrate analogs that have received increased attention of synthetic chemists owing to their relationship with C-glycosides of ulosonic acid and as versatile chiral synthons for a large range of natural complex molecular synthesis.

Since the first reports on the use of a reductive denitration of 1-nitro-C-glycosides **60** by Giese *et al.*^{15,74} in 1985, a few more examples have been found in the literature for the preparation of C-ketosides under radical intermolecular conditions, which are outlined in Scheme 7. The introduction of the required two tethers in a single step has been achieved by Praly⁷⁵ by reaction of 1-bromo- β -D-glucopyranosyl chloride **5** with

an excess of allyltributylstannane. The diallyl compound **61** was subsequently transformed into an anomeric spiro sugar (6-oxaspiro[4.5]dec-2-ene system) by way of ring-closing metathesis (RCM). C-Ketosides based on D-glucose, D-manno, and D-galacto series of N-acetyl-2-amino sugars **62** have been prepared by homolytic cleavage of the C–Se bond and α -trapping the resulting anomeric radical with *tert*-butyl acrylate and under Keck allylation conditions with allyltributylstannane. Styrene, which is not an efficient trapping agent for anomeric nucleophilic radicals, was also used, although, as expected, the corresponding addition product was obtained in low yield (29%).⁷⁶ The reaction can also be extended to seleno-C-glycoside **63**, the interesting carbohydrate-based δ -amino acid derivative **64** being obtained as a single diastereomer. A diastereoselective synthesis of the starting compound **63** has been achieved using a radical azidoselenation of *exo*-glycals as the key step (see **193** in Scheme 26).⁷⁷ The preparation of C-ketosides from N-acetylneuraminic acid and other ulosonic



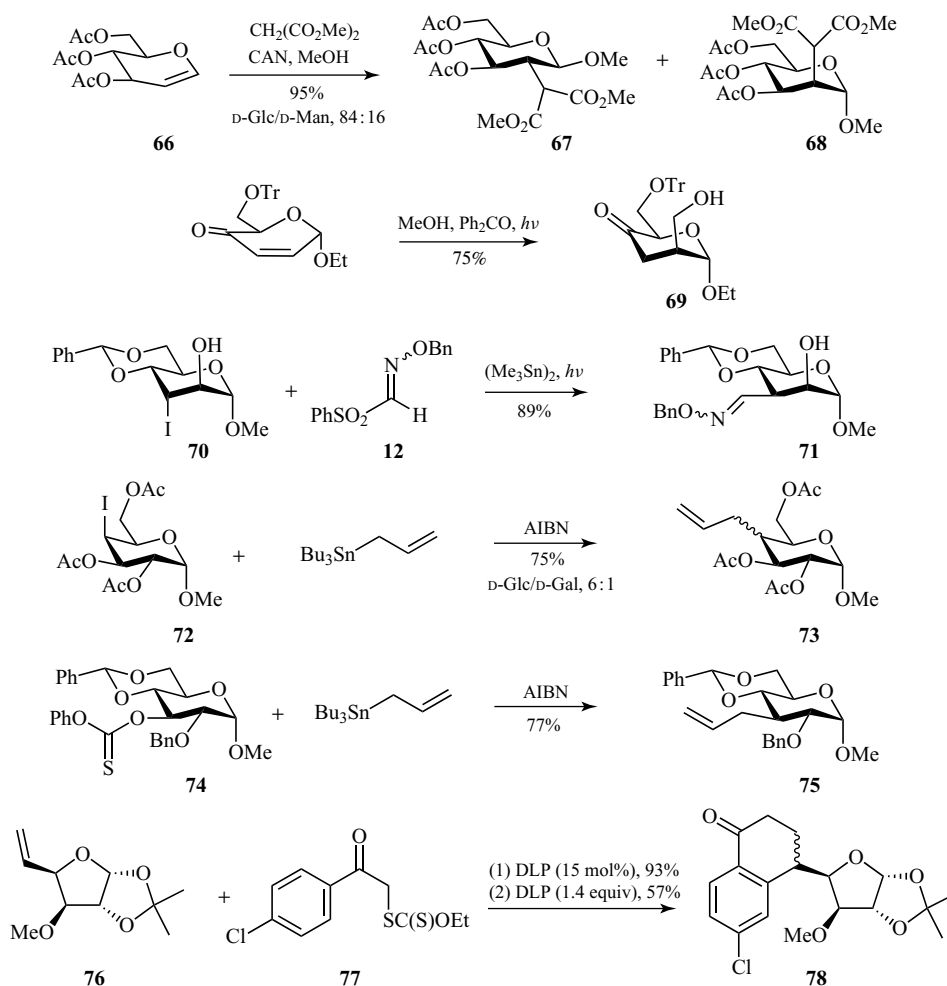
Scheme 7 Synthesis of C-ketosides by intermolecular addition of C-glycos-1-yl radicals to double bonds.

acid derivatives has been extensively studied. A variety of anomeric substituents such as chloride,⁷⁸ phenyl sulfone,⁷⁹ 2-pyridyl sulfide,^{69,70} 2-pyridyl sulfone,⁷¹ and acetate **65**⁸⁰ are useful precursors through reductive samarium in the presence of carbonyl compounds (see also **2** in Scheme 1).

2.4 Synthesis of Branched-Chain Sugars

Cerium(IV) ammonium nitrate (CAN) mediated radical addition of malonates (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**) to glycals has been thoroughly investigated by Linker⁸¹ and constitute a

general and convenient strategy for the synthesis of 2-C-malonyl carbohydrates. The reaction has been applicable to glycals of the hexose and pentose series and to disaccharide systems, and the corresponding 1,2-trans addition products were always obtained. For instance, acetyl glucal **66** with anhydrous CAN in methanol afforded a mixture of methyl β -D-glucoside **67** and α -D-mannoside **68** in excellent yield (Scheme 8). This work follows the pioneering CAN-mediated radical azidonitration of glycals by Lemieux and Ratcliffe.⁸² The benzophenone-initiated photoaddition of methanol to endocyclic conjugated α -enones developed by Fraser-Reid⁸³ provides a method for the preparation of C-2 and C-4 branched



Scheme 8 Synthesis of branched-chain sugars. DLP, dilauroyl peroxide.

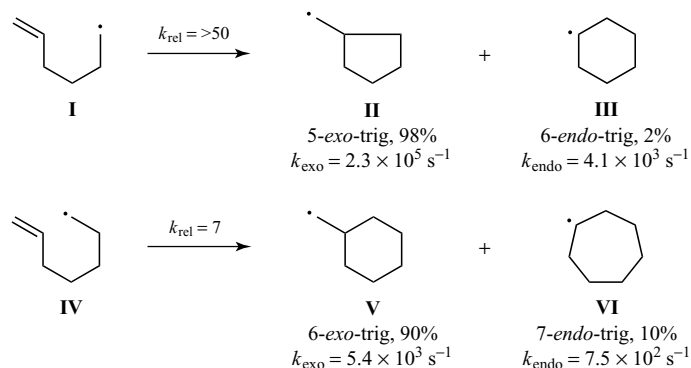


Figure 3 Ring-closure of 5-hexenyl and 6-heptenyl radicals. Rate constants taken from Ref. 89.

sugars such as **69**. The analogous additions of isopropanol to carbohydrate γ -lactones have been reported by Mann and Weymouth-Wilson.⁸⁴ The one-carbon extended C-glycosylation of Kim,³³ already described in Scheme 2, has also been applied by the authors to C-2, C-3, and C-6 positions of the sugar skeleton. For instance, ultraviolet irradiation of 3-iodo-D-mannoside **70** in the presence of phenylsulfonyl oxime ether **12** provided C-3-branched-chain glycoside **71** with total inversion of configuration. Postema *et al.*,⁸⁵ during the development of a general methodology for the synthesis of β -C-disaccharides by RCM, prepared C-2, C-3, and C-4 allyl branched-chain sugars. The reaction of iodine glycoside **72** with allyltributylstannane under Keck allylation conditions afforded a mixture of D-Glc/D-Gal **73** in a diastereomeric ratio, 6:1. Similarly, Castellón⁸⁶ also used Keck conditions to prepare C-3 and C-4 allyl-substituted carbohydrates such as 3-allyl-D-glucoside **75** from the 3-O-xanthate **74**. We have also included in this section the new strategy for the synthesis of naturally occurring C-aryl glycosides that has been developed by Cordero-Vargas *et al.*⁸⁷ The xanthate-mediated radical addition–cyclization sequence (see **Xanthates and Related Derivatives as Radical Precursors**) of xanthate **77** onto olefin **76** afforded tetralone **78**, which was subsequently aromatized.

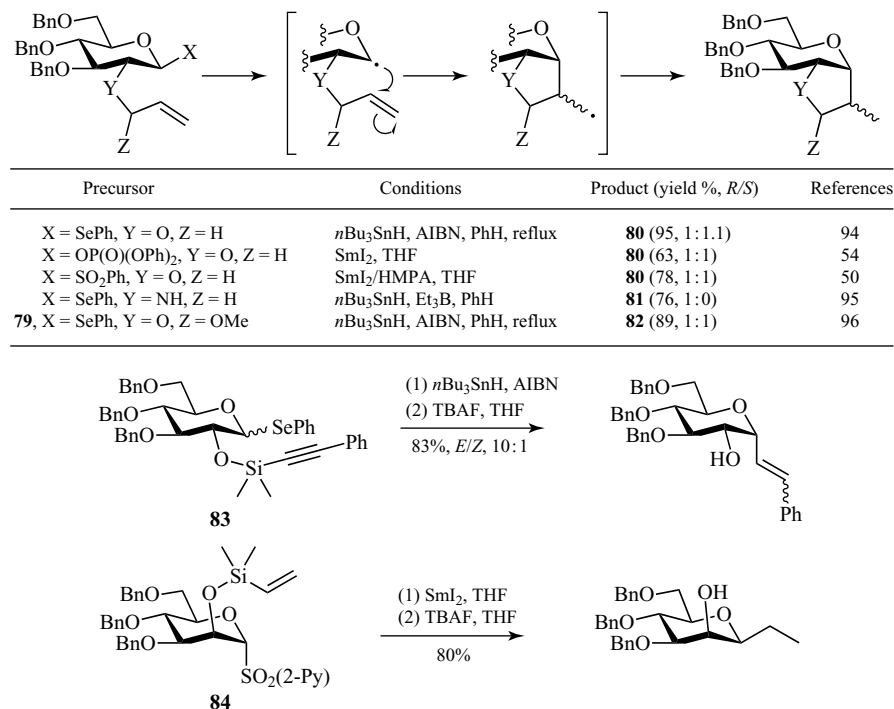
frameworks by intramolecular cyclization of acyclic carbohydrates has received considerable attention among synthetic organic chemists.⁶ By far, the most frequently used radical cyclizations involve the formation of five- and six-membered rings. According to the Baldwin rules, 5-hexenyl **I** and 6-heptenyl **IV** radicals cyclize predominantly through favored *exo*-trig processes to give the smaller rings **II** and **V**, respectively, the minor products **III** and **VI** being formed by *endo*-trig cyclizations (Figure 3).⁸⁸ The 5-hexenyl **I** and 6-heptenyl **IV** cyclization reactions proceed under kinetic control to give the thermodynamically less stable primary radicals **II** and **V** much faster than the secondary radicals. Beckwith has explained this regioselectivity on the basis of steric and stereoelectronic effects, suggesting that a major factor is the strain engendered in the transition states (TSs).^{89,90} The regioselectivity changes if the 5-hexenyl radical cyclization is reversible and the reaction is run under thermodynamic conditions; six-membered rings are formed predominantly.⁹¹ Substitution at the double bond or the presence of a silicon group in the chain can also favor the formation of six-membered rings.¹⁸ Calculated TSs for the ring closures of ω -alkenyl radicals have been extensively studied by different computational methods and are in excellent agreement with the stereo- and regioselectivity observed.⁹²

3 INTRAMOLECULAR CARBON–CARBON BOND-FORMING PROCESSES

The ability of free-radical chemistry to construct polyfunctionalized carbocyclic and heterocyclic

3.1 Synthesis of C-Glycosides

C-Glycosides can be prepared by the addition of a glycos-1-yl radical donor onto an acceptor group suitably anchored to the sugar ring by



Scheme 9 Synthesis of *C*-glycosides by intramolecular addition of glycos-1-yl radicals to an unsaturated acceptor. TBAF, tetrabutylammonium fluoride.

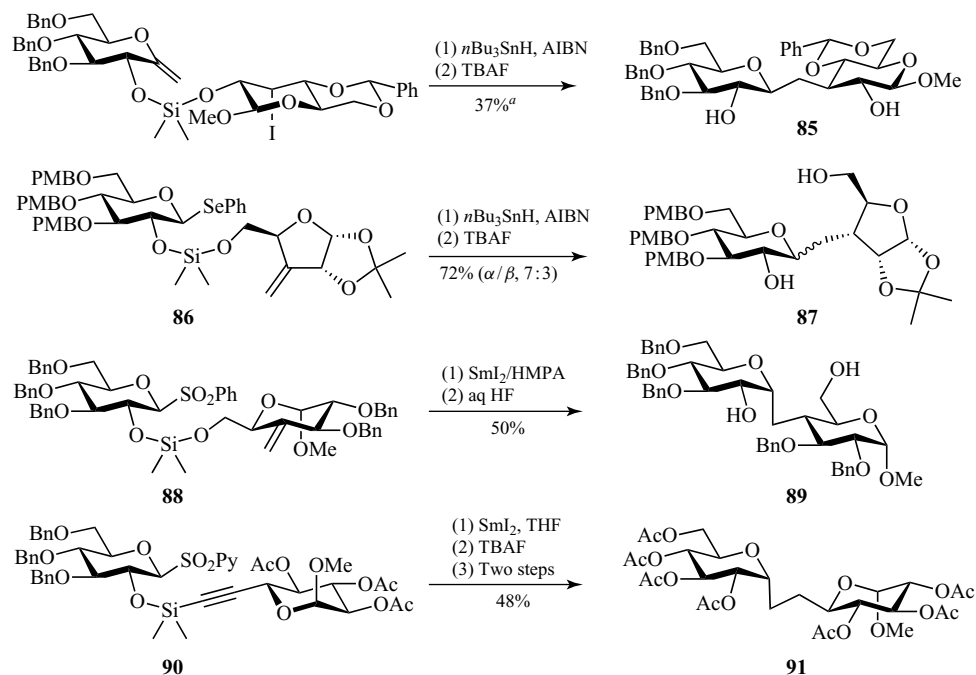
carbon or heteroatom linkage. An early example of this methodology is the formation of bicyclic dideoxy sugars by intramolecular radical cyclization after Giese.⁹³ De Mesmaeker *et al.*,⁹⁴ Hung and Wong,⁵⁴ Sinaÿ,⁵⁰ and Czernecki *et al.*⁹⁵ took advantage of this protocol for the synthesis of different cyclic *C*-glycosides **80–82** (Scheme 9). De Mesmaeker demonstrated, moreover, the usefulness of an easily removable acetal-linked group in **79** to obtain an acyclic 1,2-*cis*-*C*-glycoside through the corresponding fused cyclic α -*C*-glycoside **82**.⁹⁶ A noteworthy extension of this strategy by Stork achieves this challenge by the cyclization of an acceptor group tethered to the sugar ring through a temporary silicon linkage, such as **83**.⁹⁷ Subsequently, Skrydstrup and Beau demonstrated that the silicon-tether approach is also compatible with samarium diiodide reduction of mannosylpyridyl sulfone **84** to develop stereocontrolled radical cyclizations.⁹⁸

Sinaÿ transferred this temporary silicon linkage methodology to the synthesis of α -^{99–103} and β -*C*-disaccharides^{104,105} based on eight or

nine *endo*-trig radical cyclizations from two silaketal-tethered linked monosaccharides. The selective synthesis of a β -*C*-disaccharide **85** was accomplished successfully through an eight-membered TS (Scheme 10).¹⁰⁵ Shuto planned to use this type of radical coupling reaction for synthesizing α -*C*-glycosidic analogs of natural adenophostin A.¹⁰⁶ The tin-promoted glucopyranos-1-yl radicals from **86** triggered a nine-membered TS cyclization to give the α -*C*-disaccharide **87** in good yield and modest diastereoselectivity. A similar process for the 1,2-*cis*-*C*-disaccharide generation is also achievable using samarium diiodide. Starting from suitable anomeric radical precursors such as sulfones **88** and **90**, α -*C*-disaccharides **89**¹⁰⁷ and **91**^{98,108} were obtained, respectively.

3.2 Synthesis of *C*-Ketosides

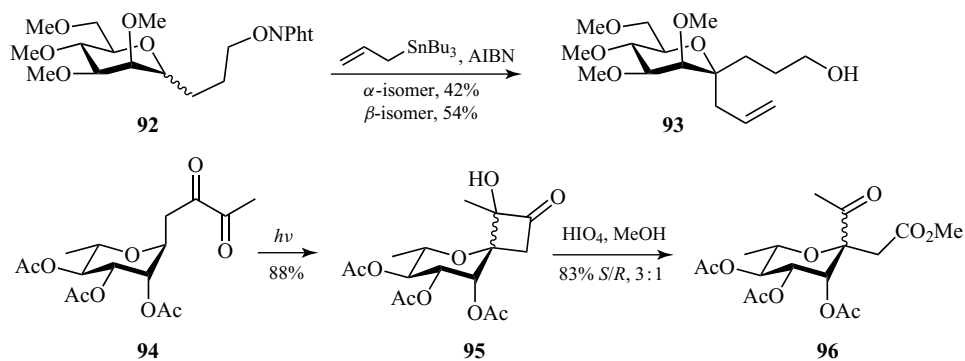
We envisaged a simple methodology for the preparation of *C*-ketosides, using an intramolecular HAT reaction as the key step.¹⁰⁹ A conveniently



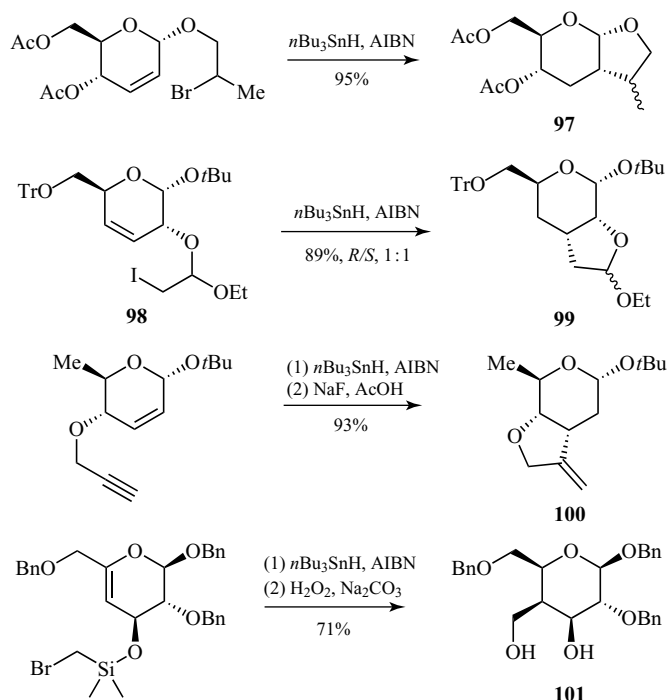
Scheme 10 Synthesis of C-disaccharides by intramolecular addition of carbohydrate radicals to an unsaturated acceptor, using a temporary silicon linkage. ^aOverall yield from starting monosaccharides.

disposed alkoxy radical generated from phthalimide **92** would trigger the HAT reaction, and the C-radical intermediate could be added to allylstannane to give C-ketoside **93** as depicted in Scheme 11. The stereochemistry of the quaternary carbon, carrying two differently functionalized tethers, is stereoelectronically controlled and independent of that of the starting isomer. In

a recent work, we prepared new spirocyclic C-ketoside derivatives by a diastereocontrolled Norrish–Yang photocyclization of 2,3-diulose **94** (see **Synthetic Radical Photochemistry**).¹¹⁰ The 2-hydroxy-cyclobutanone **95** intermediate could be converted into γ -ketoester **96** through oxidative ring cleavage with periodic acid.



Scheme 11 Intramolecular synthesis of C-ketosides.



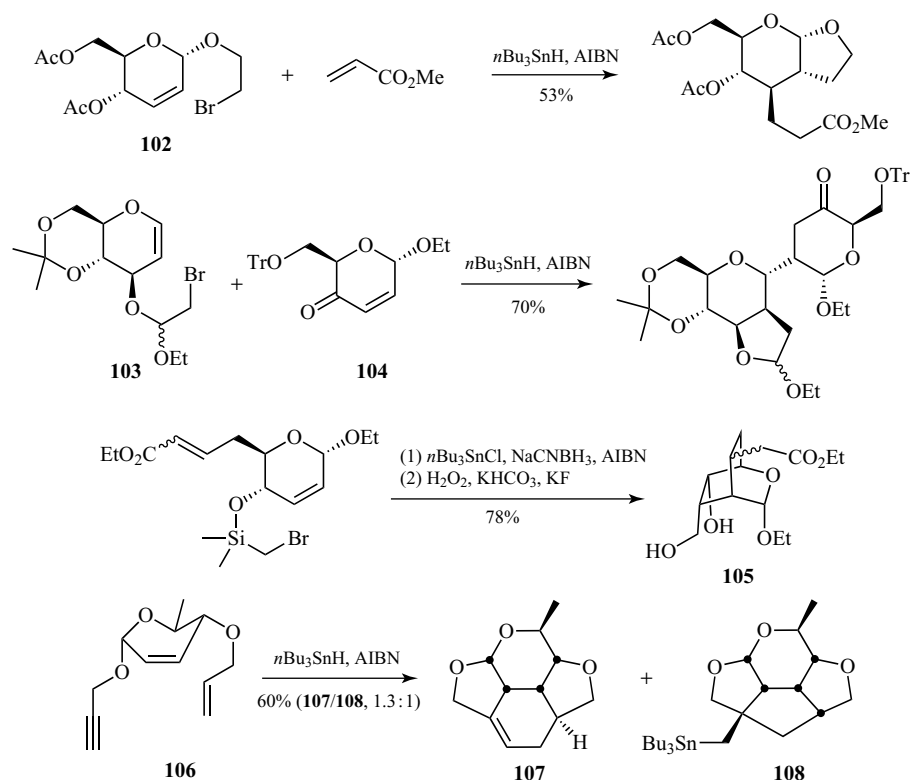
Scheme 12 Synthesis of branched-chain sugars by intramolecular addition of tethered radicals to unsaturated carbohydrates.

3.3 Synthesis of Branched-Chain Sugars

For the introduction of carbon chains on a carbohydrate template, two main approaches can be considered. In the first one, an unsaturated sugar model acts as a radical acceptor while a C radical is generated on a tether carbon chain. The reverse principle is applied in the second version, in which the radical donor is generated on the sugar template and cyclizes onto a tether radical acceptor. The radical addition on unsaturated carbohydrates has been successfully used with 2,3-, 3,4-, and 4,5-unsaturated sugars to form C-2, C-3, and C-4 branched-chain carbohydrates (Scheme 12). In the first example, De Mesmaeker studied the stereochemical outcome of the 5-*exo*-trig cyclization to form *cis*-fused 4*H*-furo[2,3-*b*]pyran bicycle **97**.¹¹¹ Similarly, Chapleur¹¹² and Fraser-Reid¹¹³ used the radical cyclization of temporary α -halogen acetal tethers to synthesize C-2 or C-3 branched-chain sugars with predictable stereochemistry. The reaction of iodo acetal **98** to give α -fused product **99** is illustrative.¹¹² Furthermore, Chapleur also demonstrated that vinylic radicals, generated by

tributyltin hydride addition on triple bonds, add efficiently on 2,3-double bonds.¹¹⁴ In recent times, Kelly and Picton¹¹⁵ and Chiara¹¹⁶ have proficiently used this methodology. The Chiara application is shown for the stereoselective synthesis of **100**, the glycosidic moiety of antifungal GM222712. The strategy of the silyl ether temporary linkage, developed by Nishiyama *et al.*¹¹⁷ and Stork and Sofia,¹¹⁸ was used by Sinay,¹¹⁹ Herdewijn,¹²⁰ and Fraser-Reid.¹¹³ This procedure has been successfully employed for the hydroxymethylation of sugars at positions 3, 4, and 6. The synthesis of 4-deoxy-4-hydroxymethyl- β -D-galactose derivative **101** is a representative example.¹¹⁹

Radical addition to an unsaturated carbohydrate model generates an intermediate C radical located on the sugar template which may subsequently add inter- or intramolecularly to a new radical acceptor via a serial radical process. The pioneering works on sequential radical cyclization–intermolecular trapping reactions were developed by Ferrier and Petersen¹²¹ on differently tethered unsaturated sugar derivatives, such as **102**, and Fraser-Reid¹¹³ during the reaction

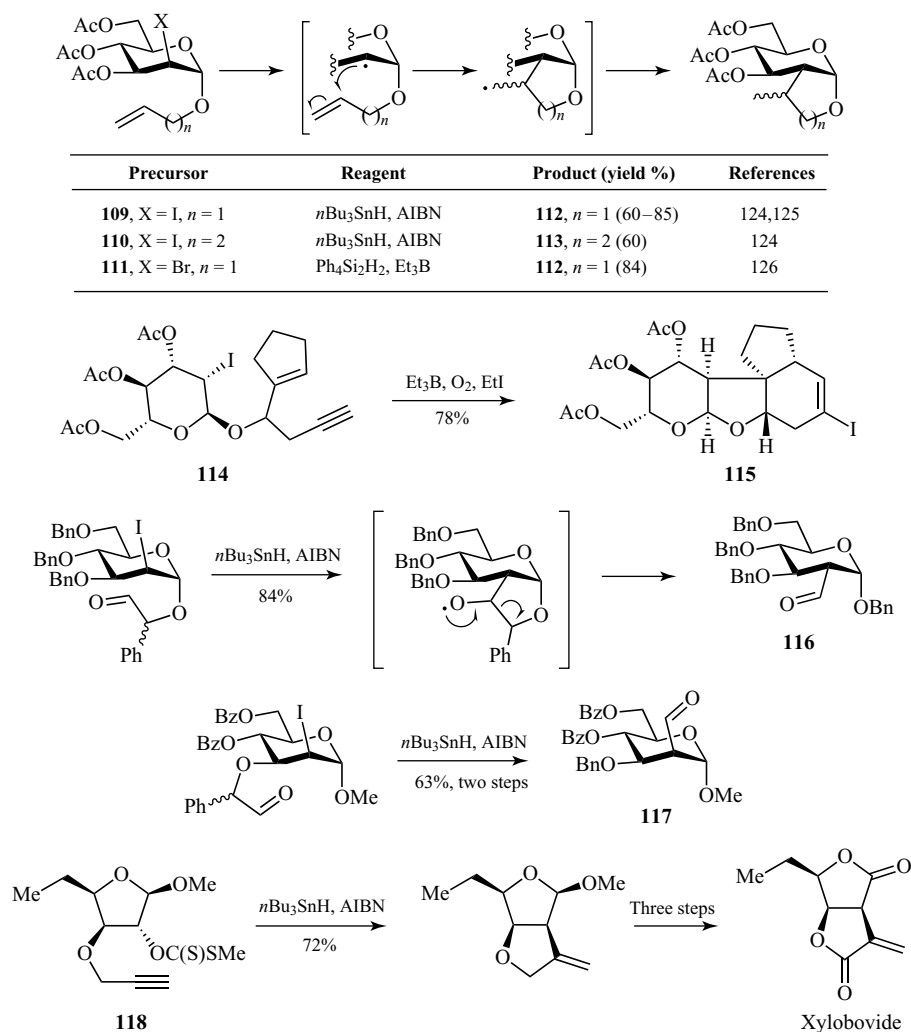


Scheme 13 Synthesis of branched-chain sugars by sequential addition of radicals to unsaturated carbohydrates.

of glycal **103** with enone **104** (Scheme 13). Alternative intramolecular trapping processes were described by Fraser-Reid¹²² for the stereocontrolled synthesis of Woodward's densely functionalized intermediate **105** for reserpine synthesis and by Kelly and Picton¹²³ who reported successful alkyne–alkene–alkene and alkyne–alkene–alkyne tin-initiated catalytic cascade tricyclizations, in which the three new rings are constructed in a single step. The cyclization of 4-*O*-allyl-1-*O*-propargyl sugar **106** produced the expected tetracycle **107** and an additional noncatalytic compound **108**.

In the second version of the intramolecular synthesis of branched carbohydrates, the radical is generated on the sugar template and adds to an exocyclic acceptor. As in the preceding approach, several different connections of the acceptor partner onto the sugars, such as acetal,^{124–128} ether,^{63,129} carbon,^{130–132} or silyl linkages,^{133,134} have been used. The pioneering works for the synthesis of C-2 branched pyranosides where the radical acceptor is linked by an acetal group came from Beau¹²⁴ and De

Mesmaeker *et al.*,¹²⁵ who used *O*-alkenyl (such as **109** or **110**) or alkynyl iodo glycosides to synthesize cis-fused bicycles by treatment with *n*Bu₃SnH (**112** or **113**, respectively), confirming that the cyclization is under kinetic control and proceeds exclusively via the favored *exo* mode (Scheme 14). Consequently, Togo used a similar synthetic approach from glycoside **111** to bicyclic sugar **112**, but using Ph₄Si₂H₂ which is a less toxic radical reagent.¹²⁶ Moreover, Hoffmann developed a stunning radical tandem cyclization of 2β-iodo glucopyranosides **114**.¹²⁷ The process afforded doubly annulated enantiomerically pure glycoside **115**, in a 5-*exo*-trig, 6-*endo*-dig cascade. Subsequently, Choe and Jung described a new method to prepare 2-formyl-glucoside **116** employing a radical formyl transfer process driven by the formation of a stable benzyl radical.¹²⁸ This was similarly used by Skrydstrup and Beau to prepare 2-formyl-mannopyranoside **117**, this time using an ether connection to the carbohydrate sugar at C-3.⁶³ Ongoing with the ether linkage, Sharma achieved the first total synthesis of xylobovide by an

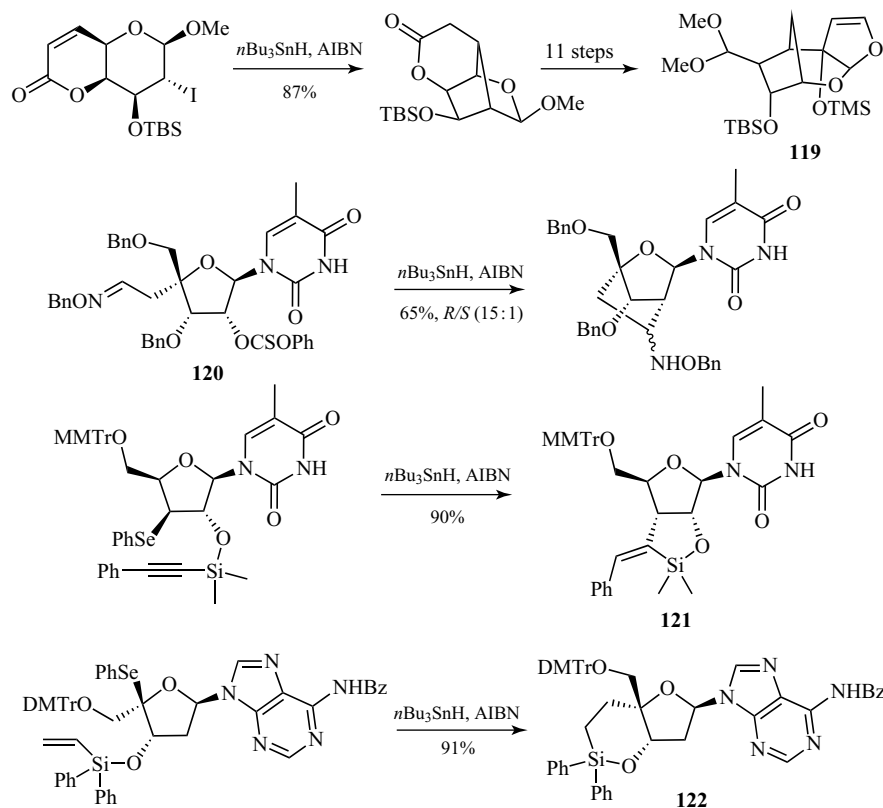


Scheme 14 Synthesis of C-2 branched-chain sugars by intramolecular addition of radicals positioned on the carbohydrate skeleton to unsaturated tethers.

intramolecular radical cyclization-based route promoted by a xanthate precursor **118**.¹²⁹

The earliest works for the synthesis of branched pyranosides in which the radical acceptor is linked to the sugar by a carbon atom are from Hashimoto for the synthesis of cyclopentane-annelated pyranosides.¹³⁰ Subsequently, Fraser-Reid took advantage of this strategy for preparing densely functionalized natural products or segments thereof from carbohydrate precursors as shown in Scheme 15 for the synthesis of the tricyclic dihydrofuran portion of azadirachtin **119**.¹³¹ Chattopadhyaya developed an intramolecular free-radical ring-closure

reaction between a radical generated at C-2 and a distant C=N double bond of an oximino-ether **120**.¹³² Finally, some appealing approaches to branched-chain nucleosides have also been described.^{133–135} Chattopadhyaya used silicon-tethered acetylene to accomplish a 5-*exo*-trig cyclization giving exclusively the *cis*-fused isomer **121**.¹³³ Some studies implemented by Matsuda¹³⁴ and Mayon and Chapleur¹³⁵ on *O*-linked vinyl-silicon tethers emphasize that the presence of a silicon atom in the tether strongly influences the cyclization process. The thermodynamic 6-*endo* product **122** is formed only at low concentration of



Scheme 15 Synthesis of branched-chain sugars by intramolecular addition of radicals positioned on the carbohydrate skeleton to unsaturated tethers. MMTr, 4-monomethoxytrityl; DMTr, 4,4'-dimethoxytrityl.

hydride; at higher concentrations the corresponding 5-exo product was exclusively produced.¹³⁴

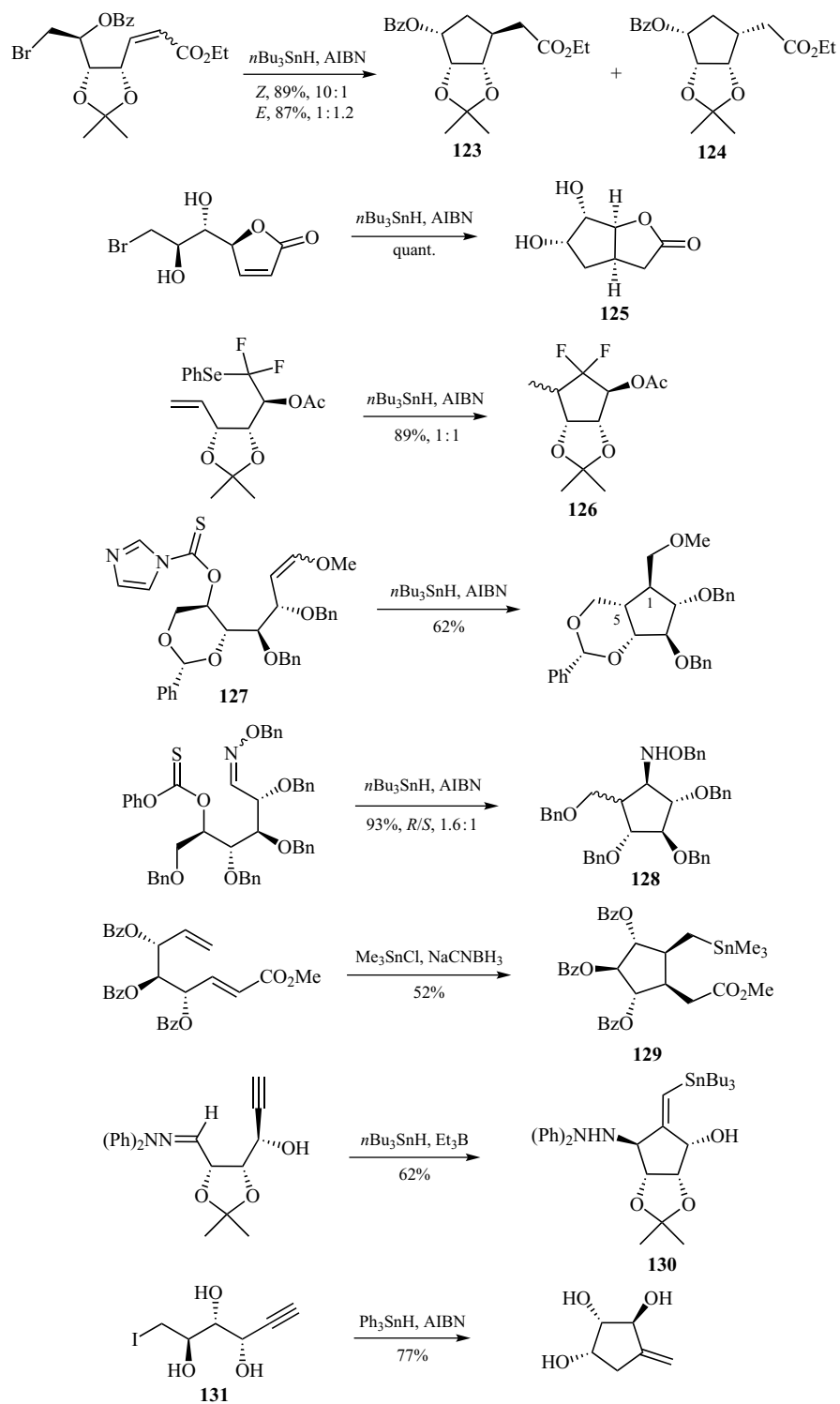
Marco-Contelles¹⁴⁰ can also be found in the literature.

3.4 Synthesis of Carbocycles from Acyclic Sugar Derivatives

Carbasugars, previously known as *pseudosugars*, are a family of carbohydrate mimics that has been attracting great interest among chemists and biochemists for the last two decades.¹³⁶ They are structurally similar to normal sugars, although the hemiacetal ring oxygen has been replaced by a methylene group. Gómez and López have recently reported a comprehensive review that exemplifies the progress made in the synthesis, conformational studies, and biological aspects of carbasugars.⁶ Earlier reviews by Fraser-Reid and Tsang,¹³⁷ Ferrier,¹³⁸ RajanBabu,¹³⁹ and Martínez-Grau and

3.4.1 Synthesis of Carbafuranoses and Polyfunctionalized Cyclopentane Analogs

The 5-exo cyclization is especially useful for the synthesis of cyclopentanes. In this field, Wilcox developed the first example of the radical 5-exo-trig cyclization derived from unsaturated halo-aldoses to prepare epimeric cyclopentanes **123** and **124** (Scheme 16).¹⁴¹ It was observed that the cyclization of the *Z* isomer proceeded with a greater degree of stereocontrol and the major product had an exo orientation of the ester group. In a similar reaction, Kita found that the use of V-70L instead of AIBN as radical initiator made it possible to achieve a higher stereoselective synthesis

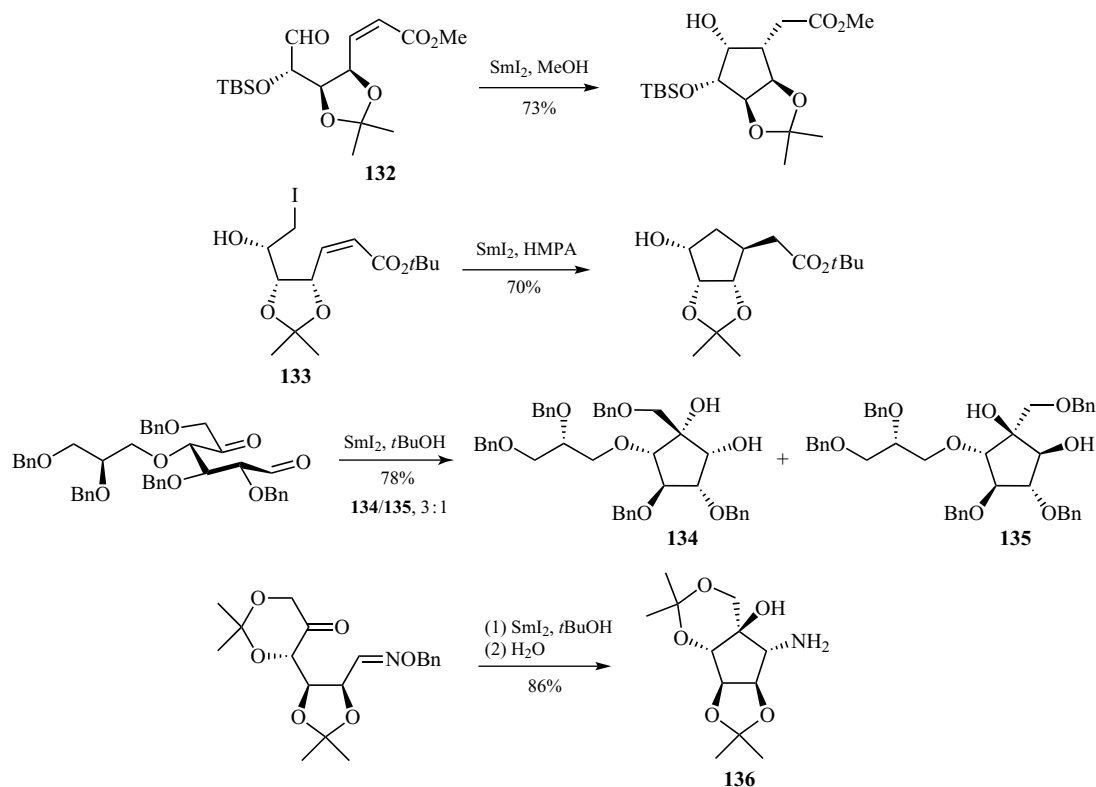


Scheme 16 Synthesis of cyclopentane derivatives via 5-*exo*-cyclizations with tin reagents.

of **123** and **124**.¹⁴² Roberts used an analogous methodology to synthesize different carbafuranoses starting also from primary haloderivatives,¹⁴³ while Lundt applied a related strategy for the synthesis of carbapentofuranoses such as **125** starting from bromodeoxyheptonolactones.¹⁴⁴ Similarly, Leclerc devised a general route to difluorinated carbocyclic 5-deoxypentofuranose analogs **126** but using a phenylselenenyl group.¹⁴⁵ In a related study, RajanBabu successfully employed secondary imidazole carbothioate **127**, observing that the corresponding hex-5-enyl radical cyclizes efficiently with exclusive formation of a cis-fused bicyclic system and 1,5-trans stereochemistry.¹⁴⁶ Bartlett opened up a straightforward approach to aminocarbafuranoses as **128** using a radical cyclization of carbohydrate-derived oxime ethers.¹⁴⁷ This procedure has been extended subsequently by a number of groups for the preparation of aminocyclopentitols.¹⁴⁸ Hanessian reported that trimethylstannyl radicals add to the unsubstituted terminal olefinic carbon atom of activated and

unactivated dienes to produce cyclopentane compounds such as **129** with the preponderance of the isomer with a syn orientation of the carbon substituents.¹⁴⁹ Similarly, Marco-Contelles disclosed the first examples of $n\text{Bu}_3\text{SnH}$ -promoted free-radical cyclization of δ -alkynyl tethered oximes, imines, and N,N -disubstituted hydrazones to provide a simple synthesis of enantiomerically pure aminocyclitol derivatives as **130** in moderate yields.¹⁵⁰ The 5-*exo*-dig radical cyclization of 1,2,6-trideoxy-6-iodo-*L*-arabino-hex-1-ynitol **131** could be a useful method to prepare exocyclic methylene cyclopentanes in good yields.¹⁵¹

A useful alternative to trialkyltin hydride-based reductive coupling is supplied by one-electron reducing agents such as samarium diiodide. In a pioneering approach to carbafuranoses, Enholm described, in 1989, the stereoselective SmI_2 -mediated intramolecular cyclization of aldehydes and electron-deficient alkenes, as depicted in **132**, to give cyclopentanols (Scheme 17).¹⁵² It was observed that a cis-olefin in the starting

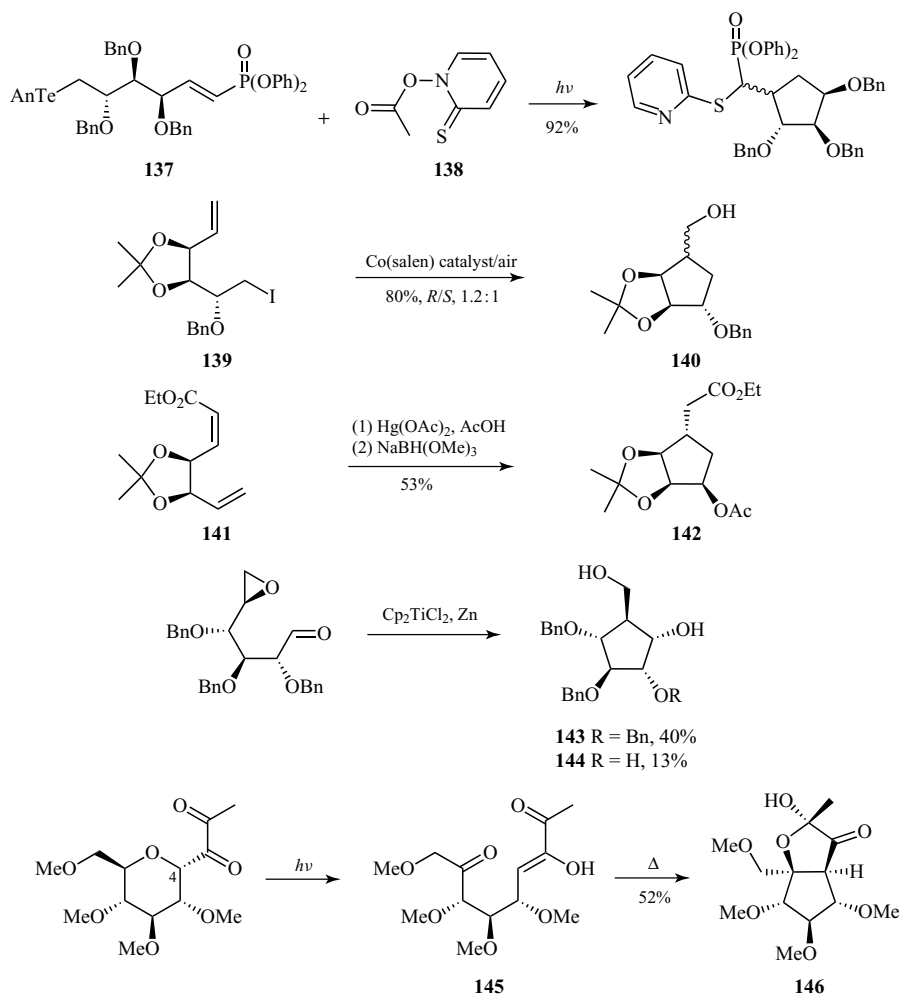


Scheme 17 Synthesis of cyclopentane derivatives by SmI_2 -mediated reductive coupling.

substrate favored a syn product, while a trans-olefin gave preferably the anti product. More recently, Holzapfel¹⁵³ and Matsuda¹⁵⁴ have also applied this methodology to convert selectively substituted carbohydrates into the analogous stereodefined cyclopentanols. Subsequently, Zhou and Bennett¹⁵⁵ used the SmI₂/HMPA system to perform the radical cyclization of D-ribonolactone-derived alkenyl halides **133**. Sinaý reported in 1995 a SmI₂-promoted stereoselective ring contraction of methyl hexodialdo-pyranosides to give highly functionalized cyclopentanes.¹⁵⁶ More recently, this method was applied by Jenkins and Potter¹⁵⁷ and Iadonisi¹⁵⁸ to develop a pinacolization in carbohydrate derivatives and by Sinaý¹⁵⁹ to give an

inseparable mixture of two cis-diol intermediates **134** and **135** in the total synthesis of calditol. The Giese¹⁶⁰ and Chiara *et al.*¹⁶¹ groups have described one of the most suitable methods for the synthesis of aminocyclopentitols such as **136** by SmI₂-based reductive couplings of polyhydroxylated oxime ethers¹⁶² or *N,N*-disubstituted hydrazones¹⁶³ in studies toward the synthesis of trehalamine.

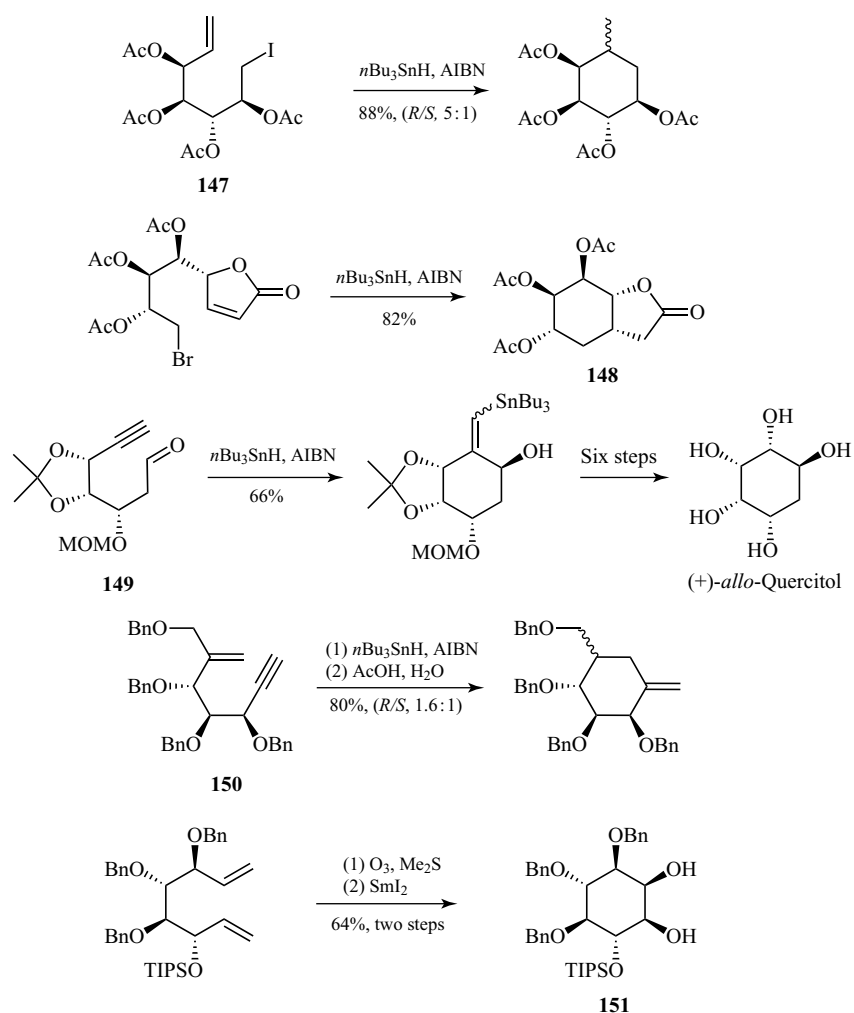
Besides samarium diiodide, there are also other alternatives to tributyltin hydride-promoted reductive coupling, such as the use of tellurium, cobalt, mercury, and titanium derivatives (Scheme 18). Barton designed a new source of alkyl radicals by radical exchange.¹⁶⁴ The process involves the use of



Scheme 18 Alternatives to tin and samarium reagents for the synthesis of cyclopentane derivatives. An, anisyl.

the acetyl derivative of *N*-hydroxy-2-thiopyridone **138** as a convenient source of methyl radical which can react with an anisyltelluride derivative such as **137** to afford the desired alkyl radical intermediate. This C radical is able to cyclize intramolecularly with a proper olefin to generate the corresponding carbocycle. On the other hand, Prandi developed a cobalt-catalyzed radical cyclization of 6-iodohex-1-enitol derivative **139** to give the expected hydroxymethyl-substituted cyclopentane **140**.¹⁶⁵ A process involving chemoselective mercuriation of diene **141**, followed by reductive radical cyclization, has been described by Gallos for the synthesis of carbocycle **142**.¹⁶⁶ Chiara has

shown that the reductive cross-coupling of epoxides with carbonyl groups promoted by titanocene chloride can also be successfully applied to the stereoselective synthesis of highly functionalized branched cyclitols such as **143** and **144** from readily available hexose precursors.¹⁶⁷ Recently, we developed a conceptually different approach for the synthesis of branched cyclopentitols such as **146** by photolysis of 4,8-anhydro-2,3-diuloses. The proposed mechanism implies a HAT reaction promoted by a Norrish type II photoelimination followed by a highly diastereoselective thermally induced enolexo aldol cyclization of an isolable photoenol intermediate **145** which acts as a preformed enolate.¹⁶⁸



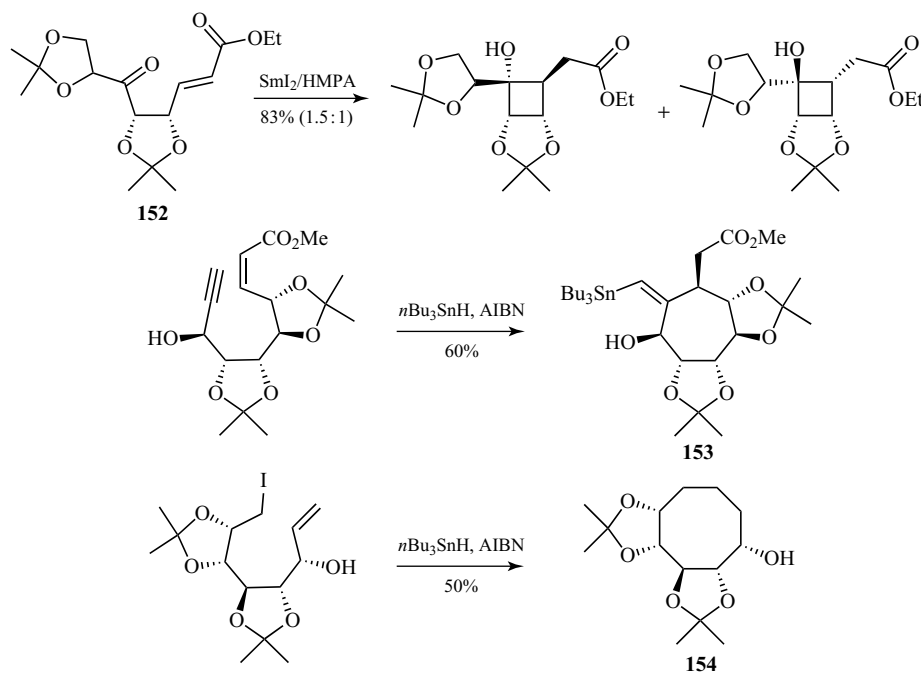
Scheme 19 Synthesis of cyclohexane derivatives.

3.4.2 Synthesis of Carbapyranoses and Polyfunctionalized Cyclohexane Analogs

The cyclization of 6-heptenyl radicals proceeds much more slowly than that of the 5-hexenyl radicals (Figure 3). In consequence, there are relatively few examples for the preparation of carbapyranoses by 6-*exo* or 6-*endo* radical ring closure.

Although the first examples of the synthesis of a 5a-carbapyranose by 6-*exo*-trig radical cyclization were published almost simultaneously by Samuelsson¹⁶⁹ and Schmid and Whitesides,¹⁷⁰ Redlich reported a comprehensive study on the scope of the radical ring closure of 7-deoxy-7-iodohept-1-enitols as **147** leading to several 6-deoxy-5a-carbapyranoses (Scheme 19).¹⁷¹ Marco-Contelles showed that, if the 6-*exo*-trig radical cyclization occurs on an α,β -unsaturated ester,¹⁷² an enol-ether double bond,¹⁷³ or an oxime¹⁷² the resulting carbasugars are useful building blocks for the preparation of differently substituted inositols. On other hand, Lundt extended the previous work developed on carba-furanoses¹⁴⁴ to 8-bromo-8-deoxy-oct-2-eno-1,

4-lactones for the regio- and stereoselective preparation of carbapyranoses **148**.¹⁷⁴ Yadav reported the first examples of the 6-*exo*-trig radical cycloisomerization of polyoxygenated alkyne-tethered aldehydes, of the type depicted by **149**, to prepare (+)-*allo*-quercitol and (+)-*talo*-quercitol with high diastereoselectivity.¹⁷⁵ The synthesis of carbasugars involving 6-*exo*-dig radical cyclization was first shown by McDevitt and Fraser-Reid¹⁷⁶ and afterward by Wightman.¹⁷⁷ More recently, Gómez and López have studied the different factors that favor the 6-*endo* versus 5-*exo* radical ring closure to lead to carbapyranoses.¹⁷⁸ They found that enyne **150**, which includes at least two regiodirecting features (vinyl radical and substitution at C-5), is able to undergo 6-*endo*-trig radical cyclization in good yields. Since the original works by Chiara and Martín-Lomas¹⁷⁹ and Mioskowski¹⁸⁰ on SmI₂-promoted pinacol coupling in a carbohydrate 1,6-dialdehyde to provide an inositol ring, others such as Kornienko and d'Alarcao¹⁸¹ or Matsuda¹⁸² have recently performed further studies in this field. As a representative example, the synthesis of a *myo*-inositol derivative **151** from a D-xylose derivative is shown in Scheme 19.¹⁸¹



Scheme 20 Synthesis of four-, seven-, and eight-membered carbocycles.

3.4.3 Synthesis of Four-, Seven-, and Eight-Membered Carbocycles

Chiral, nonracemic cyclobutanols form integral parts of various antiviral and sedative agents. In this field, Williams developed a procedure for the conversion of carbohydrate precursors into highly functionalized cyclobutanes employing SmI_2 by pinacol coupling,¹⁸³ or 4-*exo*-trig cyclization, as in **152** (Scheme 20).¹⁸⁴ On other hand, an emerging interest in the preparation of carbasugars containing rings larger than five or six members has arisen in recent years. In the radical approach, Marco-Contelles has described 7-*exo* and 8-*endo* free-radical carbocyclization of acyclic radical precursors derived from sugars for the synthesis of highly functionalized medium-sized rings such as **153** and **154**.¹⁸⁵

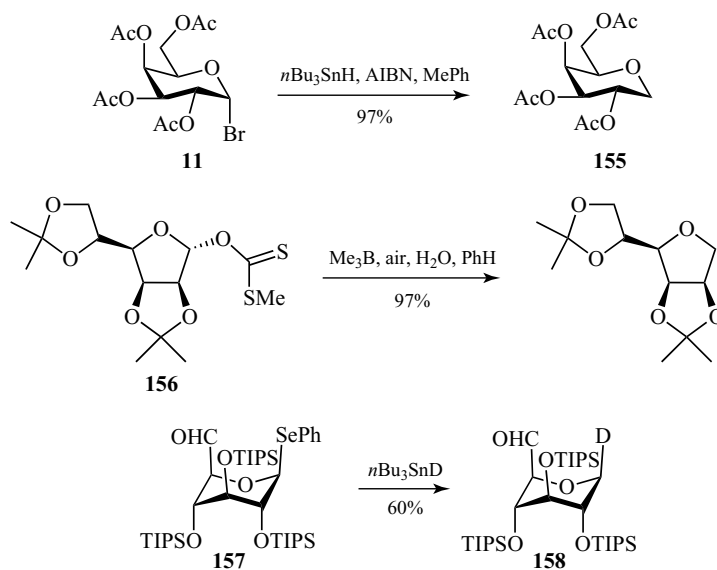
4 CARBON–HYDROGEN BOND-FORMING PROCESSES

In this section, we focus our attention on the deliberated reduction, namely formation of carbon–hydrogen bonds concerning anomeric and

non-anomeric C radicals generated under reductive conditions in carbohydrate models of significant synthetic interest.

4.1 Synthesis of Anhydroalditols

Hydrogen quenching of anomeric C radicals constitutes a simple method not only for the synthesis of anhydroalditols but also for the stereoselective preparation of β -C- or β -O-glycosides and 2-deoxy-sugars. In this context, Praly in 2001 reported a comprehensive review that exemplifies the progress made in the structure of anomeric glycosyl radicals and their transformations under reductive conditions.¹⁴ Augé and David published the first example of radical synthesis of 1,5-anhydroalditols starting from glycosyl chlorides by treatment with $n\text{Bu}_3\text{SnH}$ and AIBN.¹⁸⁶ Later work by Kocienski employed more reactive glycosyl bromides and photochemical initiation.¹⁸⁷ Recent selected examples include the synthesis of the disaccharide 1,5-anhydromaltitol by Vismara¹⁸⁸ and the reduction of galactopyranosyl bromide **11** to give 1,5-anhydro-galactitol **155** in nearly quantitative yield by Thiem (Scheme 21).¹⁸⁹ In addition to glycosyl halides, 1,5-anhydrohexitols



Scheme 21 Synthesis of anhydroalditols.

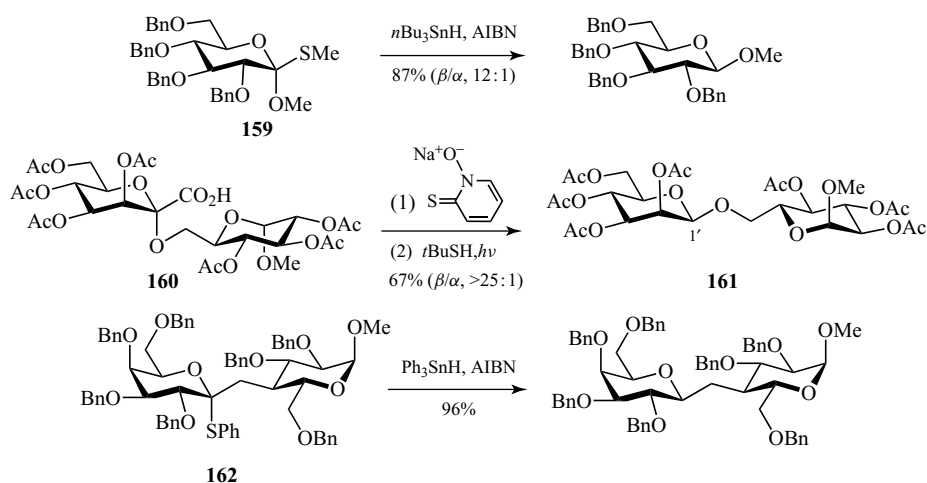
have also been frequently prepared in good yields from phenylselenides,^{190,191} xanthates,¹⁹² or organotellurides,¹⁹³ among others. Apart from tin reagents, other alternative reductants such as tris(trimethylsilyl)silane (TTMSS) (see **Silanes as Reducing Reagents in Radical Chemistry**),¹⁹⁴ hypophosphorous salts,¹⁹⁵ and arylthiols¹⁹³ for the case of telluroglycosides have been used as well. Compared that of to 1,5-anhydrohexitols, the preparation of 1,4-anhydroalditols has received only limited attention, although a few examples can be found in the recent literature starting from anomeric xanthates.^{196,197} For instance, Wood¹⁹⁷ used a trialkylborane/air/water system to accomplish the radical-mediated deoxygenation of xanthate **156**. To analyze the stereoselectivity of the HAT reaction promoted by anomeric C radicals, some deuterium studies have been carried out. It was observed that in the $n\text{Bu}_3\text{SnD}$ reduction of α - and β -D-glucosyl and α -D-mannosyl halides, with the pyranose ring in $^4\text{C}_1$ chair conformation, the stereochemistry of the deuterium in the 1,5-anhydroalditol is very predominantly α -axial and independent of the stereochemistry of the starting halide.^{198,199} Recently, Shuto studied the stereoselectivity using conformationally $^1\text{C}_4$ -restricted glucose derivative **157**; deuteration by β -axial attack gave exclusively the β -deuterated product **158**.¹⁹¹ These results reflect that stereoelectronic effects play an important role in radical reactions at the anomeric center, as was commented upon in Section 2.

4.2 Stereocontrolled Synthesis of β -O- and β -C-Glycosides

There are two different main routes to give β -O- and β -C-glycosides. The first approach involves a single radical intermediate generated regioselectively and directly at the anomeric center. However, the second route engages a preliminary radical generated somewhere in the molecule which subsequently promotes a favorable regioselective hydrogen-atom abstraction at the anomeric center to lead to the corresponding anomeric C-radical intermediate formed by radical translocation. In both cases, the final hydrogen trapping of the anomeric C radical is the key step in terms of stereoselectivity.

4.2.1 Diastereoselective Hydrogen Quenching of Anomeric Radicals

Within the framework of this first approach, Kahne pioneered the application of alkoxy-substituted anomeric radicals for the synthesis of β -O-glycosides.²⁰⁰ These radicals were prepared from hemithio ortho esters such as **159** by treatment with $n\text{Bu}_3\text{SnH}$, observing that hydrogen quenching led preferentially to the β anomer in high yields (Scheme 22). Moreover, Crich²⁰¹ proved that the Barton radical decarboxylation of *O*-acyl thiohydroxamates of 2-ulopyranosonic acids, as depicted by **160**, gave the β -D-Manp-(1 $\rightarrow$ 6)- α -D-Glcp



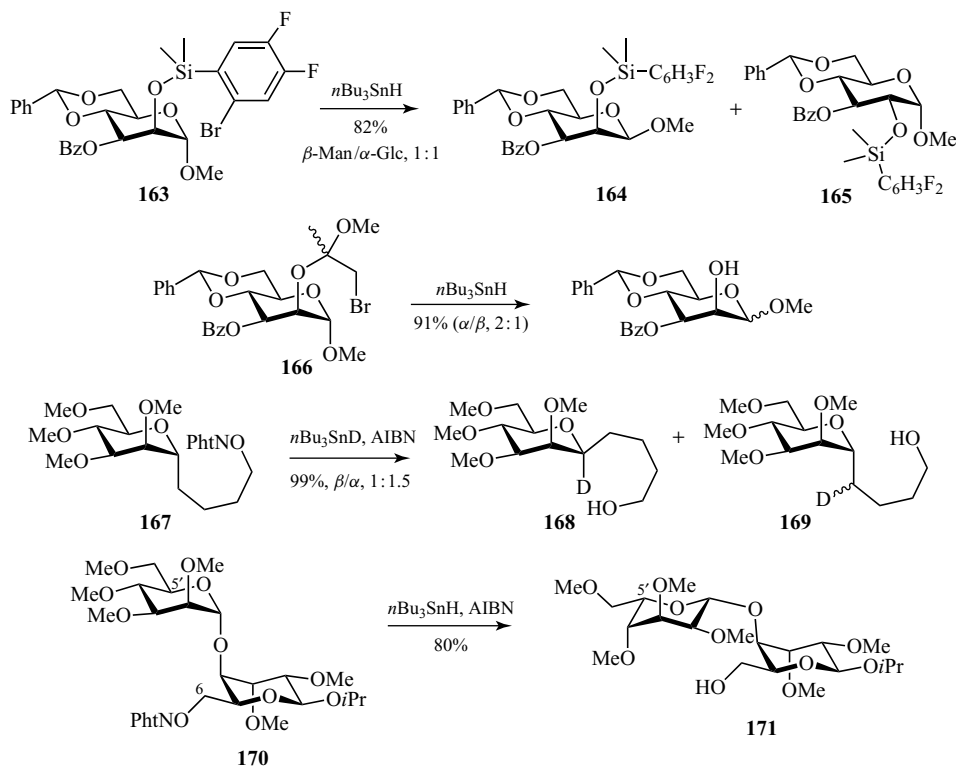
Scheme 22 Synthesis of β -O- and β -C-glycosides.

disaccharide **161** with inversion of configuration at C-1'. Examples of these decarboxylations in the 2-ulofuranosonic acid series have also been reported by Crich and Ritchie²⁰² and Garner.²⁰³ Among C-glycosyl derivatives, those having halogen atoms or nitro groups attached to the anomeric center and thio- or seleno-glycosides are able to undergo radical-mediated reduction in the presence of tin or silicon hydrides as described earlier for the synthesis of β -C-glycosides (Schemes 1 and 7).²⁷ Aware that monothioketals are usually reduced with excellent stereoselectivity with tin hydrides, Kishi extended this procedure to C-disaccharide systems such as **162** to obtain exclusively the β isomer.²⁰⁴

4.2.2 Radical Translocation

The second approach to β -O- and β -C-glycosides involves a sequence of radical reactions involving first an intra- then an intermolecular HAT. This alternative has been applied almost exclusively

to manno- or rhamnopyranosides where a silyl or acetal linkage at C-2 could be particularly useful. Curran reported that α -mannoside **163** underwent radical translocation to give two products: the inverted β -mannoside **164** resulting from 1,6-HAT and α -glucoside **165** obtained via competing 1,5-HAT (Scheme 23).²⁰⁵ A similar approach starting from the mixed acetal **166** has been developed by Crich, but under their best conditions a relatively low anomeric inversion was obtained.²⁰⁶ We have also included in this section the translocation between O and C radicals observed in the reactions of phthalimides **167** and **170**. The alkoxyl radical generated from C-mannosyl glycoside **167** triggered a 1,6-HAT which afforded inverted β -C-glycoside **168** in moderate yield; by employing $n\text{Bu}_3\text{SnD}$ as reductant, it was evident that the major product **169** has been formed via a competitive 1,5-HAT process.²⁰⁷ Recently, in our laboratory we have implemented a translocation methodology based on an intramolecular 1,8-HAT reaction between the two pyranose units



Scheme 23 Radical translocation between carbon-carbon and carbon-oxygen radicals.

in suitably substituted (1 $\rightarrow$ 4)-*O*-disaccharides.²⁰⁸ The alkoxyl radical at C-6 was generated by reaction of an *N*-hydroxyphthalimide derivative, such as **170** (α -D-Manp-(1 $\rightarrow$ 4)- β -L-Gulp), with the *n*Bu₃SnH/AIBN system and the abstraction occurs exclusively at C- 5' with predominant inversion of configuration to give the disaccharide **171** (β -L-Gulp-(1 $\rightarrow$ 4)- β -L-Gulp).

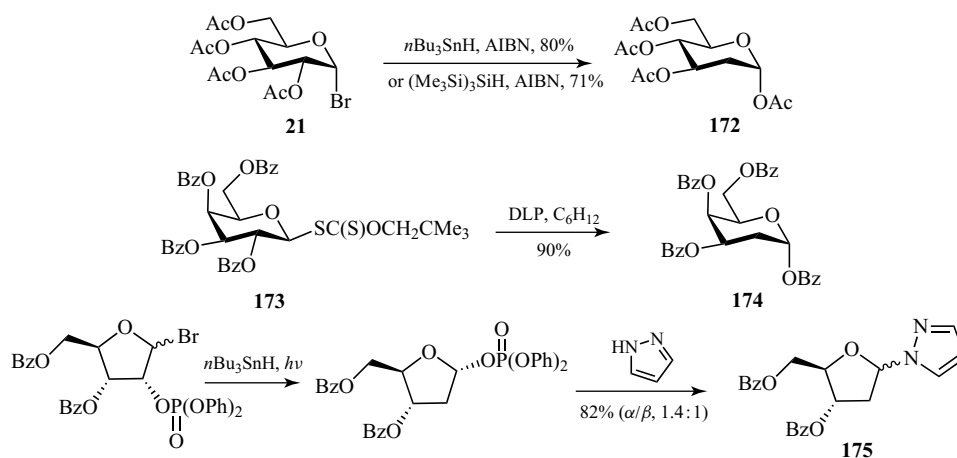
4.3 Synthesis of 2-Deoxy Sugars by Radical-Induced 1,2-Ester Rearrangement

The 1,2-migrations of acyloxy and phosphonyloxy groups in the carbohydrate field involve initial generation of an anomeric C radical and its subsequent rearrangement to a C-2-centered radical which finally leads to 2-deoxy sugars.^{209,210} The thermodynamic driving force that explains this rearrangement is derived from the formation of the strong anomeric C–O bond despite the reduction step occurring through the less electronically stabilized C-2 radical. Giese was the first to expand this 1,2-migration to carbohydrates, observing that, starting from acetylated models, such as **21**, or benzoylated glycopyranosyl, or furanosyl halides or selenides, 2-deoxy sugars **172** were obtained in good yields by a cis-selective rearrangement (Scheme 24).^{211,212} It was also demonstrated that the slow addition of *n*Bu₃SnH required to avoid the direct reduction of the starting substrate may be circumvented by the

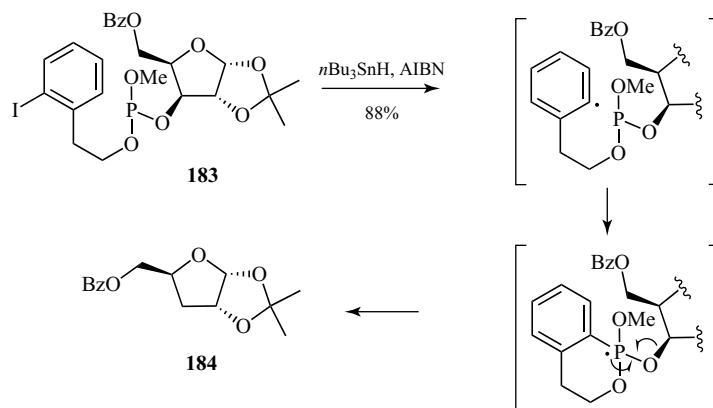
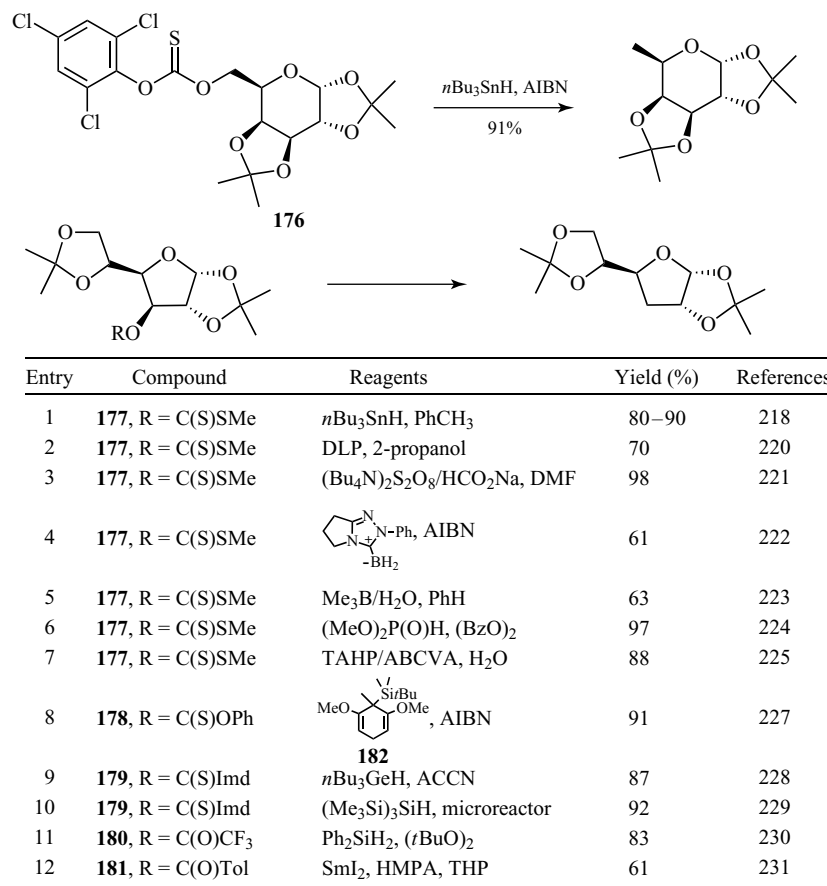
use of alternative reductants such as TTMSS.²¹³ A further alternative to tin hydrides was proposed by Quiclet-Sire and Zard,²¹⁴ using *S*-glycosyl xanthates, such as **173**, as radical precursors in refluxing cyclohexane, which surprisingly acts as an effective hydrogen donor, and dilauroyl peroxide (DLP) as initiator to give 2-deoxy carbohydrates **174** in good yields. In contemporaneous works, Crich and Giese firstly described phosphonyloxy radical migration in 1993.^{215,216} The preparative potential of this migration in carbohydrates was recognized and exploited by the Giese group. Thus, although the 2-deoxyglycosyl phosphates were too unstable to be isolated, they could be coupled *in situ* to various acceptors to give 2-deoxy disaccharides or nucleosides such as **175**.²¹⁶

4.4 Non-anomeric C-Radical Reduction

The radical deoxygenation of thiocarbonyl derivatives, known as the *Barton–McCombie reaction*, is one of the most widely employed methods for the deoxygenation of primary and secondary alcohols (see **Tin Hydrides and Functional Group Transformations**).^{217,218} In Scheme 25, deoxygenation of a primary *O*-trichlorophenyl thiocarbonate **176** is shown using this procedure.²¹⁹ The well-known and effective classical conditions used trialkyltin hydrides but, considering the toxicity of these tin compounds and



Scheme 24 Synthesis of 2-deoxy sugars by 1,2-ester migrations.



Scheme 25 Deoxygenation of non-anomeric alcohols. TAHP, tetraalkylammonium hypophosphite; ABCVA, 4,4'-azobis(4-cyanovalic acid); ACCN, 1,1'-azobis(cyclohexanecarbonitrile).

the unresolved difficulty of removing tin derivatives, extensive efforts have been focused in recent years in developing more environmentally benign and more easily handled alternatives, as

shown for the substrates **177–181**. For comparative purposes, the deoxygenation of xanthate **177** under the original Barton–McCombie conditions is included in Entry 1.²¹⁸ Zard reported on a

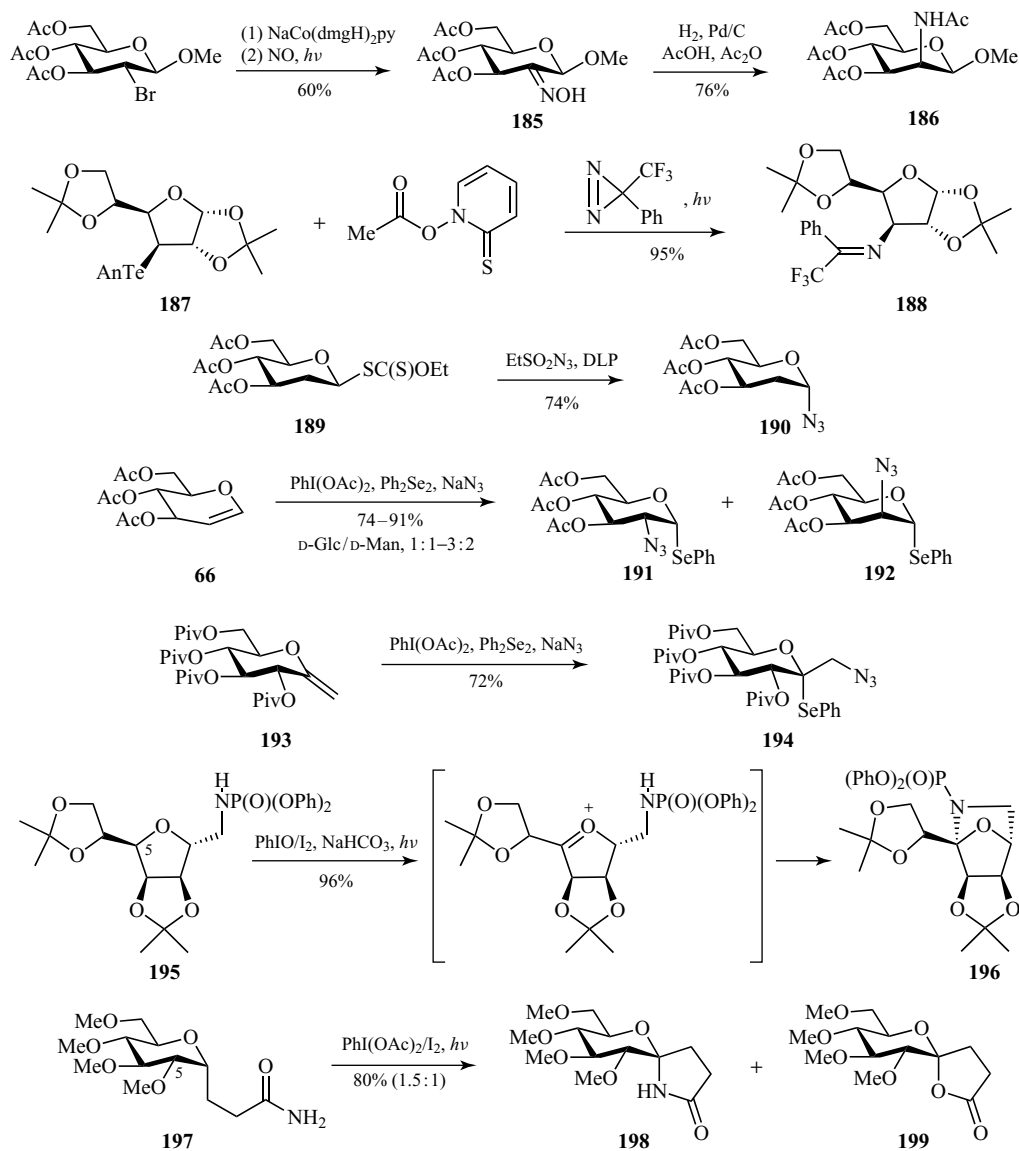
simple and efficient method by using 2-propanol as hydrogen-atom donor and DLP as radical initiator (Entry 2).²²⁰ Radicophilic cleavage of thiocarbonyl derivatives has been studied by Kim using $(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ and HCO_2Na as a new alkyl radical generator (Entry 3).²²¹ In a more recent work, it has been discovered that complexes of boranes and *N*-heterocyclic carbenes are competent radical hydrogen-atom donors to achieve the deoxygenation of secondary xanthates in good yields (Entry 4).²²² On other hand, Wood provided evidence that the trialkylborane/air system using water as the only hydrogen-atom source is capable of mediating the deoxygenation of xanthate esters (Entry 5).²²³ The utility of hypophosphorous compounds as cheap and ecologically acceptable replacements for triorganostannanes was first demonstrated by Barton (Entry 6).²²⁴ Recent examples include aqueous tetraalkylammonium hypophosphites (TAHPs) by Jang (Entry 7),²²⁵ and the use of dimethyl phosphite employed by Morvan.²²⁶ Several silylated 1,4-cyclohexadienes have also been examined as replacements for organotin compounds.²²⁷ The highly efficient deoxygenation of thiocarbonate **178** with silylated cyclohexadiene **182** provides a neat demonstration of the considerable synthetic potential of this methodology. Tributylgermanium hydride has also been described as a useful alternative to trialkyltin hydrides in radical reductions of thiocarbonylimidazolide **179** (Entry 9).²²⁸ A work from the Seeberger group in 2008 combines the use of TTMSS with a continuous-flow microreactor to perform deoxygenation of **179** (Entry 10) (see **Radical Chemistry by Using Flow Microreactor Technology**).²²⁹ This technique was also reported to be effective with iodinated sugars. Jang proposed an alternative method in which the deoxygenation of trifluoroacetate derivative **180** is implemented efficiently with diphenylsilane (Entry 11).²³⁰ More recently, Markó investigated the monoelectronic reduction of aromatic esters with SmI_2 , observing that the toluate moiety **181** could be a particularly useful function to achieve radical deoxygenations (Entry 12).²³¹ Also in this field, Koreeda developed a highly versatile method for the deoxygenation of alcohols starting from phosphites such as **183**.²³² Initially, an aryl radical is generated that attacks the phosphorous atom to give a phosphoranyl radical, which promotes a favored β -scission reaction producing the corresponding

C radical which should lead to the reduction product **184**.

5 CARBON–HETEROATOM BOND-FORMING PROCESSES

5.1 Carbon–Nitrogen Bond-Forming Processes

Two basic approaches to the homolytic formation of C–N bond in carbohydrate systems are available: the amination of carbon-centered radicals, and the inter- or intramolecular addition of nitrogen-centered radicals. Only a few procedures for the amination of C radicals in the carbohydrate field have been reported. The first work used the photolysis of a cobaloxime intermediate in presence of nitrous oxide as an efficient radical trap. The nitroso compound tautomerized readily to an oxime, such as **185**, which was subsequently reduced and acetylated to mannosamine **186** as a single stereoisomer (Scheme 26).²³³ Barton conveniently used diazirines as carbon radical traps.²³⁴ The carbohydrate carbon-centered radical, produced via radical exchange from the organotelluride **187**, adds to 3-(trifluoromethyl)-3-phenyldiazirine, to furnish the imine **188** in good yield. More recently, Renaud reported a practical approach for the azidation of alkyl radicals using sulfonyl azides as radical traps (see **Unusual Radical Acceptors**).²³⁵ The process involves the reaction of anomeric dithiocarbonate **189** with ethanesulfonylazide in the presence of DLP as radical initiator: the anomeric azide **190** is obtained as a single α -anomer. The azidophenylselenation of glycols, first reported by Santoyo–González *et al.*,²³⁶ Czernecki and Randriamandimby,²³⁷ and Tingoli *et al.*,²³⁸ is a powerful heterogeneous procedure that allows the one-pot preparation of phenyl 2-azido-2-deoxy-selenoglycosides such as **191** and **192**, regioselectively in high yield. This occurs when glycols are treated with (diacetoxyiodo)benzene (DIB), sodium azide, and diphenyl diselenide to generate an electrophilic azide radical which adds to the electron-rich double bond of the glycal. More recently, Nifantiev performed an improved homogeneous preparative method using trimethylsilyl azide allowing reduced reaction times and reliable scaleup.²³⁹ The reaction has also been extended to *exo*-glycals; thus D-*gluco*-hept-1-enitol



Scheme 26 Radical formation of carbon–nitrogen bonds. dmgH, dimethylglyoxime monoanion.

derivative **193** under the same conditions afforded C-glycoside **194** as a single diastereoisomer.⁷⁷ The CAN-mediated azidonitration of glycals of Lemieux and Ratcliffe provides another efficient method for the introduction of the azide group at C-2.⁸² We have devoted some attention to the 1,5- or 1,6-HAT promoted by N radicals, reporting the synthesis of different pyrrolidines and piperidines in carbohydrate systems.^{240–243} As a representative example, a suitably protected amine

195²⁴⁰ reacts with hypervalent iodine reagents in the presence of iodine to generate an N radical, which triggers the 1,5-HAT reaction to give the 7-oxa-2-azabicyclo[2.2.1]heptane system **196** after one-electron oxidation and cyclization of the amine group onto the oxocarbenium ion intermediate. Next, this work was extended to the HAT promoted by amidyl radicals generated from **197**, showing that there is an O- and N-ambident nucleophilic reactivity of the amide group.²⁴³ This reactivity

depends on the electrophilicity of the oxocarbenium ion intermediate modulated by tuning the electron-withdrawing ability of the substituents at C-5 to trigger the reaction specifically to give spiro-lactams **198** or spiro-lactones **199**.

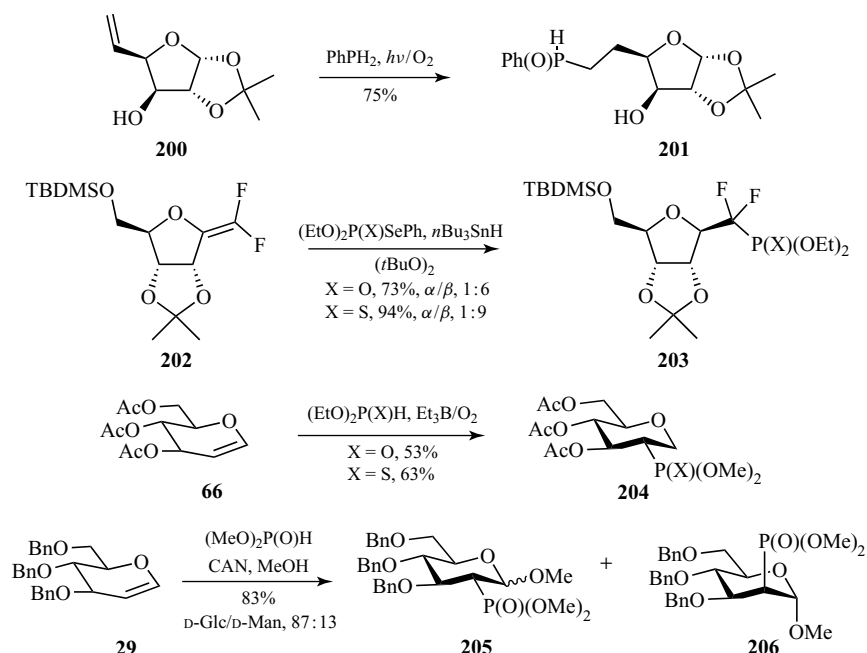
5.2 Carbon–Phosphorus Bond-Forming Processes

The addition of phosphorus-centered radicals to olefins on a carbohydrate skeleton was first reported by Whistler in 1968.²⁴⁴ The photochemically initiated reaction of phenylphosphine with alkene **200** afforded, after oxidation under the reaction conditions, the phosphine oxide **201** (Scheme 27). *C*-Glycosides with difluoromethylene phosphonates and phosphonothioates as anomeric tethers such as **203** have been prepared by Motherwell²⁴⁵ starting from *exo*-glycal **202**. The required phosphonyl or thiophosphonyl radicals were generated by *n*Bu₃SnH reduction of diethyl(phenylselenenyl)phosphonate or diethyl(phenylselenenyl)thiophosphonate, respectively, using di-*tert*-butyl peroxide as initiator. Analogously, the radical addition of diethyl phosphite to a difluorinated

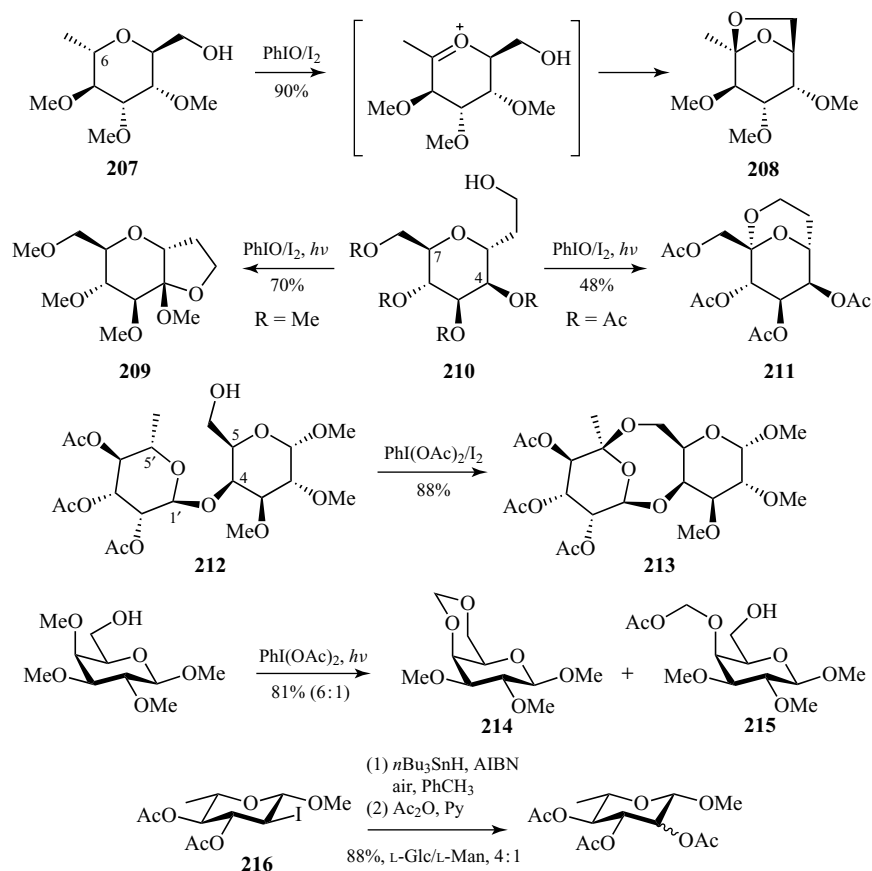
exo-glycal closely related to **202** using *tert*-butylperoxypivalate as initiator has been described by Sinay.²⁴⁶ Addition of diethyl phosphite or diethyl thiophosphite, in the presence of the triethylborane/O₂ system, to the electron-rich enol-ether of tri-*O*-acetyl-*D*-glucal afforded adducts **204** (X = O or X = S, respectively) with complete regio and diastereoselectivity.²⁴⁷ Phosphonyl radicals, generated under oxidative conditions from dimethyl phosphite and CAN, added efficiently to pentopyranose, hexopyranose, and disaccharide glycals.²⁴⁸ This strategy permitted the preparation of a variety of 2-deoxy-2-phosphonate derivatives, such as **205** and **206**. The stereochemistry can be rationalized on the basis of steric interactions; the phosphonyl radical attacks preferentially anti to the substituent at C-3. Related applications of the CAN-mediated radical addition to glycals have been described in Section 2.4.^{81,82}

5.3 Carbon–Oxygen Bond-Forming Processes

Intramolecular HAT promoted by alkoxy radicals is one of the most interesting processes for the radical generation of C–O bonds. However, it is



Scheme 27 Radical formation of carbon–phosphorus bonds.



Scheme 28 Radical formation of carbon–oxygen bonds.

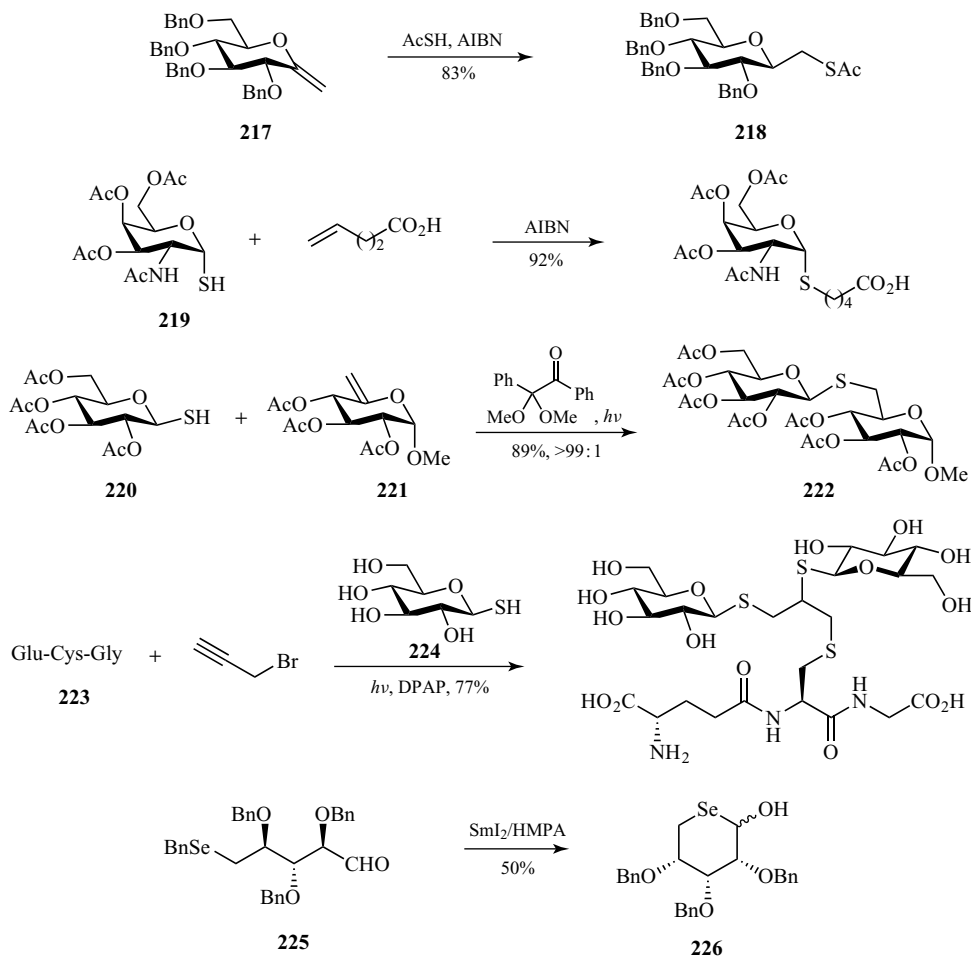
worth noting that the C–O bond formation does not arise directly from the radical abstraction, but by a mixed method combining a radical HAT step and an ionic cyclization (see below). In carbohydrate chemistry, Descotes²⁴⁹ launched the application of this methodology to the synthesis of spiroorthoesters by cyclization of 2-hydroxyethyl glycosides using HgO/I_2 for the generation of the hypoiodite intermediate. We have prepared spiroacetals with 1,6-dioxaspiro[4.5]decane and 1,7-dioxaspiro[5.5]undecane bicyclic structures by cyclization at the anomeric center of C-glycosides of the 4,8-anhydro-nonitol and 5,9-anhydro-decitol type, respectively, using hypervalent iodine compounds and iodine for the generation of the alkoxy radicals.^{250,251} Chatgililoglu has also used this reagent for the preparation of anomeric spironucleotides.²⁵² Apart from the anomeric center, some other positions of the carbohydrate

skeleton have also been functionalized. For example, we have described that the alkoxy radical generated from C-glycoside **207** abstracts exclusively the hydrogen atom at C-6 to give the 6,8-dioxabicyclo[3.2.1]octane **208** after oxidation of the radical to the oxocarbenium ion intermediate (Scheme 28).²⁵³ The reaction of **210** (R = Me), possessing a two-carbon tether at C-3, abstracts the hydrogen atom at C-4 through a 1,5-HAT affording exclusively **209**. Notwithstanding, the presence of an EWG at C-4 as in **210** (R = Ac) switches the reaction to a 1,6-HAT by abstraction of the C-7 hydrogen to give the 2,9-dioxabicyclo[3.3.1]nonane **211** with complete regioselectivity.²⁵⁴ Remote functionalization between the two pyranose units of a (1 $\rightarrow$ 4)-disaccharide can also be achieved under these conditions. For instance, the reaction of alcohol **212** with the DIB/ I_2 system afforded the 1,3,5-trioxocane derivative **213** through a

rare 1,8-HAT in good yield.²⁵⁵ Taking advantage of the strict conformational requirements of the HAT TS, these reactions have been used for the selective deprotection of suitably positioned benzyl²⁵⁶ and methyl ethers²⁵⁷ in the carbohydrate framework. The reaction of methyl 2,3,4-tri-*O*-methyl- β -D-galactoside to give a mixture of methylenedioxy acetal **214** and acetate **215**, which can be subsequently hydrolyzed to methyl 2,3-di-*O*-methyl- β -D-galactoside, is illustrative. Direct radical transformation of a carbon–halogen bond into a carbon–oxygen bond is possible with molecular oxygen,²⁵⁸ as depicted for iodine **216**, or TEMPO (see **Nitroxides in Synthetic Radical Chemistry**).²⁵⁹

5.4 Carbon–Sulfur/Selenium Bond-Forming Processes

The radical addition of thiols to alkenes (thiol-ene coupling or TEC), known for more than a hundred years,²⁶⁰ has recently been considered to be a thio-click process (see **Radical Thiol–X Click Chemistry**).^{261,262} In the carbohydrate field, the addition of thiyl radicals to *endo*-glycals has also been known for some time. Igarashi and Honma²⁶³ reported that the reaction of thioacetic acid with tri-*O*-acetyl-D-glucal proceeded with C-2 addition of a thioacetyl radical to give a 7:3 ratio of D-Man/D-Glc diastereomers. When the reaction is performed with ethanethiol catalyzed by CAN, a reverse addition at C-1, which finally leads to



Scheme 29 Radical formation of carbon–sulfur and carbon–selenium bonds. DPAP, 2,2-dimethoxy-2-phenylacetophenone.

2-deoxy-1-thioglycosides, has been observed. This last result seems to be more consistent with an oxocarbenium ion mechanism.²⁶⁴ The diastereoselective radical addition of thioacetic acid to *exo*-glycals of D-Glcp **217** and L-Fucp has also been described (Scheme 29).²⁶⁵ In both cases, β -C-glycoside thioacetates, such as **218**, are formed exclusively by axial radical quenching. A number of α -D-GalpNAc thioconjugates have been prepared by reaction of 1-thio- α -D-GalpNAc derivative **219** with different olefins using AIBN as the radical initiator.²⁶⁶ A new photoinduced coupling of glucosyl and mannosyl thiols with hex-5-enopyranosides and pent-4-enofuranosides to give thiodisaccharides has been developed by Dondoni.²⁶⁷ The TEC reaction of 1-thio- β -D-glucopyranose derivative **220** with the sugar alkene **221** using 2,2-dimethoxy-2-phenylacetophenone (DPAP) as photoinitiator to give 1,6-linked *S*-disaccharide **222** is a representative example. A natural extension of the TEC reaction is the radical-mediated hydrothiolation of terminal alkynes, which serves to introduce two thiol substituents across the triple bond.²⁶⁸ This methodology has been exploited by Dondoni²⁶⁹ for the double *S*-glycosylation of cysteine-containing peptides. The one-pot, two-step sequence comprises the selective *S*-propargylation of the cysteine unit **223** followed by photoinduced radical thiol-yne coupling of 1-thio- α -D-glucopyranose (**224**). 5-Deoxy-5-seleno-D-ribose derivative **226** can be formed from benzylseleno aldehyde **225** with Sml_2 , presumably via an intramolecular homolytic substitution.²⁷⁰

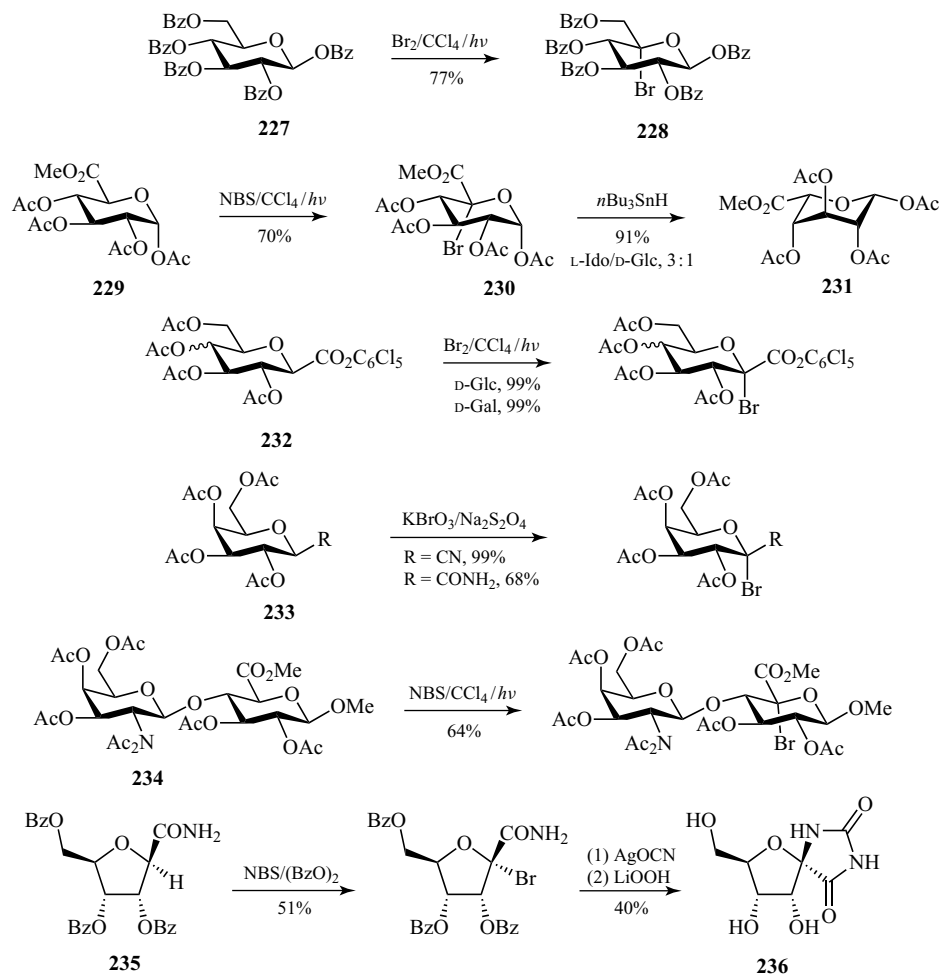
5.5 Carbon–Bromine Bond-Forming Processes

The discovery that carbohydrate derivatives can be specifically brominated under free-radical conditions was made by Ferrier in 1977^{271,272} and the results obtained up to 1991 have been thoroughly reviewed by Somsák and Ferrier.²⁷³ In general, bromine, *N*-bromosuccinimide (NBS), or the $\text{KBrO}_3/\text{Na}_2\text{S}_2\text{O}_4$ system are used as brominating agents, and the radical reactions are initiated with either irradiation with visible light, benzoyl peroxide, or AIBN. The reaction occurs preferentially at the C-1 or C-5 (C-4 in furanose systems) positions of the carbohydrate skeleton, and the regioselectivity depends largely on the substituents at these positions. The reaction of

the 1,2,3,4,6-penta-*O*-benzoyl- β -D-glucopyranose (**227**) to give regio- and diastereoselectively the 5-bromine derivative **228** is illustrative (Scheme 30).²⁷⁴ The bromination of methyl D-glucopyranuronate has been studied in some detail, since the 5 α -bromo derivative obtained is an intermediate in the synthesis of methyl α -L-idopyranuronate, which is a constitutive fragment of heparine.²⁷⁵ The bromination of the α -isomer derivative **229** afforded regio- and stereoselectively the 5 α -bromo derivative **230**. Subsequently, free-radical reduction with $n\text{Bu}_3\text{SnH}$ gave a 3 : 1 ratio of L-Ido **231**/D-Glc **229** isomers.^{276,277} Interestingly, the reduction of the isomeric methyl 1,2,3,4-tetra-*O*-acetyl-5-bromo- β -D-glucopyranuronate (β -isomer of **230**) gave an inverted 1 : 2 ratio of the respective L-Ido/D-Glc isomers.²⁷⁸ Cyclic C-glycosides with an electron attractor group at the anomeric center (CN, CO_2R , or CONH_2) give regioselective bromination at this position, via a captodative stabilized radical.²⁷⁹ This situation is similar to that encountered at C-5 of the pyranuronates mentioned earlier. This methodology has been exploited by Somsák^{280,281} in the highly efficient bromination of 2,6-anhydro-aldonic acid derivatives **232** and **233**. An excellent example of the importance of the captodative effect in the regioselectivity is the bromination of the disaccharide **234**; directed by the carboxyl group, the substitution occurs exclusively at C-5 of the glucuronate moiety.²⁸² The bromination of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonamide (**235**) was used by Harrington and Jung²⁸³ as a key step in the synthesis of (+)-hydantocidin **236**. During the synthesis of a number of analogs of hydantocidin, Fleet²⁸⁴ have also applied this bromination of C-glycofuranosides to 2,5-anhydro-L-talonic acid derivatives.

6 β -FRAGMENTATION PROCESSES PROMOTED BY ALKOXYL RADICALS

The alkoxy radical fragmentation (ARF) involves the reversible homolytic cleavage of a σ C–C bond located on the sugar template α, β to an O radical giving rise to a carbon-centered radical and a C=O double bond. The conditions that have been employed most frequently in the β -fragmentation reaction in carbohydrates may be broadly classified into two types: oxidative and reductive methods.²⁸⁵

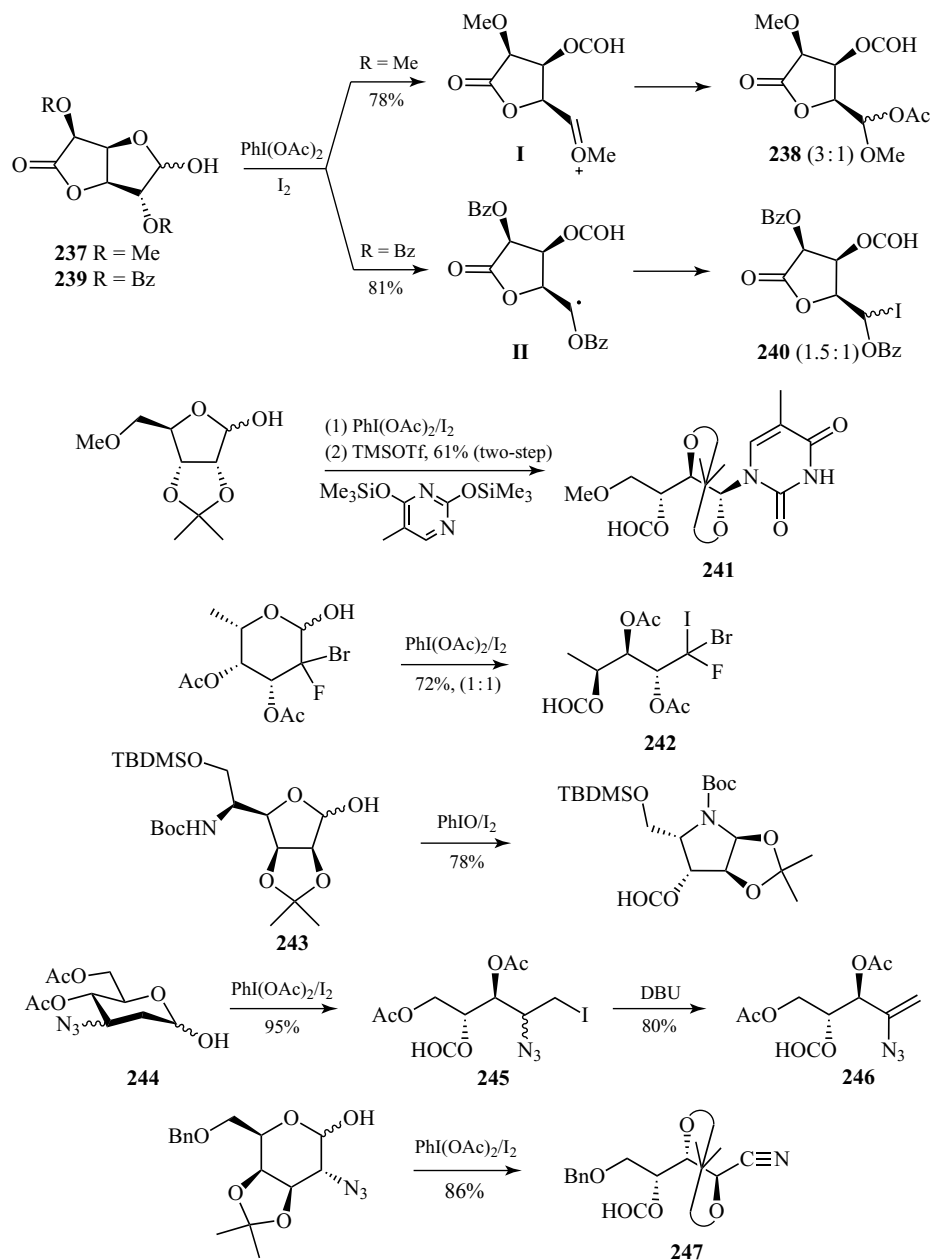


Scheme 30 Radical bromination of sugars.

6.1 Fragmentation of Alkoxy Radicals under Oxidative Conditions

The formation of anomeric alkoxy radicals and its fragmentation reaction proceed smoothly in high yields using hypervalent iodine compounds, especially DIB, and iodine via the corresponding hypoiodite intermediates. In this process, the equilibrium is strongly displaced to the acyclic C radical, the anomeric carbon is transformed into a formate group, and the sugar is degraded to a lower member of the aldose series of carbohydrates. Using an electron-donor protecting group at C-2 (e.g., ether, isopropylidene), oxidation of the C radical to an oxocarbenium ion intermediate **I** is

favoured, which may be trapped intermolecularly by an acetate anion from the medium to give a mixed acetyl acetal (Scheme 31). Nevertheless, the presence of an electron-withdrawing group at C-2 (e.g., ester, carbonate, halogen, 2-deoxy carbohydrate) decreases the electron density at this position, disfavoring the oxidation and allowing the competitive trapping of the C radical **II** by an iodine atom.^{286,287} For instance, the methylether **237** gave the acetyl product **238**, whereas the benzoyl ester **239** afforded the iodide **240** in good yields. Inanaga applied this procedure to give the corresponding mixed-acetal formates which were further converted to furanose derivatives by acid-catalyzed transacetalization.²⁸⁸ We have



Scheme 31 β -Fragmentation of alkoxy radicals under oxidative conditions.

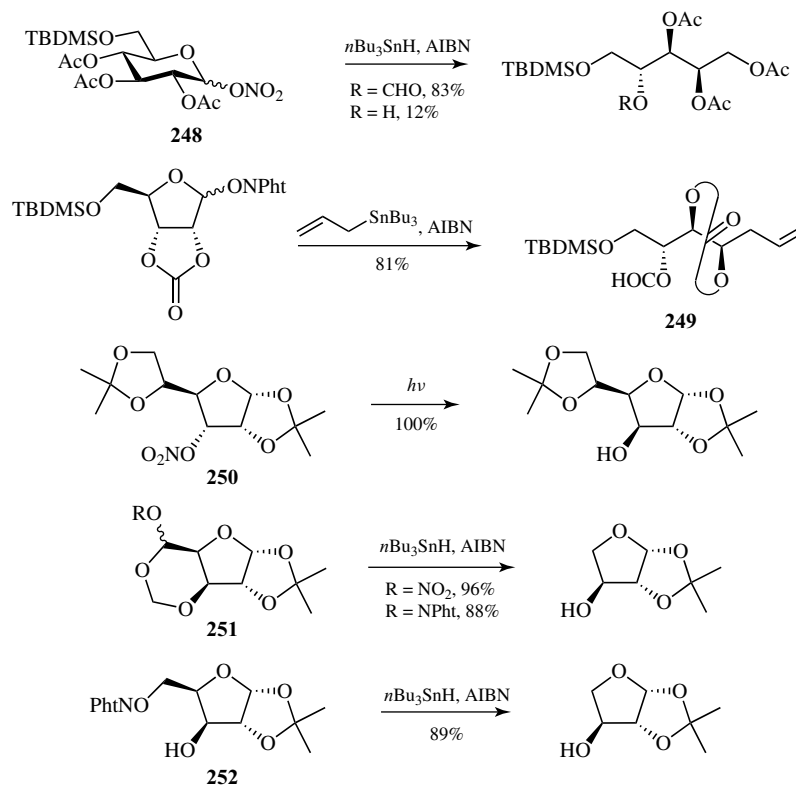
demonstrated that both inter- and intramolecular trapping of the oxocarbenium ion intermediate are possible. In the intermolecular approach, besides the acetate anion coming from the reagent, other proper nucleophiles could be added to the reaction medium, such as the thymine base shown in Scheme 31

for the synthesis of the acyclic nucleoside analog **241**.^{289,290} In recent years, we have extended this tactic to the synthesis of chiral 1,1-dihaloalditols and 1,1,1-trihaloalditols by ARF of 2-halo- or 2,2-dihalo-carbohydrate anomeric alcohols, as described for the synthesis of **242**.^{291,292} On the

other hand, the intramolecular trapping requires suitably positioned nucleophiles in the carbohydrate precursor structure. Some of these internal nucleophiles could be hydroxyl groups,^{293,294} for preparing specific furanose or pyranose forms of aldotetroses and aldopentoses; carboxyl groups²⁹⁵ giving aldo-pyranosuronic or furanosuronic acid lactones; or amine groups such as **243**,²⁹⁶ which are particularly interesting since imino sugars could be obtained in high yields. Starting from 3-azido-2,3-dideoxy-hexopyranose compounds **244**, we had the opportunity to synthesize chiral β -iodoazides **245** in good yields, which by subsequent base treatment afforded vinyl azides **246**.²⁹⁷ Analogously, the corresponding vinyl sulfones could be prepared from the oxidative fragmentation of 2,3-dideoxy-3-phenylsulfonyl-hexopyranoses.²⁹⁸ We also reported on an extension of the ARF methodology to 2-azido-2-deoxyaldoses to lead to aldonitriles such as **247** by oxidation to the α -azido cation which delivers nitriles upon loss of nitrogen.²⁹⁹

6.2 Fragmentation of Alkoxy Radicals under Reductive Conditions

The required glycopyran-1-*O*-yl or glycofuran-1-*O*-yl radicals were generated by reaction of anomeric nitrate esters such as **248** or *N*-phthalimide glycosides with *n*Bu₃SnH and AIBN giving the corresponding alditols with one carbon less (Scheme 32).³⁰⁰ Recently, Hartung highlighted the efficiency of alkoxy radical formation from 5-substituted and unsubstituted 3-alkoxy-4-methylthiazole-2(3*H*)-thiones under reductive conditions.³⁰¹ We further extended our methodology to sequential ARF-intermolecular allylation starting from *N*-phthalimide derivatives and using allyltributylstannane as radical trap to give a range of 1,2,3-trideoxyhept-1-enitol derivatives such as **249**.³⁰² Concerning non-anomeric *O*-adicals, Binkley and Koholic, who discovered nitrate esters as good sources of alkoxy radicals, described the conversion of 3-nitro-D-allofuranose



Scheme 32 β -Fragmentation of alkoxy radicals under reductive conditions.

250 into the inverted alcohol by a radical β -fragmentation-recyclization reaction as shown in Scheme 32.³⁰³ In our laboratory, a simple synthesis of L-threose by the ARF of nitrate ester and *N*-phthalimide derivatives of readily available hemiacetal **251** (*R* = H) has been developed.³⁰⁰ Along this line, Sánchez *et al.* reported the β -fragmentation of primary alkoxyl radicals from their corresponding *N*-phthalimide derivative **252**, highlighting that an internal hydrogen bond seemed to be the driving force for such a reaction.³⁰⁴

7 CONCLUSIONS

The selected examples provided in this article have hopefully demonstrated the importance of free-radical reactions in carbohydrate chemistry. The neutral reaction conditions, functional group tolerance, and experimental simplicity make these procedures highly attractive for selective transformations in this field. The predictable stereoselectivity of hexopyranos-1-yl radical reactions suggests that this may be a method of choice for the diastereoselective carbon–carbon bond formation at the anomeric center of carbohydrates. Radical chemistry provides also convenient methods for the synthesis of polyfunctionalized carbocycles by radical cyclization of acyclic carbohydrate precursors and for the introduction of heteroatoms into the sugar ring. Finally, the remote intramolecular functionalization via HAT from alkoxyl radicals and the β -fragmentation of anomeric alkoxyl radicals offer interesting new perspectives, allowing the preparation of structures that would otherwise be very difficult to synthesize.

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Radical Arylations

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1 INTRODUCTION

Substitution reactions are one of the most useful transformations in organic chemistry. In aromatic systems, the mechanism of the substitution process depends on the nature of the substrate and reagent as well as on the reaction conditions applied. In this regard, substitutions involving radicals are usually performed under mild and neutral conditions, and it is noteworthy that many functional groups are tolerated. Moreover, many different solvents can be used in radical chemistry; even water is tolerated to conduct synthetically important radical transformations. These reasons, together with the fact that many different functional groups can be used as radical sources, make radical reactions particularly suitable and attractive for arylation of a wide range of compounds. Radical arylations can be achieved by the $S_{RN}1$ reaction, by homolytic aromatic substitution, or by reaction of aryl radicals with different radical acceptors. In this article, we focus on the latter two approaches and present a short overview on some relevant transformations involving aryl radicals. $S_{RN}1$ -type homolytic aromatic substitutions are discussed in **The $S_{RN}1$ Reaction** and homolytic substitutions at the main-group elements are covered in **Intramolecular Homolytic Substitutions in Synthesis**.

Owing to space limitations, a comprehensive overview on homolytic aromatic substitutions

cannot be given here; for further information, the reader is referred to some recent reviews on this topic.^{1–3}

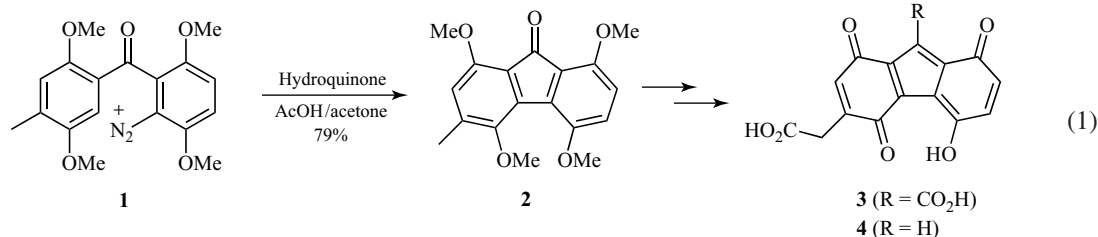
2 HOMOLYTIC AROMATIC SUBSTITUTION REACTIONS

2.1 Intramolecular Homolytic Aromatic Substitution Reactions

2.1.1 Arylation Using Nucleophilic C-Centered Radicals

Intramolecular homolytic substitution reactions of reactive aryl radicals with arenes are known for more than a century.⁴ This and some other related processes, nowadays referred to as *the Pschorr reaction*, can be used for efficient preparation of biaryl compounds. Aryl radicals obtained by treatment of aryl diazonium salts with Cu(I) salts are intramolecularly trapped with an arene moiety to give, after oxidation, cyclic biaryls with excellent regioselectivity. Other protocols for conducting these reactions use photochemical, thermal,^{5,6} or electrochemical⁷ generation of reactive aryl radicals. Moreover, various one-electron donors other than Cu(I) salts, such as Ti(III)⁸ and Fe(II)⁹ salts, as well as tetrathiafulvalene¹⁰ and iodide ions¹¹ can also be used to trigger these reactions.¹² The

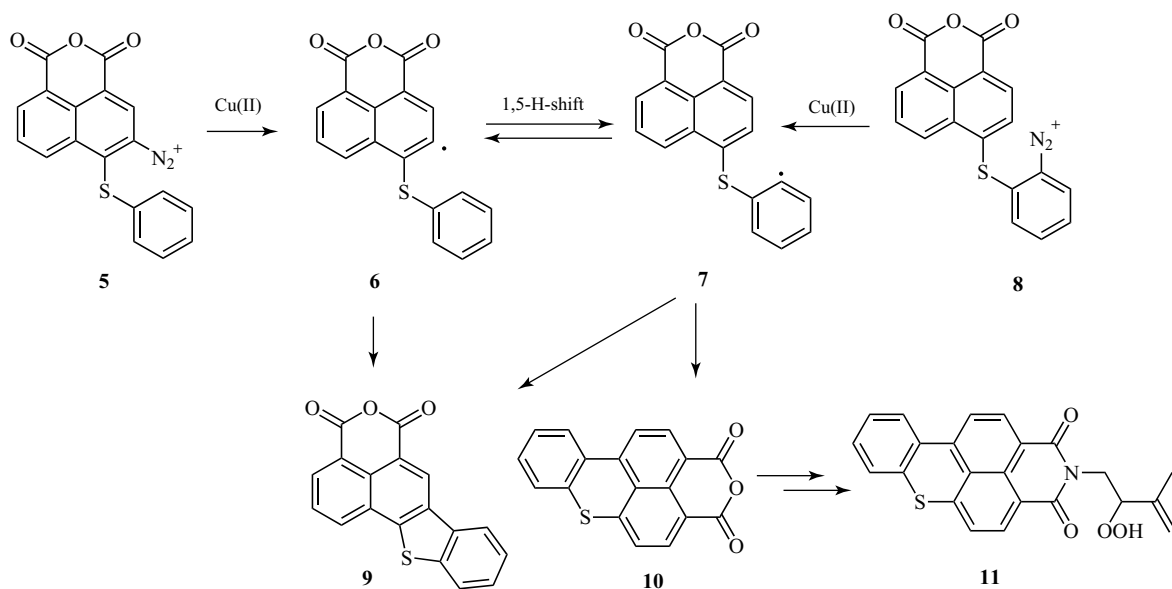
Pschorr reaction has been widely used for the synthesis of several natural products and bioactive compounds. For example, in the key step of the synthesis of the pigments hipposudoric acid **3** and norhipposudoric acid **4**, a modified Pschorr reaction of diazonium salt **1** to fluorenone **2** was used (1).¹³



An interesting application of the Pschorr reaction was reported by Guo for the synthesis of DNA-photocleaving reagent **11** (Scheme 1).¹⁴ The intramolecular homolytic substitution of naphthyl radical **6**, which is readily generated from diazonium compound **5**, afforded a mixture of five- and six-membered heterocyclic compounds **9** and **10** (ratio **9** : **10** = 86 : 14). Isomer **10** was formed via a 1,5-H shift in aryl radical **6** to give **7** and subsequent

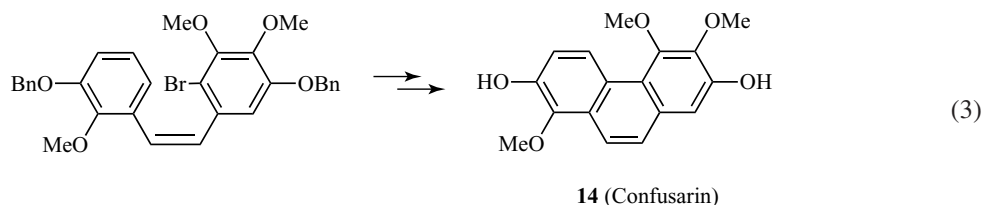
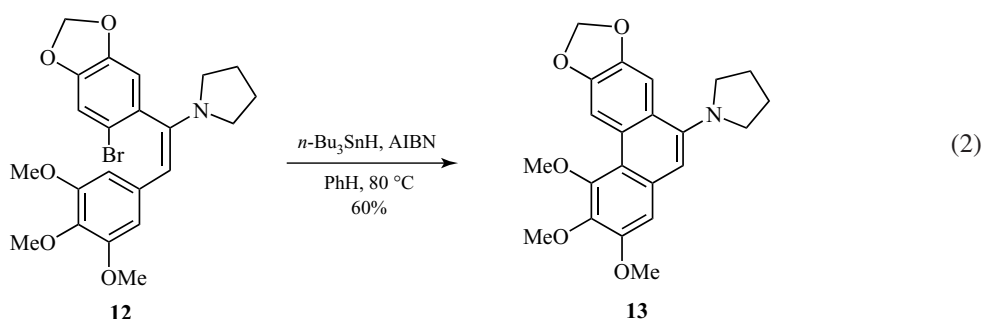
Detailed^{2–4} and recent¹⁵ investigations on the Pschorr and related processes can be found in the literature.

Halogen abstraction reaction by the tributyltin radical ($n\text{-Bu}_3\text{Sn}^\bullet$) from aryl halides (bromides and iodides) provides aryl radicals that can be used in intramolecular homolytic substitutions. This process, which was independently discovered by Narasimhan and Aidhen¹⁶ and Togo and



Scheme 1 Synthesis of DNA photocleaver **11** applying a Pschorr reaction.

Kikuchi,¹⁷ is nowadays regarded as a powerful tool for the construction of a wide range of biaryls from readily available starting materials. These reactions usually require the use of a stoichiometric amount of *n*-tributyltin hydride (*n*-Bu₃SnH); however, protocols that use only a catalytic amount of the tin hydride have also been developed. To exemplify the potential of these tin-mediated reactions, the seminal work of Narasimhan on the intramolecular homolytic substitution of bromide **12** to provide **13** is presented in (2).



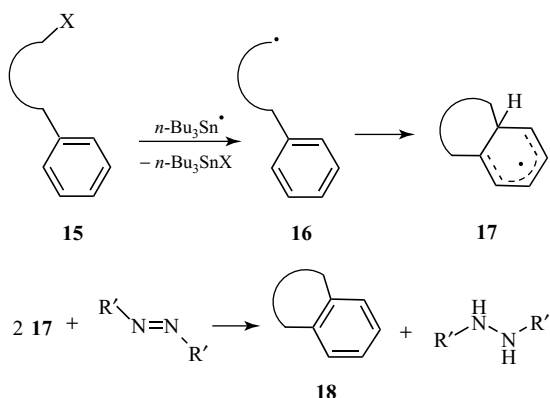
For more than 20 years, these tin hydride-mediated intramolecular homolytic aromatic substitutions have been intensively applied to the formation of C(sp²)–C(sp²) bonds to prepare various important biaryl compounds.^{18–27} For example, the key step in the synthesis of the natural phenanthrene **14** (confusarin) was recently achieved using an intramolecular homolytic substitution (3).²⁸

Aryl radicals can also be generated from aryl chlorides, bromides, and iodides by applying electrochemistry.²⁹ These electrochemically formed aryl radicals then readily undergo intramolecular homolytic aromatic substitutions. Moreover,

photochemistry has been applied to generate aryl radicals that subsequently cyclize onto arenes via homolytic substitution.³⁰ Heteroarenes have been shown to be good radical acceptors for these types of transformations and a variety of heterocyclic rings such as pyrroles, indoles, pyridones, imidazoles, pyridines, and benzimidazoles have been used as acceptors in intramolecular radical arylations.^{31–41}

For all tin hydride-mediated intramolecular arylations, the initial C-centered radical, which in the case of biaryl formation is an aryl radical, is

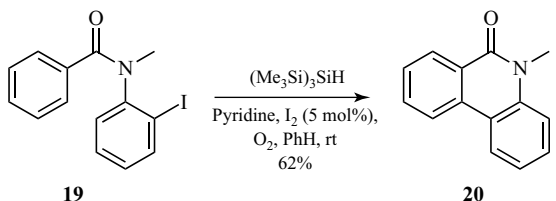
generated by halogen atom abstraction from the halide **15** by a trialkyltin radical (Scheme 2). As discussed below, the attacking radical does not need to be a reactive aryl radical. Alkyl radicals can also be used in homolytic aromatic substitutions. The C-centered radical **16** formed adds to the arene to form a rather stable cyclohexadienyl radical **17**, which is then oxidized to the targeted product **18** (Scheme 2). Noteworthy is the fact that the oxidation step has to take place under reducing tin hydride conditions. In addition, it should be pointed out that in most of the cases a stoichiometric amount (or even more) of an azoinitiator is required in order to obtain acceptable



Scheme 2 Mechanism of the homolytic aromatic substitution reaction.

yields. Although a pseudo-S_{RN}1-type mechanism was initially proposed, detailed mechanistic studies⁴² revealed that the azoinitiator is likely responsible for oxidation of the cyclohexadienyl radical **17** to arene **18**, as initially proposed by Curran and Liu.^{43,44}

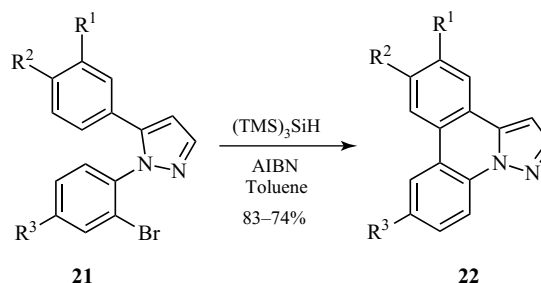
Curran also showed that oxidation of **17** can be efficiently achieved by small amounts of O₂. As documented by the conversion of iodide **19** into lactam **20**, this modification on the protocol allowed reactions to be performed at room temperature under mild conditions (4). In these reactions, O₂ acts both as an initiator and also as a reagent for oxidation of the corresponding intermediate cyclohexadienyl radical of type **17**.⁴⁵ It is obvious that the suggested mechanism is also valid for vinyl and alkyl radical additions to arenes (as indicated by the general structure of the attacking radical in Scheme 2) and of course also operates on intermolecular homolytic aromatic substitutions.



(4)

Silanes, such as tris(trimethylsilyl)silane [(TMS)₃SiH] (see **Silanes as Reducing Reagents in Radical Chemistry**), can also be used as mediating

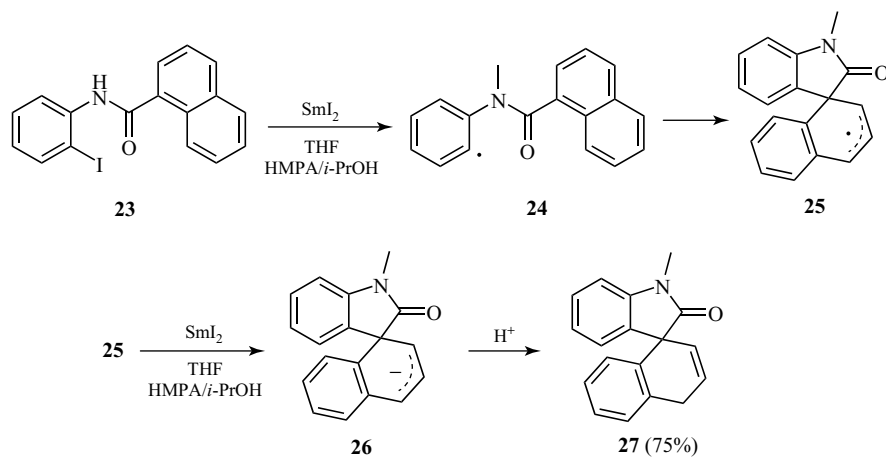
reagents to conduct homolytic aromatic substitutions. An example is shown in (4). The tin-free protocol was successfully used for preparation of various pyrazolophenanthridines **22**⁴⁶ and pyrazolopyridines (**5**).⁴⁷ The radical precursors used were obtained from readily available starting materials.



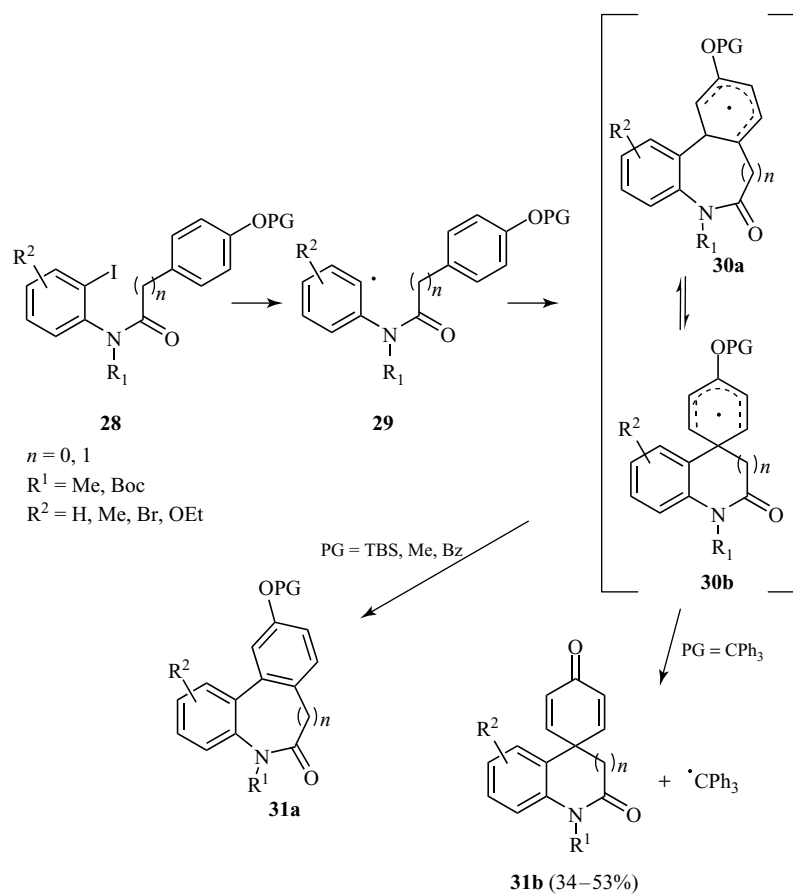
R¹ = H, OMe
R² = H, Me, OMe
R³ = H, Me, CF₃

(5)

As discussed in Scheme 2, in most cases where an aryl radical reacts with an arene, the intermediate formed cyclohexadienyl radical is further transformed to the corresponding biaryl via H transfer or oxidation/deprotonation. However, under certain conditions, the cyclohexadienyl radical can be transformed to the corresponding cyclohexadiene by either a fast reduction or fragmentation reaction. To do so, an efficient “fast” reducing reagent is necessary. Crich nicely showed that, with benzeneselenol as an additive, the intermediately formed cyclohexadienyl radical could be reduced to the corresponding cyclohexadiene.⁴⁸ Along this line, SmI₂ (see **Organic Synthesis Using Samarium Diiodide**) has also been applied to intercept the intermediate cyclohexadienyl radicals in similar reactions. An example is shown in Scheme 3. Aryl radical **24** was generated via single electron transfer (ET) from SmI₂ to aryl iodide **23**. Cyclohexadienyl radical **25**, formed by intramolecular ipso-addition of aryl radical **24** to the appropriately positioned aryl group, was reduced with SmI₂ to the corresponding allyl anion **26**. Hydrolysis during workup eventually afforded the substituted spirocyclic oxindole **27** in good yield.⁴⁹ The fast reduction of **25** suppressed a potential 1,2-acyl or 1,2-aryl migration to eventually give the typical products of a homolytic aromatic substitution.



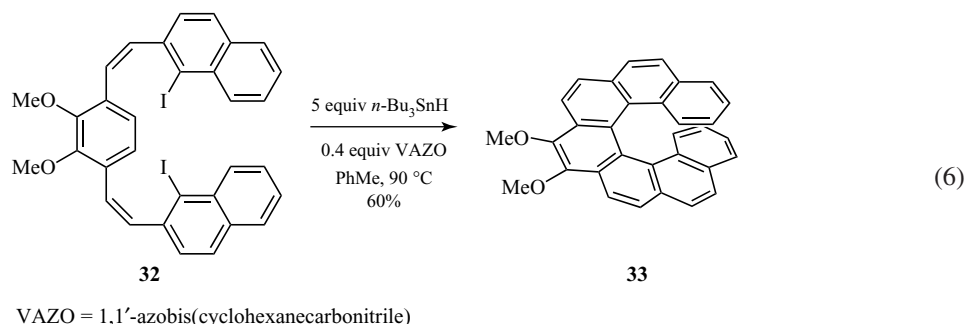
Scheme 3 SmI₂-mediated reaction.



Scheme 4 Synthesis of spirocyclic cyclohexadienones by aryl radical additions onto arenes.

Substrates of type **28**, bearing a *para*-trityloxyaryl group as an aryl radical acceptor, showed also a different reaction outcome. As shown for the formation of spirocyclohexadienones **31b**, the cyclohexadienyl radical **30b**, generated by intramolecular aryl radical addition, underwent fast fragmentation to

biaryl formation. Of course, similar chemistry has also been applied to the synthesis of unnatural compounds that might be useful in materials science. For example, an impressive tin hydride-mediated double arylation of a diiodide was used to access the helicene compound **33**, as shown in (6).^{59,60}



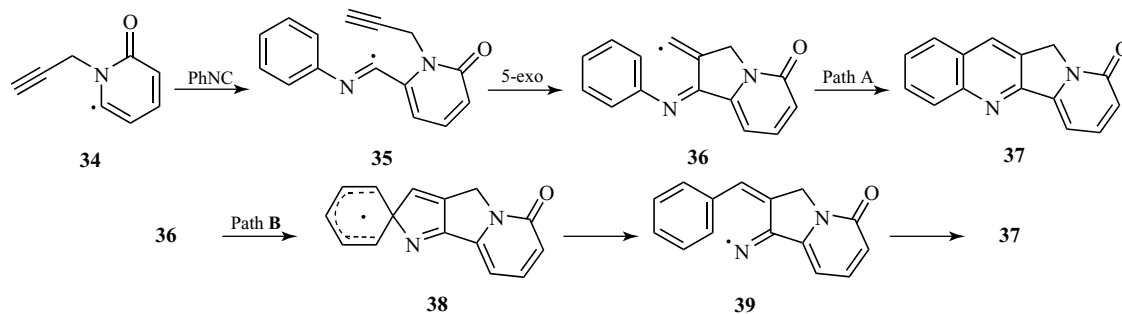
afford **31b** and the highly stabilized trityl radical. Reduction of the trityl radical sustained the chain reaction (Scheme 4).⁵⁰ It was suggested that the spirocyclic intermediate **30b** might also be formed by 1,2-aryl migration from radical **30a**. Indeed, when protecting groups (PGs) such as OTBS, Me, and Bz were installed in place of the trityl group, the main products isolated were the corresponding phenanthridinones **31a** arising by cyclization onto the ortho position via **30a** in a homolytic aromatic substitution.

Products of type **31b** can also be obtained by replacing the trityloxy group OCPH₃ by an azide substituent. In these aromatic azides, the cyclohexadienyl radical obtained after initial aryl radical addition released N₂ to provide the corresponding imine. Hydrolysis eventually delivered cyclohexadienones.⁵¹ Although there are some synthetic protocols for reduction of the intermediately formed cyclohexadienyl radicals as discussed, most cyclohexadienyl radicals rearomatize to give biaryls. The “intercepted” homolytic aromatic substitutions are rare.

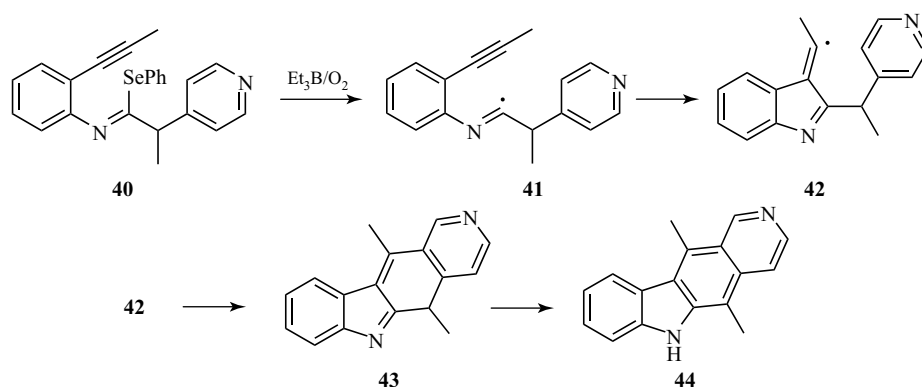
Many natural products can be synthesized via intramolecular homolytic substitution reactions. For example, the synthesis of *Amaryllidaceae* alkaloids,⁵² glaucine,^{53,54} cryptopleurine,⁵⁵ benzo[*c*]phenanthridine alkaloids,⁵⁶ luotonine A, (–)-conocarpan,⁵⁷ and rutercapine⁵⁸ were all successfully accomplished by applying radical

As already mentioned, vinyl radicals have also been used as reactive intermediates in homolytic aromatic substitutions.⁶¹ Vinyl radicals are readily generated by intramolecular addition of aryl radicals to triple bonds.^{62–70} Intramolecular aromatic substitution reactions with vinyl radicals have successfully been employed in domino radical reactions for the synthesis of various camptothecin derivatives^{71–74} and ellipticine.⁷⁵ An example is discussed in Scheme 5. Aryl radical **34** reacts with phenyl isonitrile in an intermolecular addition reaction to afford imidoaryl radical **35**, which after 5-*exo*-dig cyclization gives alkenyl radical **36**. The alkenyl radical reacts with the aryl moiety in a 6-*endo* cyclization to deliver, after oxidation, compound **37** (path A in Scheme 5). It has been suggested that the homolytic substitution can also occur by ipso attack to afford the spirocyclic radical **38** (path B in Scheme 1), followed by ring opening to form iminyl radical **39**, renewed ring closure, and oxidation.

With Et₃B/O₂ initiation, imidoaryl selenide **40** reacts via imidoaryl radical **41** and subsequent 5-*exo* cyclization to vinyl radical **42**. This radical then undergoes homolytic aromatic substitution to give **43** (Scheme 6). It has been suggested that the reaction likely occurs via an initial 5-*exo*-cyclization followed by a neophyl-type rearrangement (see path B in Scheme 5). Finally, tautomerization of **43** leads to ellipticine **44**.



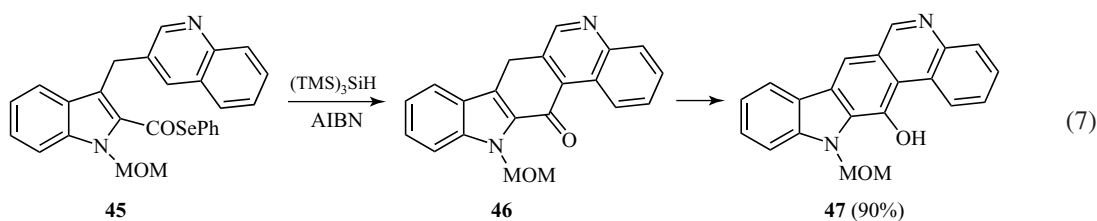
Scheme 5 Homolytic aromatic substitution with an intermediately generated vinyl radical.



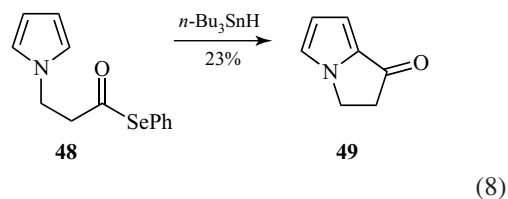
Scheme 6 Efficient synthesis of ellipticine **44** via homolytic aromatic substitution.

Acyl radicals generated from acylselenides efficiently react by homolytic substitution under standard reductive conditions.^{58,76–82} Different

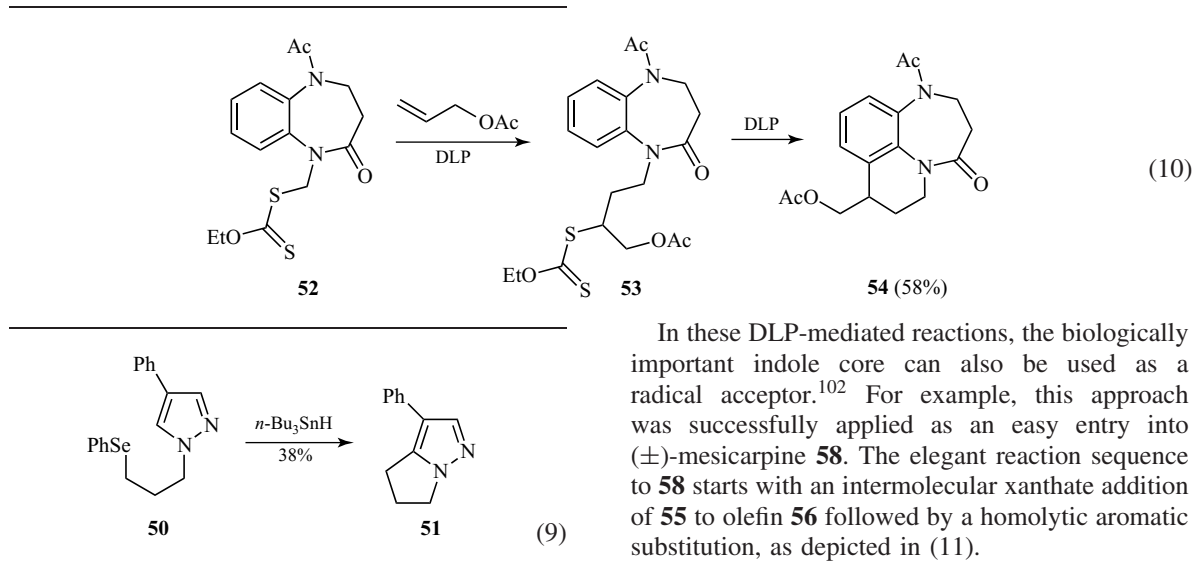
in rather low yield, by arylation of the acyl radical obtained from acyl selenide **48** under tin hydride conditions (8).⁸⁴



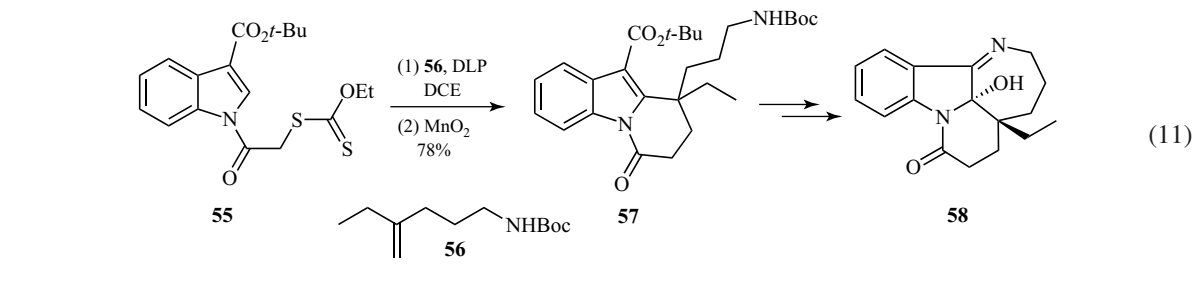
arenes and heteroarenes can be used as radical acceptors in these processes. The successful synthesis of the calothrix derivative **47** is a nice example to document the potential of this approach (7).⁸³ Acyl radical arylation delivers ketone **46** as initial product, which undergoes fast tautomerization to **47** and which was isolated in 90% yield. Nordanaidone **49** was successfully prepared, although



Intramolecular radical addition onto arenes and heteroarenes can also be performed with primary and secondary alkyl radicals.^{85–92} Alkyl radicals in these reactions are readily generated from the corresponding alkyl halides or chalcogenides (bromides, iodides, and selenides) using *n*-Bu₃SnH as mediating reagent by applying different initiators (for an overview on radical initiators, see **Overview of Radical Initiation**). Intramolecular arylation of alkyl radicals with imidazoles, pyrroles, and pyrazoles has been studied in detail.^{58,83} As an example, the synthesis of whitasomnine **51** using readily available alkyl selenide **50** is shown in (9).



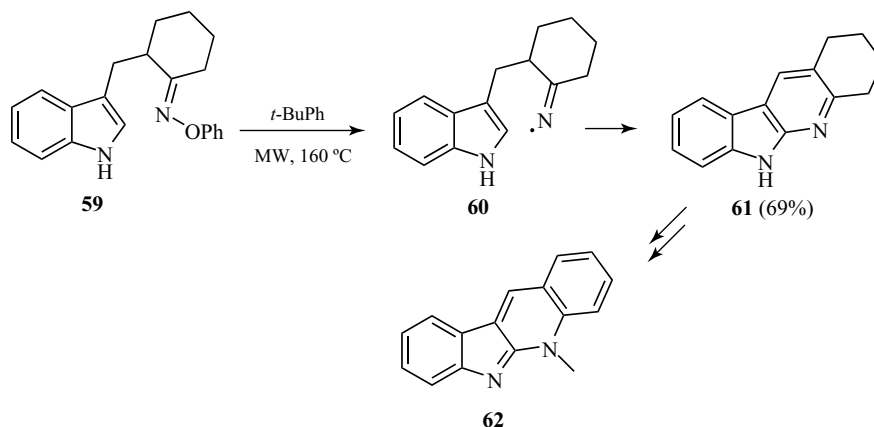
In these DLP-mediated reactions, the biologically important indole core can also be used as a radical acceptor.¹⁰² For example, this approach was successfully applied as an easy entry into (±)-mesicarpine **58**. The elegant reaction sequence to **58** starts with an intermolecular xanthate addition of **55** to olefin **56** followed by a homolytic aromatic substitution, as depicted in (11).



Along with the tin hydride-mediated arylations, electrochemical,⁹³ photochemical,^{94,95} and iodine transfer methods^{96,97} have been reported to be useful for the generation of alkyl radicals to conduct alkyl radical arylations. In addition, nucleophilic alkyl radicals generated from aldehydes with SmI₂⁹⁸ or stannyl radicals⁹⁹ also react with arenes to give intramolecular arylation products.

In a related process, the intramolecular addition of a carbamoyl radical (an N-centered radical, see **Main-Group Elements in Radical Chemistry**), generated from the corresponding carbamoyl xanthates, onto arenes was used as an attractive entry to isoindolin-1-ones.¹⁰³

Intramolecular addition of aryl radicals to olefins is another useful route for the generation of alkyl



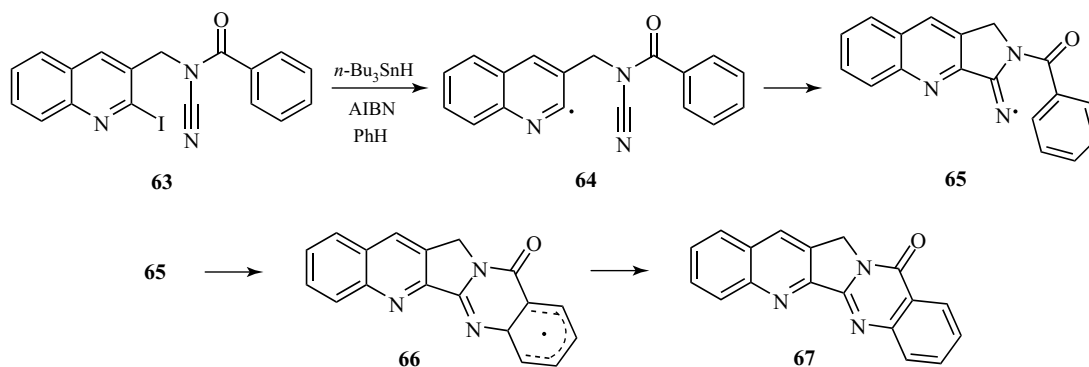
Scheme 7 Homolytic aromatic substitution with an iminyl radical as a key step in the synthesis of neocryptolepine **62**.

radicals, which can be used as reactive intermediates for arylations.¹⁰⁴ Iminyl radicals have also been studied in intramolecular homolytic aromatic substitution reactions. These radicals can be generated by addition of a C-centered radical to a nitrile,¹⁰⁵ by intramolecular 1,5-H transfer,¹⁰⁶ or directly from the corresponding oximes^{107–109} and hydrazones.¹¹⁰ Microwave-assisted reactions of readily available aryl-carbonyl *O*-phenyl oximes of type **59** have been reported to be useful substrates for the synthesis of various heterocyclic compounds such as quinolines, phenanthridines, benzonaphthiridines, and indolopyridines.¹¹¹ The scope of these reactions is exemplified by the formal synthesis of the antimalarial compound neocryptolepine **62** in which an indolyl group was used as a radical acceptor in the arylation reaction (Scheme 7). The

iminyl radical **60**, which subsequently reacted via an intramolecular arylation to **61**, was generated by thermal N–O bond homolysis. Indole derivative **61** was then further transformed to neocryptolepine **62**.

Malacria and coworkers have recently shown that amide-iminyl radicals of type **65**, readily generated from iodide **63** via aryl radical **64** and 5-exo cyclization onto *N*-acylcyanamides, undergo intramolecular homolytic aromatic substitution via cyclohexadienyl radical **66** to give luotonine A (**67**, Scheme 8).^{41,112,113}

Along with C- and N-centered radicals as discussed, intramolecular homolytic aromatic substitution with sulfur-centered radicals has been successfully conducted for preparation of benzothiazoles.¹¹⁴



Scheme 8 Synthesis of luotonine A.

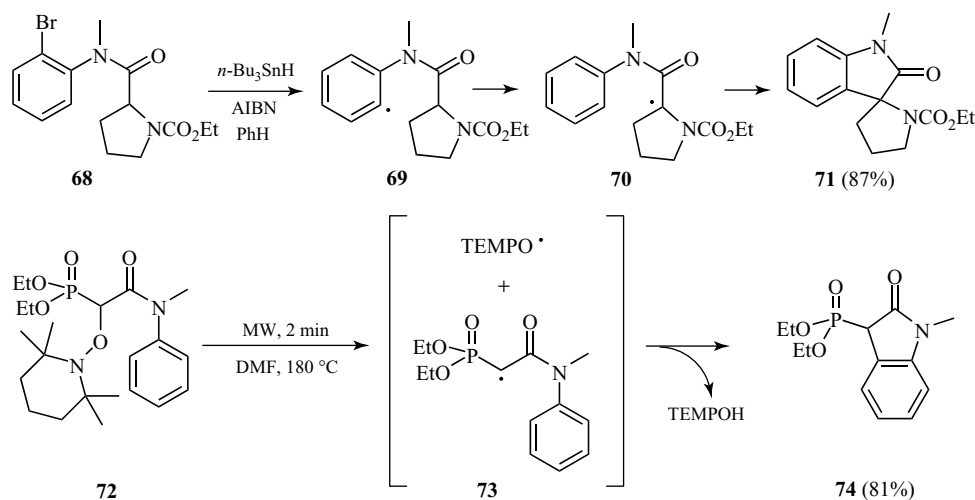
2.1.2 Arylation Using Electrophilic C-Centered Radicals

Intramolecular homolytic arylations with electrophilic radicals have been studied to a lesser extent compared to analogous reactions involving nucleophilic radicals. Most often, in these reactions electrophilic radicals have been generated by oxidation of CH acidic compounds such as dialkyl malonates or β -ketoesters with $\text{Mn}(\text{OAc})_3$ (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**).¹¹⁵ Studies on $\text{Mn}(\text{OAc})_3$ -mediated intramolecular homolytic aromatic substitution of several dialkyl malonates^{116–120} revealed that these reactions are well suited for the synthesis of five-, six-, and seven-membered fused rings.¹²¹ Arylation can also be performed on heteroarenes as radical acceptors by using this approach.¹²² Good results were obtained for formation of six-membered rings in the reaction with electron-rich and also electron-poor arenes. Hence, for six-membered systems, the “philicity” of the radical acceptor does not influence the reaction outcome to a large extent. However, for cyclizations to seven-membered rings only with electron-rich arenes as acceptors, good results were achieved for the homolytic aromatic substitution. Other oxidants such as cerium(IV) ammonium nitrate (CAN, see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**),¹²³ and iron

(III) perchlorate¹²⁴ have also been used in similar transformations.

As shown by Beckwith, electrophilic C-centered radicals can also be generated by 1,5-H shift from activated C–H bonds to intermediately formed aryl radicals. An example is provided in Scheme 9. Aryl radical **69** was generated from the corresponding bromide **68** by reaction with a stannyl radical. 1,5-H transfer allowed the generation of electrophilic C-radical **70**, which eventually further reacted to oxindole **71** by an intramolecular homolytic substitution in 87% overall yield.¹²⁵ Tin-free versions of these reactions have also been developed.¹²⁶

Other routes for the generation of electrophilic C-centered radicals that have been successfully used in intramolecular arylations are (i) direct use of selenides and bromides,^{127,128} (ii) radical addition to olefins bearing electron-withdrawing groups,^{129,130} and (iii) thermal C–O bond homolysis of adequately substituted 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)-derived alkoxyamines (see **Nitroxides in Synthetic Radical Chemistry and Nitroxide-Mediated Polymerization and its Applications**).¹³¹ An example of this “TEMPO-approach” representing a tin-free aromatic substitution is shown in Scheme 9. Microwave irradiation of alkoxyamine **72** delivers electrophilic radical **73**, which undergoes homolytic aromatic substitution to give oxindole **74**. In this

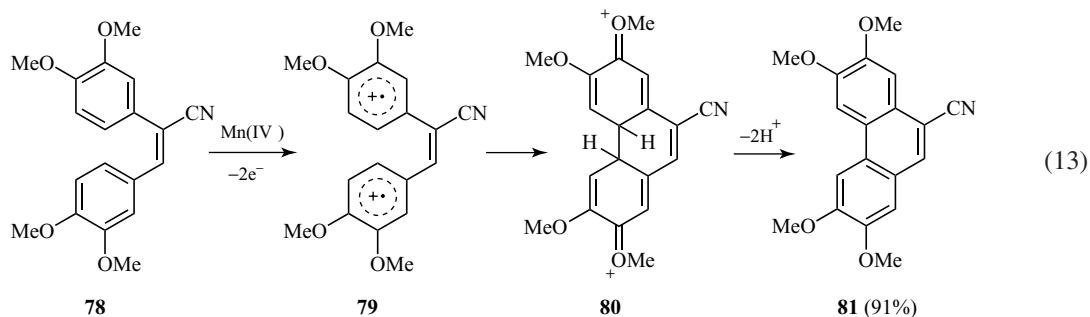


Scheme 9 Homolytic aromatic substitution with electrophilic C radicals.

process, TEMPO acts as oxidant for the transformation of the intermediately formed cyclohexadienyl radical to the arene.

Recently, Perry and Taylor^{132,133} and Jia and Kündig¹³⁴ independently disclosed a route to oxindoles by direct C–H/Ar–H coupling in arylanilides bearing electron-withdrawing groups. These reactions were promoted by KO^{*t*}-Bu as a base and

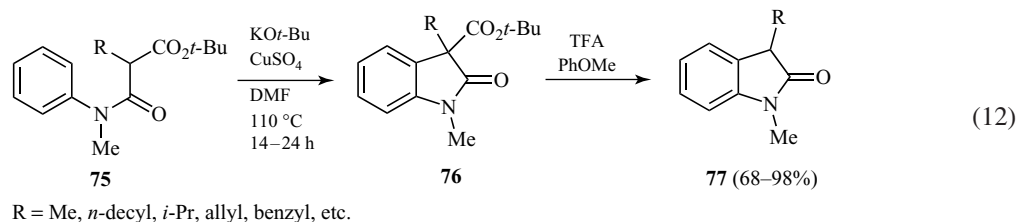
compounds.¹³⁶ As an example, oxidative coupling of **78** to **81** is shown in (13). Electron spin resonance (ESR) studies revealed that the electrophilic bis-radical cation **79** is generated as a reactive intermediate in this process. C–C bond formation affords the dication **80**, which is subsequently deprotonated to the corresponding biaryl product **81**.



Cu(II) as a stoichiometric oxidant. Mechanistic studies revealed that these reactions proceed by an intramolecular homolytic aromatic substitution process in which the electrophilic alkyl radicals are formed by oxidation of the corresponding enolates. Different electron-withdrawing groups such as CO₂R, CN, P(O)(OR)₂, and aryl groups allowed tandem enolization/oxidation/homolytic substitution reactions to give the substituted oxindoles in good yields. As shown in (12), when *tert*-butyl carboxylates of type **75** were used as substrates, homolytic aromatic substitution (see **76**) followed by *in situ* acid-promoted decarboxylation afforded the 3-substituted oxindoles **77** with good to excellent yields.

2.1.3 Radical Aryl Migrations

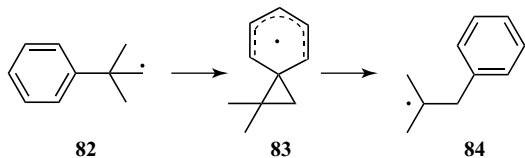
Radical aryl migration reactions are of great interest in synthetic organic chemistry. In recent years, these reactions have been successfully used as key steps for the synthesis of complex natural products.¹³⁷ The 1,2-phenyl migration of neophyl radical **82** to form the tertiary radical **84** (neophyl rearrangement, (14)) was first reported more than 60 years ago¹³⁸ and since then several related processes have been published.^{139,140} For an overview on radical rearrangements, see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**. Despite numerous efforts,



MnO₂ has recently been used for direct intra- and intermolecular coupling of electron-rich aryl

the postulated intermediate radical **83** could not be spectroscopically characterized.¹⁴¹ The neophyl rearrangement is a slow process as compared

to most other radical reactions ($k = 762 \text{ s}^{-1}$ at 25°C)^{142,143} and has been widely used as a radical clock (see **Radical Kinetics and Clocks**).^{144–146}



(14)

As an example to show the potential of the neophyl-type rearrangement in synthesis, the conversion of malonates **85** to dibenz[*b,f*]oxepines **89** under oxidative conditions is shown in Scheme 10.¹⁴⁷ On the basis of mechanistic studies, it was suggested that the stabilized tertiary radical **87** is generated by one-electron oxidation of manganese carboxylate **86**. Radical **87** undergoes rearrangement to benzyl radical **88**, which after oxidative decarboxylation affords oxepine **89**.

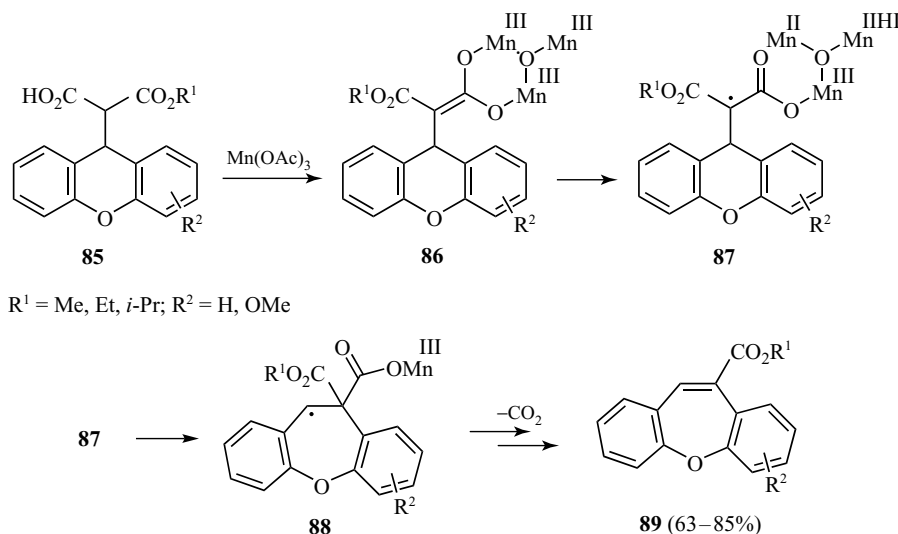
Another recent example on the use of a 1,2-aryl migration was published by Zard and coworkers.¹⁴⁸ Radical **90**, generated from the corresponding xanthate, was allowed to react with olefin **91** (Scheme 11). The adduct radical **92** is prone to undergo 1,2-phenyl migration to provide rearranged C-radical **93**. β -Elimination of the methylsulfonyl radical eventually leads to olefin **94**.

The methylsulfonyl radical further reacts via an α -elimination to SO_2 and the methyl radical that sustains the chain.

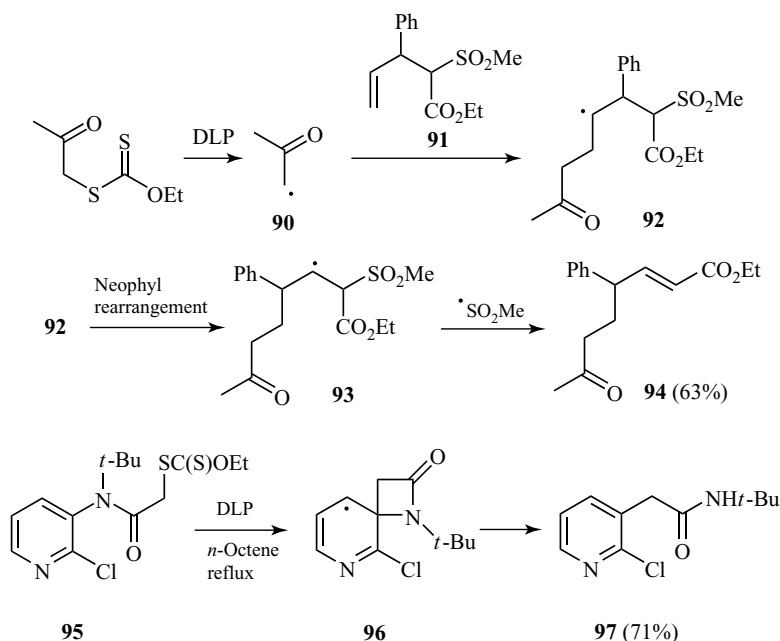
The 1,2-aryl migration from carbon to an O-centered radical is known as *O*-neophyl-type rearrangement.^{149–153} Recent studies on cumyloxyl radicals bearing cyclopropyl or 2,2-diphenylcyclopropyl groups in the para position of the phenyl ring as radical clocks strongly suggest that arylcarbinyloxyl radicals exist in equilibrium with 1-oxaspiro[2,5]octadienyl radicals, which agrees with the proposed mechanism for the *O*-neophyl rearrangement of 1,1-diaryloxy radicals.^{154,155}

1,3-Radical aryl migrations from carbon to C-centered radicals are unknown. However, the 1,3-aryl migration from N- to C-centered radicals has been reported (radical Smiles rearrangement).^{156–160} Treatment of xanthogenate **95** with DLP in octene under reflux yielded the 1,3-aryl migration product **97** in 71% yield. Product **97** was formed via radical **96**, as depicted in Scheme 11.

The 1,4-radical aryl migration from carbon to C-centered radicals is known for more than 60 years.¹⁶¹ Although 1,4-aryl migrations are usually considered as side reactions, some synthetically useful examples have been reported in the literature.^{162–176} A 1,4-radical aryl migration was



Scheme 10 Application of a neophyl-type rearrangement in synthesis.



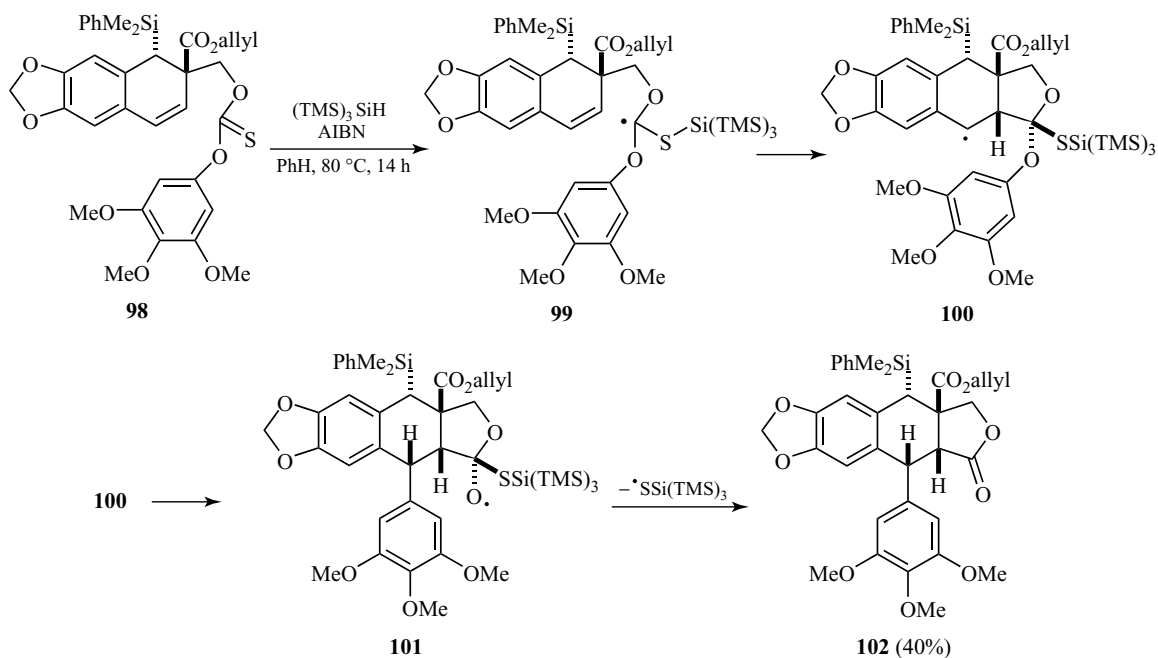
Scheme 11 Neophyl-type rearrangements in synthesis. DLP, dilauroylperoxide.

used as key step of an elegant synthesis of podophyllotoxin **102**. The tertiary alkyl radical **99**, generated from thionocarbonate **98**, reacts with the double bond in a 5-exo cyclization producing radical **100**. Stereoselective 1,4-aryl migration provides alkoxy radical **101**, which, after reduction and hydrolysis, affords lactone **102** in 40% yield (Scheme 12). Other sequences that use the 1,4-aryl migration from carbon to C-centered (aryl and alkyl) radicals in arylcarboxamides have been reported for the synthesis of phthalimides, biaryls, and β -arylethylamines.¹⁷²

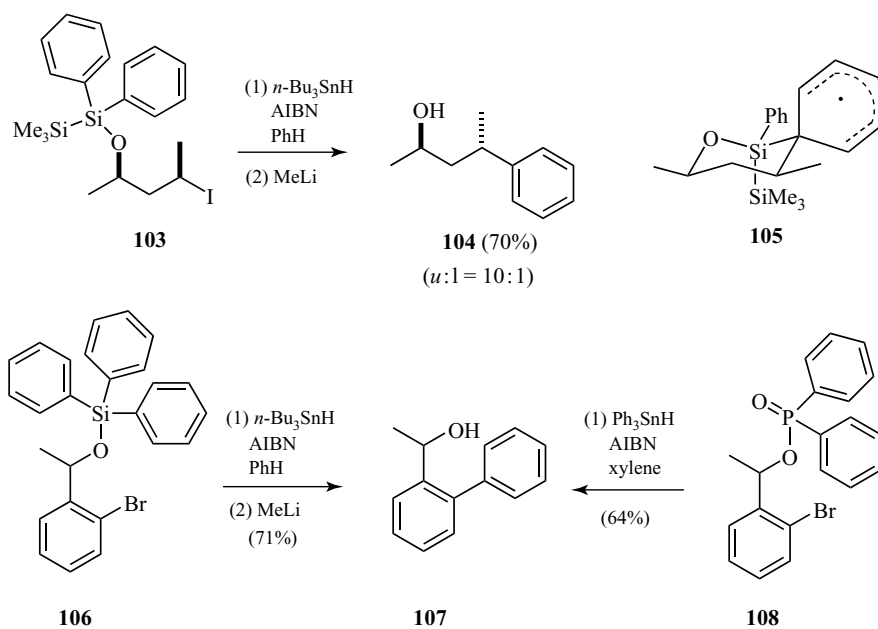
Radical 1,5-aryl migration reactions have successfully been used for the synthesis of several biaryls.^{177,178} In addition, aryl migration from the heavier group IV elements are meanwhile well-established reactions. For example, Wilt showed that 1,4- and 1,5-phenyl migration from silicon to C-centered radicals are rather efficient processes. These studies also revealed that the migration in these systems could be a reversible process.¹⁷⁹ Similar conclusions were drawn for the 1,5-phenyl migration from carbon to Si-centered radicals.¹⁸⁰ Later, Studer extended the concept to the stereoselective 1,5-aryl migration from silicon

to C-centered radicals.¹⁸¹ For example, reaction of iodide **103** under standard tin hydride conditions provided the aryl migration product **104** in 70% yield with a 10 : 1 diastereoselectivity (Scheme 13). The cyclohexadienyl radical **105**, in which both methyl groups are oriented in pseudoequatorial positions, was suggested as an intermediate on the way to the major isomer. The analogous radical 1,4-aryl migration from silicon to C-centered radicals also occurred with excellent diastereoselectivity.¹⁸² Furthermore, this approach can also be used for the preparation of biaryls.¹⁸³ For example, reaction of bromide **106** under radical conditions followed by desilylation yielded biaryl **107** in 71% yield. As shown in Scheme 13, the same product was prepared by aryl migration from phosphorous starting with the appropriate aryl radical precursor **108**.¹⁸⁴

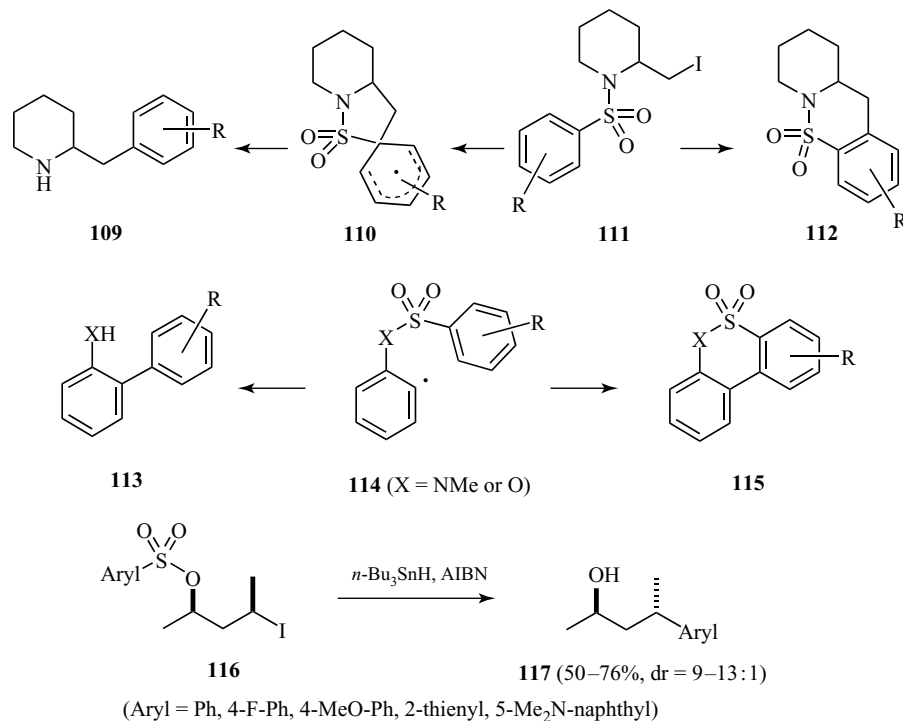
The radical 1,4-aryl migration from tin to alkyl radicals has also been reported.¹⁸⁵ Moreover, radical 1,4-aryl migrations from sulfur in sulfonamides to C-centered radicals have been well investigated.^{186,187} Iodides of type **111** reacted with $n\text{-Bu}_3\text{SnH}$ under radical conditions to afford arylated products **109** (Scheme 14). It was suggested that the intermediately generated primary alkyl



Scheme 12 Complex cascade reaction involving a radical 1,4-aryl migration.



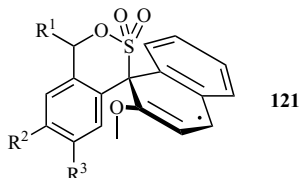
Scheme 13 Radical aryl migration from silicon or phosphorous to C radicals.



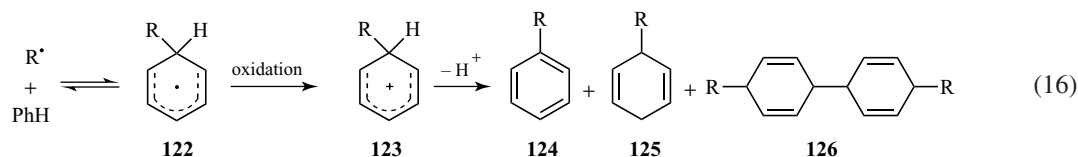
Scheme 14 Radical aryl migration from sulfur to C radicals.

radicals undergo ipso attack, forming cyclohexadienyl radicals of type **110**. Rearomatization followed by reduction and extrusion of SO₂ finally gives amine **109**. Electron-rich and also electron-poor arenes can be used in these transformations as migrating aryl groups. However, products **112** arising from homolytic aromatic substitution at the ortho position were formed as by-products in these reactions. On the basis of these results, a new radical method for the synthesis of biaryls was later disclosed by Motherwell and Pennell.^{188–191} Their method utilizes the 1,4- and 1,5-aryl migration from sulfur to aryl radicals and demonstrates that readily available arylsulfonates (X = O) and arylsulfonamides (X = NMe) are suitable substrates for that process. These reactions occur via aryl radicals of type **114**, which attack the migrating aryl group at the ipso position to eventually produce the biaryls **113** via homolytic substitution. As side products, biaryls **115** deriving from the initial ortho attack were formed. However, careful selection of the migrating aryl groups allowed suppressing the formation of this side reaction.

1,4-Aryl migration from sulfur to C-centered radicals has also been used for the synthesis of 3-arylpiperidines¹⁹² and of 2-aryl propionamides.^{193,194} Studer used the radical aryl migration from sulfur in sulfonates to secondary C radicals for stereoselective C(sp²)–C(sp³) bond formation.¹⁹⁵ Various aryl groups were transferred with high diastereoselectivities and moderate to good yields, as shown for the transformation of arylsulfonates **116** to the corresponding alcohols **117**. Analogous aryl migrations in sulfonamides turned out to be far less efficient.¹⁹⁶ The same group recently studied atroposelective radical aryl migrations in sulfonates **118** for the formation of axially chiral biaryls (**15**).¹⁹⁷ Radical precursors were prepared from readily available starting materials. Products were obtained in good yields with moderate selectivities. Importantly, the diastereoisomeric biaryls **119** and **120** were readily separated by SiO₂ column chromatography. Cyclohexadienyl radicals of type **121** were proposed as reactive intermediates in these atroposelective radical arylations.



can intermolecularly react with benzene, affording a σ complex **122**, which can readily be oxidized to cation **123** (16). The phenylation product **124** is eventually formed by deprotonation of cation **123**. Under non-oxidizing conditions, cyclohexadienyl radical **122** is rather long-lived and can dimerize to **126**, disproportionate to cyclohexadiene **125** and arene **124**, or give directly arene **124** by H-atom abstraction from intermediate **122**.



Because reactions of nucleophilic alkyl radicals with non-activated arenes are slow, many side reactions efficiently compete with the targeted homolytic substitution process. Therefore, application of this type of arylation in synthesis is limited. For example, the rate constant for the addition of the *tert*-butyl radical to benzene at 79 °C is $3.8 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$,²⁰⁴ which is clearly at the lower edge of a useful radical reaction. As a consequence of the slow radical addition, the attacking radical undergoes various side reactions such as rearrangement, dimerization, disproportionation, as well as halogen- and hydrogen-atom abstractions. The reactivity of the homolytic substitution product toward alkyl radicals is only slightly lower than

As shown in Scheme 2 for cyclizing arylations (intramolecular variant), nucleophilic alkyl radicals

that of benzene, and therefore overalkylation is an additional problem. Homolytic substitution with benzene derivatives bearing different substituents has been studied in detail. Unfortunately, in most cases low regioselectivities are obtained in the intermolecular homolytic substitution of unactivated substituted benzenes with alkyl radicals.²⁰⁵ However, high selectivities can be achieved in the reaction of nucleophilic alkyl radicals with benzene derivatives bearing electron-withdrawing groups as radical acceptors. Good selectivities were also noted for heteroarenes such as thiophene, furan, and thiazole as radical acceptors.

The intermolecular homolytic aromatic substitution using aryl radicals under reductive conditions has also been studied. In order to obtain acceptable yields, in most cases, the use of a large excess of the arene is required. In practice, arene acceptors in these arylations are used as a solvent. For example, *n*-Bu₃SnH-mediated arylation of imidazole²⁰⁶ and pyridine²⁰⁷ with aryl iodides as starting materials have been accomplished. Curran showed that aryl radical addition to benzene occurs with high yields by using (TMS)₃SiH (see **Silanes as Reducing Reagents in Radical Chemistry**) as a reducing reagent and aryl iodides as radical precursors in the presence of O₂ and pyridine at room temperature. For example, biphenyl **127** was obtained in excellent yield following this method with 4-iodoanisole as a

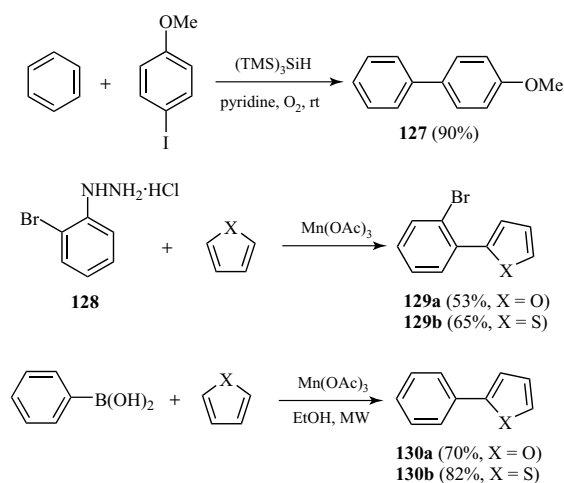
radical precursor (Scheme 15).⁴³ At higher temperature and in the absence of O₂ and pyridine, lower yields were obtained in that arylation reaction.²⁰⁸

Aryl radicals generated by the oxidation of aryl hydrazines with Mn(OAc)₃ (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**) react with arenes used as solvents to provide the corresponding homolytic substitution products. An example of such a transformation is presented in Scheme 15 in which the hydrazine hydrochloride **128** reacted with furan or thiofuran under oxidative conditions to afford acceptable yields of biaryls **129a** and **129b**.²⁰⁹ In a related process, aryl radicals, obtained upon oxidation of aryl boronic acids with manganese triacetate, reacted under microwave heating with arenes and heteroarenes to give the corresponding biaryls with good yields and excellent regioselectivities. As examples, reaction of phenylboronic acid with furan or thiofuran to give **130a** or **130b**, respectively, is presented in the scheme. It is noteworthy that electron-poor nitrogen heterocycles are suitable substrates for these oxidative arylations.²¹⁰

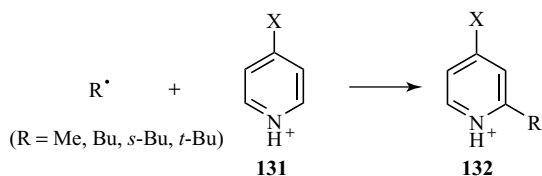
The KO^t-Bu-promoted radical arylation of electron-deficient nitrogen heterocycles has recently been studied. In this process, aryl iodides react with arenes under microwave heating yielding biaryls with excellent yields, including pyridine, pyrazine, and quinoxaline biaryl compounds.²¹¹ Although the mechanism of this interesting reaction is not clear yet, the homolytic aromatic substitution and the S_{RN}1 mechanism were suggested as the most probable reaction pathways.

Aryl radicals generated by the treatment of aryl diazonium salts with Ti(III) chloride efficiently react by a S_{RN}1-type process (see **The S_{RN}1 Reaction**) with anilines, phenols, ethers, and furans as radical acceptors.^{212,213} These reactions are of broad scope and usually give acceptable yields and regioselectivities. Notably, these biaryl syntheses have been successfully applied for the preparation of interesting natural products.

Protonated heteroaromatic compounds are electron-deficient substrates that react regioselectively with nucleophilic alkyl radicals yielding the corresponding homolytic substitution products (Minisci Reaction).^{214,215} With *p*-substituted pyridine derivatives, homolytic substitution occurred perfectly regioselective at the 2-position. Protonation is important to increase the reactivity and also the selectivity. Indeed, the same arylation



Scheme 15 Intermolecular arylation.



X	R			
	Me [•]	Bu [•]	<i>s</i> -Bu [•]	<i>t</i> -Bu [•]
CN	12.5	20.3	259.0	1890
COMe	3.6	5.6	55.6	144
Cl	2.4	—	—	11.1
H	1	1	1	1
Me	0.5	0.3	0.3	0.15
OMe	0.3	0.1	0.02	0.005

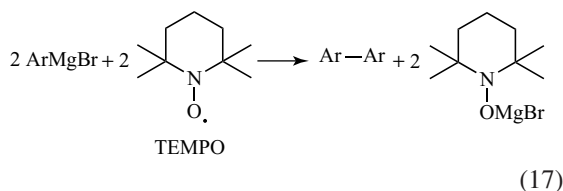
Scheme 16 Relative rates for the radical arylation of protonated pyridines with alkyl radicals.

on nonprotonated pyridine proceeded with low regioselectivity in low yield.

The rate of addition of a radical to a heteroarene correlates very well with the nucleophilicity of the attacking radical.²¹⁶ Electrophilic radicals such as $\cdot\text{CH}_2\text{CO}_2\text{H}$, $\cdot\text{CH}_2\text{CN}$, and $\cdot\text{CH}_2\text{NO}_2$ do not react with protonated pyridines. For a given nucleophilic radical, the reactivity toward homolytic substitution strongly depends on the electrophilicity of the arene. The highest rate constants were observed for the addition to the electron-deficient 4-cyanopyridinium salts **131** to give after oxidation-substituted pyridines **132** (Scheme 16). These heteroarene alkylations with protonated pyridines bearing electron-donating groups, such as a methoxy group in para-position, are up to 3.5×10^5 times slower.^{209,217} Reactivity trends indicate that polar effects are very important in these homolytic substitution reactions. In the transition state, charge is transferred from the nucleophilic radical (electron donor) to the pyridinium salt (electron acceptor).^{218,219} Frontier molecular orbital (FMO) theory²²⁰ has been used to explain the reactivity differences observed upon variation of the substituents at the pyridium salts. Furthermore, FMO can also be used to explain the regioselectivity observed in aromatic substitution reactions. The lowest unoccupied molecular orbital (LUMO) of the substituted pyridinium ions has the highest

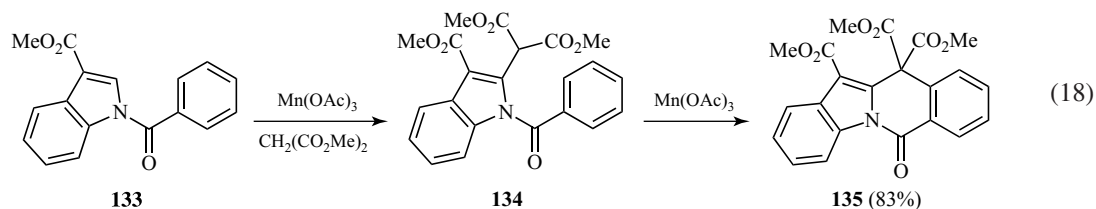
coefficients at the carbon atoms at positions 2 and 4,²²¹ and the main orbital interaction is between the singly occupied molecular orbital SOMO of the incoming nucleophilic radical and the LUMO of the protonated heteroarene. Since the 4-position in the substrates shown in Scheme 16 is blocked, addition should regioselectively occur at position 2 of the arene ring. As expected, for unsubstituted pyridinium ions nucleophilic addition occurs at positions 2 and 4.²²² The Minisci reaction has been used for alkylation of several heteroarenes including lepidine, pyrazine, quinoline, and quinoxaline.^{223–229}

Studer recently reported on the oxidative homocoupling of aryl Grignard reagents with TEMPO (see **Nitroxides in Synthetic Radical Chemistry**) as an oxidant. The mechanism of that reaction is not fully understood. It is likely that TEMPO radicals react with arylmagnesium bromides to afford Mg-complexed aryl radicals that react with the aryl-Mg derivative either intra- or intermolecularly to give biaryl radical anions, which are further oxidized under the reaction conditions to the corresponding biaryls. Products were isolated with excellent yields (17).²³⁰



2.2.2 Arylation with Electrophilic C-Centered Radicals

The first report on a homolytic aromatic substitution reaction by using electrophilic C-centered radicals was published about 40 years ago. In the presence of $\text{Pb}(\text{OAc})_4$ ²³¹ or $\text{Mn}(\text{OAc})_3$,^{232,233} toluene reacted with acetic acid to give a regioisomeric mixture of tolylacetic acids besides several side products. Reactions occur via oxidation of acetic acid with the Pb or Mn salt to generate the $\cdot\text{CH}_2\text{COOH}$ radical, which then adds to toluene to give the corresponding cyclohexadienyl radical that is readily oxidized under these conditions. It was later shown that the electrophilic enoyl radical deriving from acetone can be generated by oxidation of acetone with $\text{Mn}(\text{OAc})_3$. Reaction with substituted

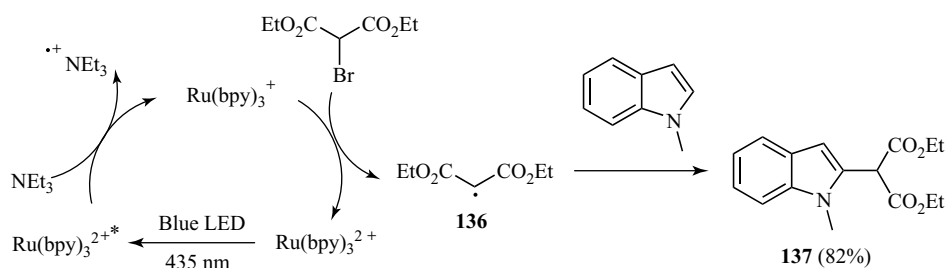


arenes affords the arylation products as a mixture of regioisomers.^{234,235} The outcome of the reaction depends on the nucleophilicity of the arene substrate. As expected for a reaction with an electrophilic C radical, better results were obtained with electron-rich arenes. In analogy, nitromethylation of electron-rich arenes was achieved by oxidation of nitromethane in the presence of an arene.²³⁶ $\text{Mn}(\text{OAc})_3$ -mediated oxidative C-radical generation is a general process that works for methylene derivatives bearing α -electron-withdrawing groups capable of increasing the acidity of the methylene protons (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**). In these processes, the most typical radical precursors are dialkylmalonates.^{237–243} A nice example documenting the potential of this arylation approach is depicted in (18). In the first step, dimethylmalonyl radical reacts in an intermolecular homolytic aromatic substitution highly regioselective at the 2-position of the indole core in **133** to give 2,3-disubstituted indole **134**. Renewed oxidative C-radical generation with $\text{Mn}(\text{OAc})_3$ and intramolecular homolytic aromatic substitution provided **135** in 83% yield.^{244,245} CAN has also been

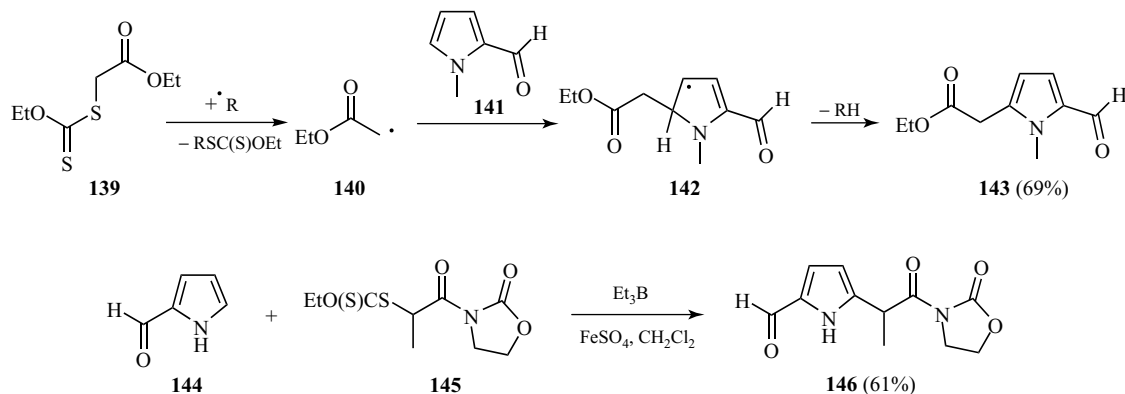
used as oxidation reagent in intermolecular aromatic malonylations.^{235,236,246,247}

Recently, an efficient photoredox-mediated direct C–H arylation of indoles, pyrroles, and furans has been accomplished.²⁴⁸ An example of an indole alkylation is shown in Scheme 17. $\text{Ru}(\text{bpy})_3^+$ (1 mol%) in the presence of diethyl bromomalonate provides after ET the malonyl radical **136** along with the oxidized $\text{Ru}(\text{II})$ complex. This malonyl radical then undergoes homolytic aromatic substitution at the 2-position of *N*-methyl indole to give **137** in a good yield. The $\text{Ru}(\text{bpy})_3^{2+}$ complex generated can be excited by visible light to become an oxidant that reacts with triethylamine via an ET process to regenerate the $\text{Ru}(\text{bpy})_3^+$ complex closing the catalytic cycle.

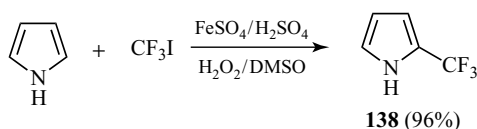
Baciocchi and Byers showed that α -iodoesters, α -iodomalonates, and α -iodocarbonitriles can be used as radical precursors for the homolytic arylation of heteroarenes.^{249–255} Importantly, perfluoroalkylation of arenes can be performed by using perfluoroalkyl iodides as radical precursors. For example, radical trifluoromethylation of pyrrole with CF_3I and $\text{FeSO}_4/\text{H}_2\text{O}_2$ in dimethylsulfoxide (DMSO) occurred with excellent yield, as shown in (19) for formation of pyrrole derivative **138**.²⁵⁶



Scheme 17 Radical indole malonylation by a photocatalytic approach.



Scheme 18 Radical pyrrole alkylations.

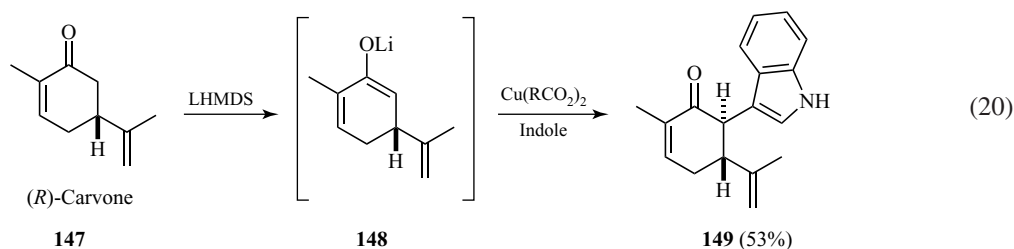


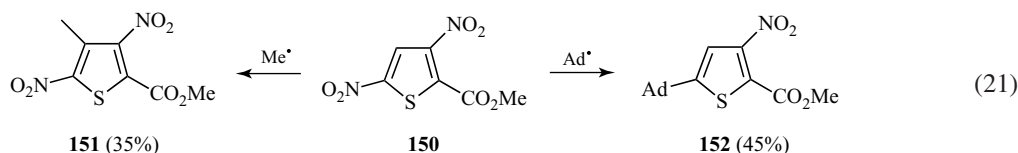
(19)

Electrophilic C-centered radicals that can be used in intermolecular homolytic substitutions were also generated from xanthates by xanthogenate transfer reactions (see **Xanthates and Related Derivatives as Radical Precursors**).^{257–260} As an example, a radical alkylation of *N*-methyl pyrrole **141** is shown in Scheme 18. DLP delivers an alkyl radical $R^\bullet$ upon heating, which then adds to xanthate **139** to provide after fragmentation the electrophilic radical **140**. Regioselective addition of radical **140** to the pyrrole derivative generates **142**, which via H transfer to radical $R^\bullet$ eventually gives substituted indole **143**. It was later shown that similar reactions can be performed using $\text{Et}_3\text{B}/\text{FeSO}_4$ as a mediator,²⁵⁴ as exemplified in the scheme for the formation of bisubstituted pyrrole **146** starting with pyrrole **144** and xanthogenate **145**.

The role of the Fe(II) salt in this reaction is not fully understood. It has been suggested that it may act as the Fe(III) source, which should facilitate oxidation (aromatization) of the adduct radical. It is noteworthy that only three equivalents of the arene were necessary to obtain a good yield. As mentioned above, intermolecular homolytic substitutions often use the radical acceptor as a solvent or co-solvent.

Baran *et al.* demonstrated that electrophilic C-centered radicals, generated by oxidation of Li-enolates with Fe(III) and Cu(II) salts, react with indoles and pyrroles to give arylated heterocycles with excellent yields (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**).^{261–263} For example, Cu(II)-mediated oxidation of the Li-enolate **148**, which is readily generated by deprotonation of (*R*)-carvone (**147**), in the presence of indole gave arylation product **149** in 53% yield as a single diastereoisomer (20). This type of radical arylation was successfully used as key step in the synthesis of hepalindoles, (*S*)-ketorolac, (+)-ambiguine, acremoauxin A, and ozanin 3.²⁶⁴





Heteroatom-centered electrophilic radicals can also be used in homolytic aromatic substitutions. For example, dialkyl aminyl radical cations react efficiently with arenes yielding aniline derivatives. N-centered radical cations can readily be generated from the corresponding *N*-chloroamines by using catalytic amounts of metal salts, such as those of Fe(III), Cu(I), Ti(III), and Cr(III). As expected, these amination reactions work best with electron-rich arenes such as phenol and aryl ethers as radical acceptors. By using mono-substituted benzene derivatives as acceptors, amination occurs nonselectively and a mixture of ortho and para (major product) arylation products is obtained.²¹⁴ Thiocyanate radicals, obtained upon treatment of ammonium thiocyanide with Mn(OAc)₃, react with indoles and anilines affording the corresponding homolytic substitution products with excellent yields and regioselectivities.^{265,266}

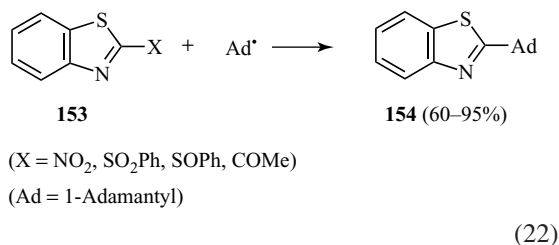
2.2.3 Intermolecular Ipso Substitutions

Compared to the aforementioned methods, the intermolecular ipso substitution reaction has received little attention in organic synthesis.^{267,268} This ipso substitution occurs only in selected cases, most often nucleophilic radicals in combination with electrophilic arenes. In addition, the group to be replaced should be small to allow ipso attack, and, in addition, must behave as a good radical leaving group. Taking into account that the leaving group increases the steric hindrance at the ipso position, very often the radical attack occurs at the cine position in such systems. Therefore, ipso attack and also intermolecular cine homolytic substitution is usually observed in these reactions. In fact, in most cases the latter process is the preferred reaction pathway. For example, thiophene **150** reacted with the adamantyl (Ad•) radical to afford a 45% yield of the ipso product **152**, whereas the same reaction with the methyl radical yielded exclusively the homolytic substitution product **151** (21).

With the nucleophilic adamantyl radical, regioselectivity of the attack is controlled by polar effects. In contrast to methyl radicals, where polar effects are less pronounced, the stability of the intermediate σ complex is responsible for the regioselectivity of the initial addition step. Along this line, a change in the regioselectivity was also noted in the reaction of 1,3,5-trinitrobenzene with nucleophilic C radicals by switching from the adamantyl to the methyl radical.²⁶⁹

Radical arylation of para-substituted nitrobenzenes (*p*-X-C₆H₄NO₂) with nucleophilic 1-adamantyl radicals works only for electron-poor arenes. For nitrobenzenes bearing electron-donating substituents at the para position (X = OMe, H, and Me), ipso substitution products were not identified, whereas good yields of alkylidenation products (45–60%) were achieved with nitrobenzenes bearing electron-withdrawing groups at the para position (X = NO₂, CN, SO₂R, CO₂R, CHO).²⁷⁰

The effect of the nature of the leaving group on the ipso substitution with the 1-adamantyl radical was studied for reaction of various benzothiazole derivatives **153** to give **154** (22).²⁷¹ As expected, the best result was achieved with the arene bearing the nitro group (95%, X = NO₂). Good yields of ipso substitution were also obtained with the phenylsulfonyl, phenylsulfinyl, and acyl-substituted benzothiazoles (80%, X = SO₂Ph; 80%, X = SPh; 60%, X = CO₂Me). Halides,²⁷² methylsulfonyl, and methoxy turned out to be not good leaving groups for these ipso substitution reactions. Ipso substitutions in which the phenylsulfonyl radical acts as leaving group have been used for the synthesis of various stannylated heterocycles.²⁷³

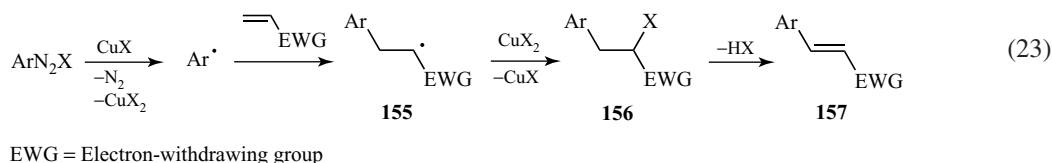


3 ARYLATION USING ARYL RADICALS

3.1 Additions onto Olefins: Meerwein Arylation and Related Reactions

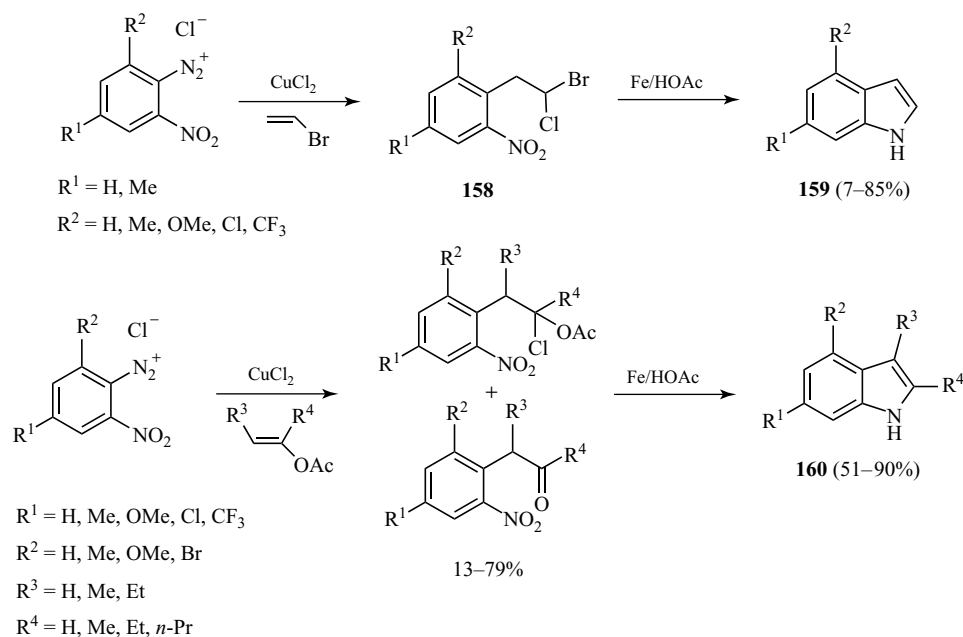
The Cu(I)-catalyzed reaction of aryldiazonium salts with olefins (Meerwein arylation) is a powerful and well-established method for arylation of various

reaction mixture.^{277,278} Alternatively, the reaction can be started with a Cu(I) salt. ET reaction from the Cu(I) species (CuX) to the aryldiazonium salt affords CuX₂ and the corresponding aryl radical, which then adds to the double bond providing the adduct radical **155**. Halide abstraction of radical **155** from CuX₂ provides the arylated product **166** and CuX which propagates the chain reaction. Arylated olefin **157** is eventually formed by an ionic HX elimination.



olefins.^{274,275} Good results were obtained for radical acceptors bearing electron-withdrawing groups such as carbonyl, cyano, aryl, and alkenyl. Depending on the nature of olefin and diazonium salt, the reaction can afford either the oxidized product **157** or the atom-transfer product **156** (23).²⁷⁶ In the Meerwein arylation, the catalytically active Cu(I) species is generated from a Cu(II) salt by reduction either with the solvent or with the impurities in the

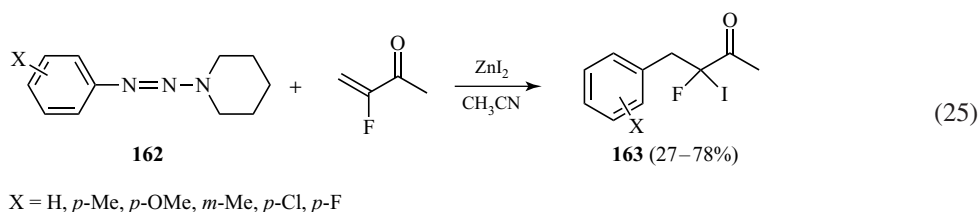
Various radical acceptors, such as nonconjugated alkenes, acetylenes, styrene derivatives, α,β -unsaturated ketones, α,β -unsaturated aldehydes, α,β -unsaturated acids, quinones, conjugated dienes, and ene-yne have been arylated under Meerwein conditions. As an example to document the scope of the reaction, an indole synthesis that uses a Meerwein arylation as the key step is presented in Scheme 19. Radical addition of



Scheme 19 Indole synthesis using a Meerwein arylation.

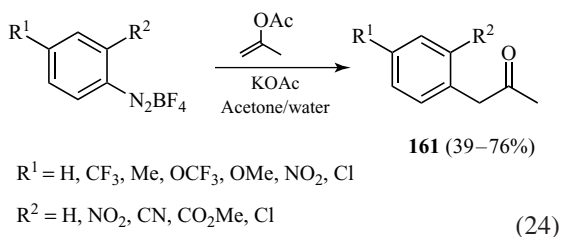
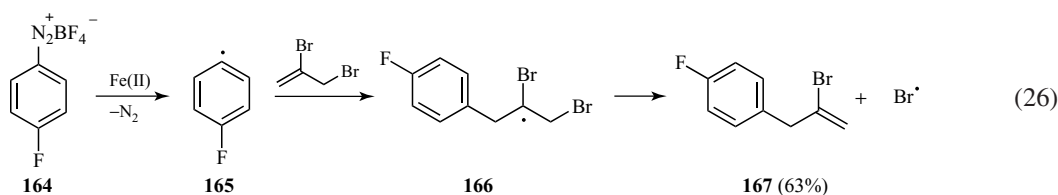
substituted nitrophenyl diazonium chlorides to vinyl bromide under typical Meerwein conditions provided chlorides **158**. Reduction of the nitro group followed by cyclization afforded the corresponding indoles **159**. Tetra-substituted indoles **160** were obtained with moderate yields by following the same synthetic strategy.²⁷⁹ Other heteroarenes, such as quinolones,²⁸⁰ benzothiophenes,²⁸¹ and benzylthiazoline-2,4-diones^{282,283} can also be obtained by applying the Meerwein reaction.

Aryltriazenes **162** react with ZnI_2 to give aryl radicals, which in the presence of acrylonitrile derivatives undergo 1,4-addition. The adduct radicals are then iodinated to afford products of an aryliodination.²⁸⁶ Along with acrylonitriles, α, β -unsaturated ketones have been used as radical acceptors for this arylation. For example, by using 3-fluorobutenone as radical acceptor, α -fluoro- α -iodo- β -arylated ketones **163** were obtained in moderate to good yields (25).²⁸⁷



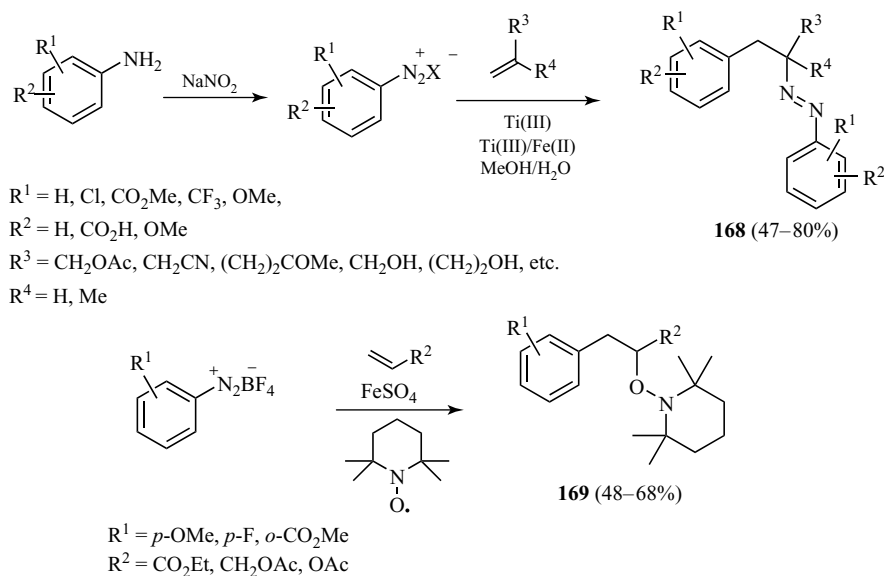
Other one-electron reductants are also suitable to mediate the Meerwein arylation. For example, it has been shown that Ti(III) chloride can be used for efficient generation of aryl radicals from diazonium salts.²⁸⁴ Noteworthy is the fact that a metal-free variant of the Meerwein arylation has been developed and applied for multikilogram preparation of α -arylmethyl ketones **161** (24).²⁸⁵ Although the mechanistic details on this process are unknown, an $\text{S}_{\text{RN}}1$ -type reaction (see **The $\text{S}_{\text{RN}}1$ Reaction**) seems to be feasible.

Allylation and vinylation of aryl radicals generated from diazonium salts by treatment with Fe(II) sulfate have been achieved with allyl halides (chlorides and bromides) and vinyl chlorides as aryl radical acceptors in non-chain reactions.²⁸⁸ As an example, the reaction of aryl diazonium tetrafluoroborate **164** with 2,3-dibromoprop-1-ene is presented in (26). Aryl radical **165**, which is readily formed by reduction of diazonium salt **164** with an Fe(II) salt, adds to the olefin, thereby generating the adduct radical **166**. β -Fragmentation leads to product **167**



along with a bromine radical which is then reduced by Fe(II) sulfate.

Alkyl radicals **155** generated by addition of aryl radicals onto an olefin can be trapped with various other radical acceptors. Cyanoarylation, carbodiazenylation, carboaminohydroxylation, carbohydroxylation, carboacetoxylation, carbothiolation, and carbohalogenation (Cl, Br, and I) have



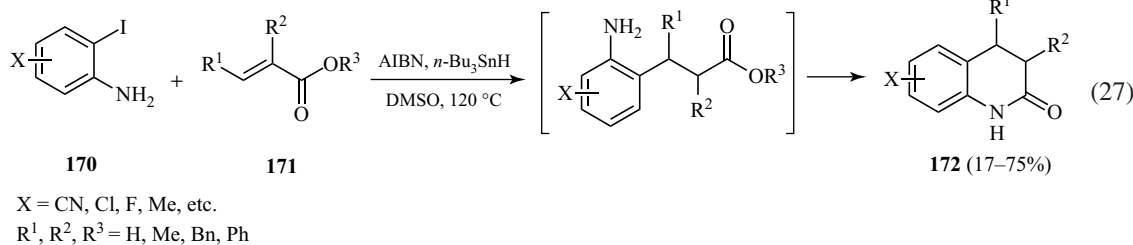
Scheme 20 Radical carbodiazenylation and carboaminohydroxylation of olefins.

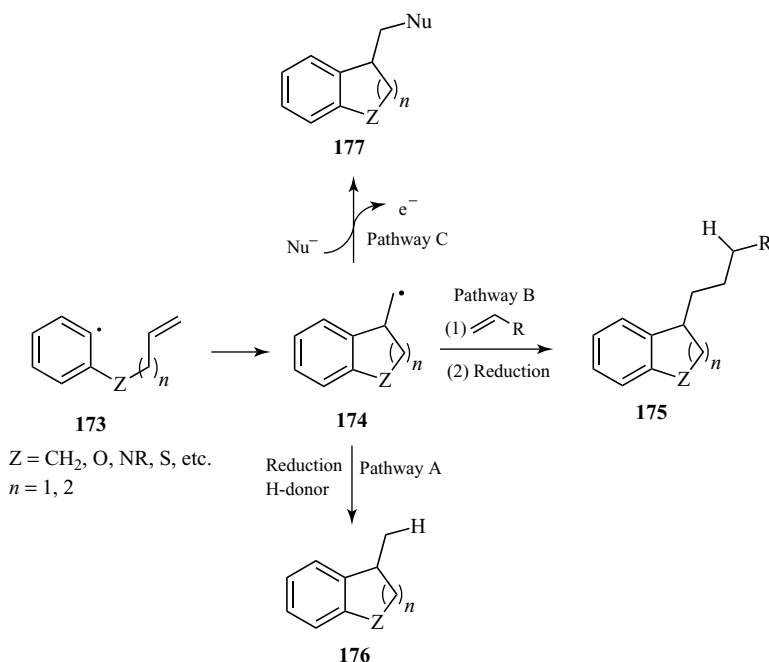
been disclosed.²⁸⁹ To show the potential of such processes, the carbodiazenylation (see **168**)^{290,291} and the carboaminohydroxylation²⁹² using TEMPO as radical acceptor (see **169**) are depicted in Scheme 20.

Aryl radicals generated under reductive tin hydride conditions can be trapped with activated alkenes if the intermolecular addition of the aryl radical is faster than its reduction by tin hydride. This reaction was successfully used for the synthesis of 3,4-dihydroquinolin-2-ones **172**. Reductive radical addition of various substituted ortho-iodoanilines **170** to α - β -unsaturated esters **171** afforded β -arylated esters, which further reacted by cyclization to lactams **172** (27).²⁹³

3.2 Aryl Radical Cyclizations

Ring-closure reactions using aryl radicals are useful processes for the synthesis of cyclic and heterocyclic compounds such as benzofurans, chromans, indanes, indolines, and tetrahydroquinolines, among others.^{294–296} The synthetic strategy used in these cases involves generation of an aryl radical, which then cyclizes, mostly in a 5-*exo* or 6-*exo*-trig process, to provide an alkyl radical that can further react via different pathways (Scheme 21). The intermediate radical **174**, generated after ring closure of aryl radical **173**, can be reduced with a suitable hydrogen donor to give **176** (pathway A), or react with a





Scheme 21 Radical cyclization using aryl radicals.

nucleophile affording **177** ($\text{S}_{\text{RN}}1$ reaction, pathway C), or react with a radical acceptor to provide after reduction products of type **175** (pathway B).

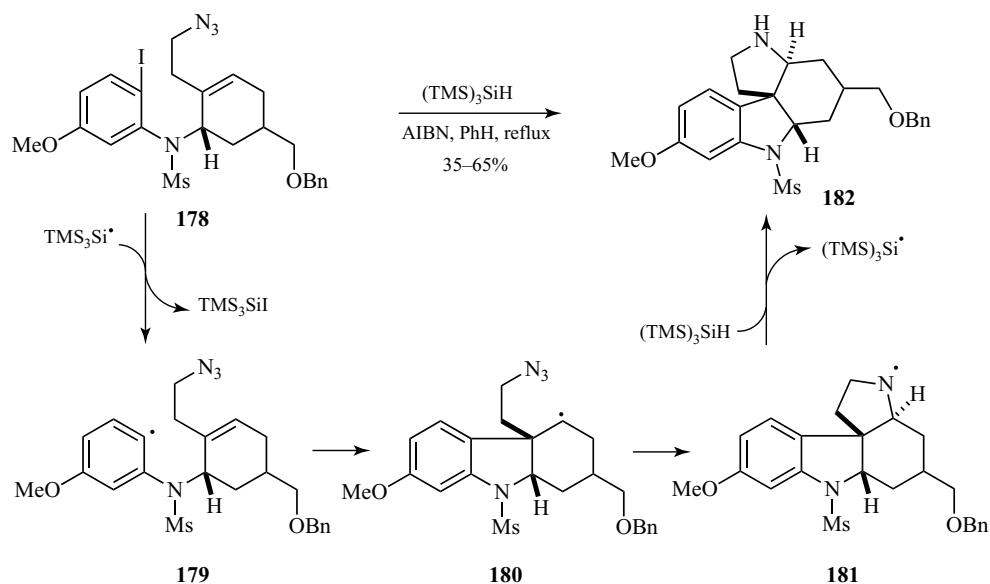
Aryl halides (bromides and iodides) as well as aryl diazonium salts can be used as aryl radical sources in these reactions. For example, aryl diazonium tetrafluoroborates were shown to be excellent substrates for the synthesis of substituted dihydrobenzofurans and related products.^{297,298} Along with the typical processes using tin hydrides, aryl radical formation can also be achieved by ET to the aryl halides or diazonium salts in a process closely related the well-known Sandmeyer reaction.^{299,300}

Although various environmentally benign hydrogen donors,^{301,302} such as TMS_3SiH (see **Silanes as Reducing Reagents in Radical Chemistry**) and *N*-ethyl piperidine hypophosphite, can be employed to mediate the chain reaction, $n\text{-Bu}_3\text{SnH}$ turns out to be the most useful reagent to conduct these cyclizations. Reductive cyclization of aryl radicals has been successfully used in natural-products synthesis. For example, ($\pm$)-vindoline **182** (key steps shown in Scheme 22), ($\pm$)-horsfiline, ($\pm$)-aspidoespermidine, and ($\pm$)-aphanorphine were prepared using a 5-exo aryl radical cyclization as the key step.^{303–306} Aryl

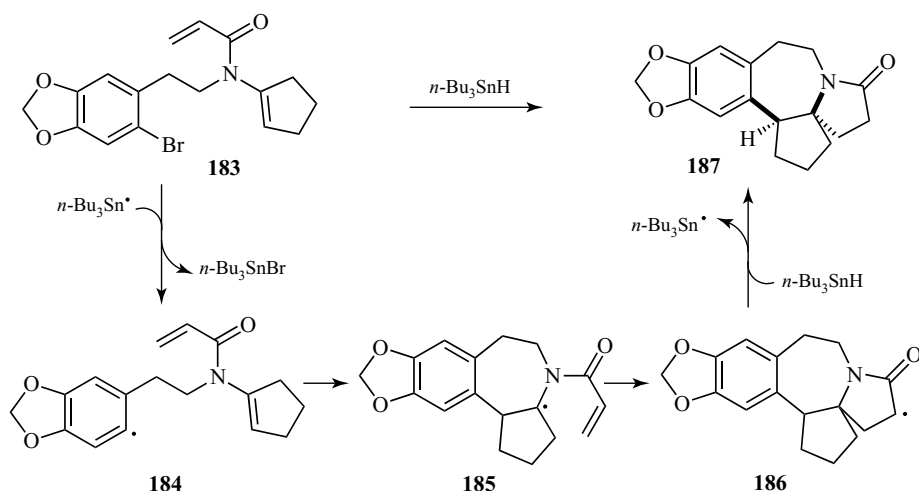
radical **179**, generated by iodine atom abstraction from **178**, undergoes 5-exo cyclization, affording the secondary alkyl radical **180**. Addition onto the azide group followed by N_2 elimination provides aminyl radical **181**, which is finally reduced to amine **182**.

To further illustrate the scope of aryl radical cyclizations in the field of natural-products synthesis, the key step of the synthesis of the antileukemic alkaloid (–)-cephalotaxine **187** is presented in Scheme 23. An elegant 7-endo/5-endo tandem radical cyclization afforded the (–)-cephalotaxine core in 32% yield under standard reductive radical conditions.³⁰⁷ Reaction of $n\text{-Bu}_3\text{Sn}^{\bullet}$ with bromide **183** affords aryl radical **184**, which undergoes a 7-endo-type cyclization to give **185**, which then further cyclizes to **186**. Tin hydride reduction eventually leads to the core structure of the natural product.

Unsaturated C–heteroatom bonds can also be used as aryl radical acceptors in radical ring-closure reactions. For example, an intramolecular aryl radical amination involving an imine as radical acceptor has been used as the key step in the synthesis of the ABC tricyclic core of ambiguine G.^{308,309}



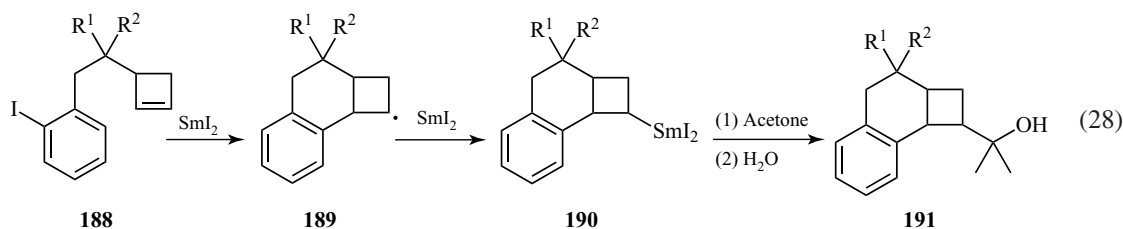
Scheme 22 Radical cascade reaction initiated by an aryl radical cyclization.



Scheme 23 Cascade radical cyclization using aryl radicals.

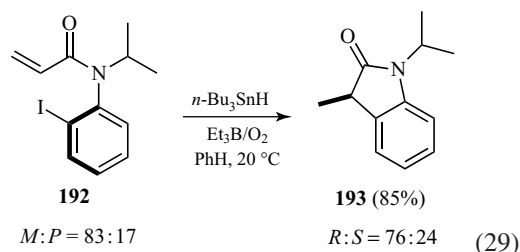
Aryl radicals can also be generated starting with the corresponding aryl iodides by one-electron reduction with SmI_2 (see **Organic Synthesis Using Samarium Diiodide**). A radical/polar crossover reaction of aryl iodides adequately substituted at the ortho position with a cyclobutenyl group was used as the key step in the synthesis of penitrems **191** (see 28). Reaction of aryl

iodide **188** with SmI_2 gives the corresponding aryl radical, which undergoes fast 6-exo cyclization affording alkyl radical **189**. Reduction (radical polar crossover) of **189** provides the intermediate organosamarium compound **190**, which can be trapped with acetone to give after hydrolysis penitrem building blocks of type **191**.³¹⁰

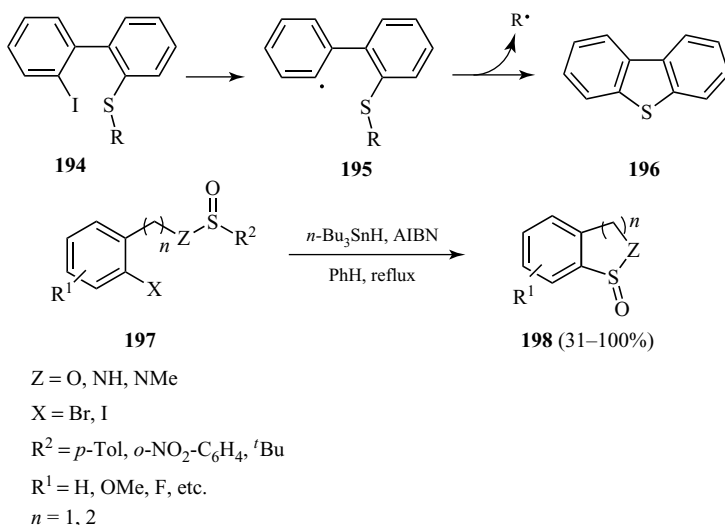


In related work, a radical/polar crossover reaction starting with an aryl halide applying hexamethylditin as nonreductive radical mediator together with Et_3Al and oxaziridine as traps was used as the key step in the synthesis of (–)-acutumine.^{311–313}

Atropisomers of *N*-substituted *o*-iodoacrylamides such as **192** and structurally related carbamates are configurationally stable at room temperature. These compounds show a high barrier (about 20–30 kcal mol^{–1}) for racemization. Curran showed that it is possible to transfer the axial chirality of enantioenriched axially chiral aryl iodides into centrochirality by a 5-exo cyclization under standard reductive conditions (see **193**, (29)). In this reaction, the 5-exo cyclization occurs faster than racemization of the intermediately formed axially chiral aryl radical. This has been shown for several examples. Transfer of chirality in these reactions usually lies around 90%.^{314–316}



Intramolecular homolytic substitution reaction of aryl radicals at group VI heteroatoms (S, Se, and Te) has been intensively used for the synthesis of heterocyclic compounds (see **Intramolecular Homolytic Substitutions in Synthesis**). For example, aryl radicals **195** readily obtained from aryl iodides **194** under reductive conditions undergo homolytic substitution at sulfur to provide benzothiophenes **196**, as shown in Scheme 24.³¹⁷ These reactions are efficiently only if the leaving radical $\text{R}^\bullet$ is stabilized. Among other applications,



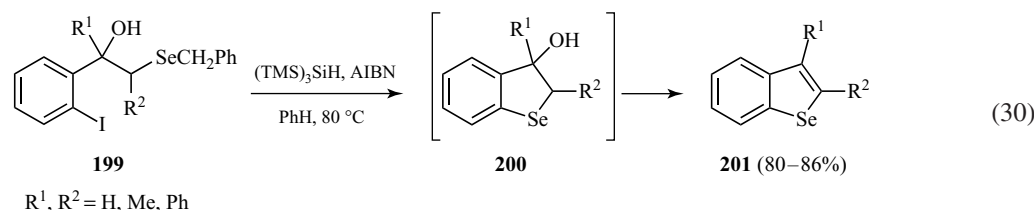
Scheme 24 Intramolecular homolytic substitution at sulfur with aryl radicals.

this approach has been used for selective deoxygenation of the 6-hydroxymethyl group in mannose derivatives.^{318,319} Different fused benzosultines and cyclic sulfinamides **198** can be prepared with good yields from halides **197** using an intramolecular homolytic substitution at the sulfur atom.³²⁰ These reactions allowed the synthesis of biaryl sulfinates in acceptable yields.³²¹ It has also been demonstrated that the leaving group R can be a phosphorus-centered radical.^{322,323}

Moreover, selenides **199** react under reductive radical conditions via a homolytic substitution at selenium to give cyclic selenium derivatives **200**, which upon water elimination provide selenophenes **201** with excellent yields (30).^{324,325} In a similar way, Te-containing heterocyclic compounds have been prepared.³²⁶

of $\text{Mn}(\text{OAc})_3$ to give phosphonates with good yields and good regioselectivities. Phosphonation of benzene derivatives was achieved with a $\text{Mn}(\text{II})/\text{Co}(\text{II})/\text{O}_2$ redox couple and dialkyl phosphites as P-radical precursors.^{327,328} It has also been demonstrated that phenyl compounds substituted with electron-withdrawing and electron-donating groups are good substrates for that phosphonation reaction. Phosphonation of benzonitrile and of 1,3-benzodioxole with diethyl phosphite to give phosphonates **202** and **203** is depicted in Scheme 25.^{329,330}

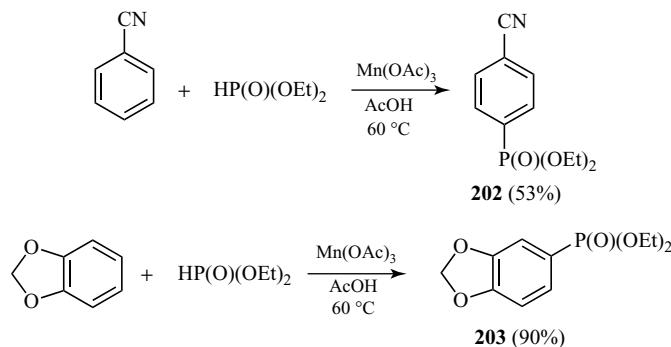
The homolytic substitution at trivalent phosphorous has recently been disclosed as a new alternative for the formation of P–C bonds. It was shown that tetraphenylbisphosphane ($\text{X} = \text{PPh}_2$) reacts under standard radical conditions with aryl radicals, which



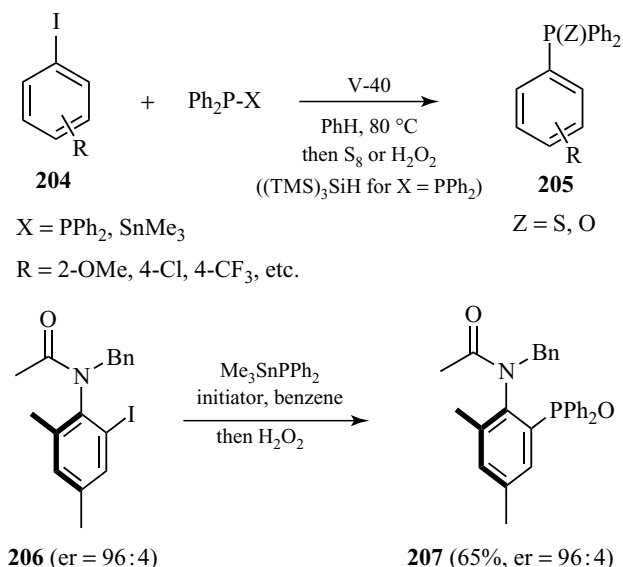
3.3 Phosphonation and Borylation Reactions

Radical phosphonation of arenes and heteroarenes can be achieved by addition of P-centered radicals to arenes under oxidative conditions. For example, activated furans, pyrroles, and thiazoles react with dialkylphosphates in the presence

are generated from aryl iodides **204**, affording after oxidation the corresponding aryldiphenylphosphane oxides or sulfides **205** depending on the oxidant used (Scheme 26).³³¹ Very recently, P_4 (white phosphorous) was shown to efficiently react with aryl radicals to form the corresponding triarylphosphines.³³²



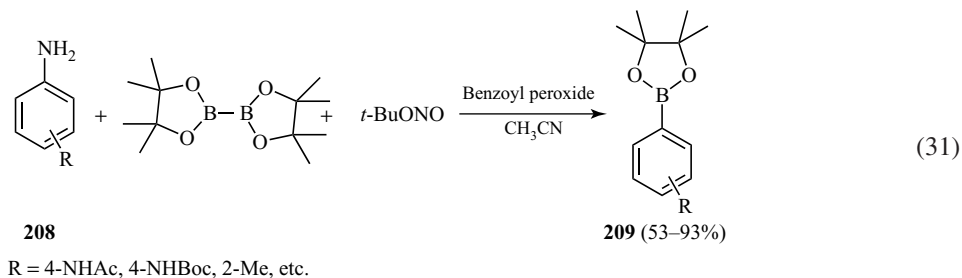
Scheme 25 Radical phosphonation with dialkyl phosphites under oxidative conditions.



Scheme 26 Aryl radical phosphonylation with phosphines.

Readily available trimethylstannyldiphenylphosphane (X = SnMe₃) was also used as a highly efficient radical acceptor for the formation of triarylphosphanes. Various aryl iodides **204** were reacted with Me₃SnPPh₂ to give, after oxidation, aryl diphenylphosphane oxides **205** in good yields.³³³ Addition of an aryl radical to Me₃SnPPh₂

formed from the intermediately generated diazonium salt reacts with B₂pin₂ in a formal homolytic substitution at boron (see **Boron in Radical Chemistry**) to afford boronate **209** in good yield (31).³³⁵ Notably, no metal catalysts were required to conduct these reactions.



was reported to occur at near-diffusion-controlled rate. This was nicely documented by stereospecific trapping of axially chiral aryl radicals, as documented for the transformation of aryl iodide **206** to phosphine oxide **207**.³³⁴

Recently, it was shown that *in situ* generated aryl diazonium salts (from anilines **208**) react with bispinacol borane (B₂pin₂) under radical conditions to afford pinacol boronates as valuable synthetic intermediates. It was suggested that the aryl radical

4 CONCLUSIONS

Important initial work on radical arylation appeared decades ago. These pioneering studies have paved the way to modern radical arylation chemistry. In particular, the better knowledge on kinetic data has allowed planning complex cascade processes comprising radical arylation reactions. Radical arylations are meanwhile also used in complex

natural product synthesis as nicely documented by the selected examples in this article. Despite these recent efforts, a great deal of qualitative and quantitative work remains to be done, especially in the area of stereoselective radical arylations. To conclude, we consider radical chemistry as a highly useful, promising, and important method that nicely complements ionic- and transition-metal-mediated arylation reactions. Many groups are currently engaged in this field and therefore interesting new developments can be expected in the future.

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Electrochemically Initiated Radical Reactions

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1 INTRODUCTION

Electrochemical transformations can, in principle, be considered. “Green Chemistry” because oxidation and reduction reactions are initiated by electron transfer from the substrate to the electrode or vice versa.¹ Therefore, the redox process is not associated with an additional reagent that has to be added in stoichiometric amounts and, consequently, the spent redox reagent does not have to be removed. These reagents are often toxic transition-metal complexes, the avoidance of which is most favorable from an environmental standpoint. In addition, electrochemical reactions can be controlled by the current passed through the solution through the current density at the electrode surface (galvanostatic conditions), or the applied redox potential which can be controlled in a three-electrode setup utilizing a reference electrode as internal standard. Another factor that controls the reaction is whether the electrochemical reaction is performed in an undivided cell or the anode and cathode compartments are separated by a diaphragm. In general, the less complex the electrochemical setup, the easier it is for nonelectrochemists to reproduce such transformations. In the simplest setup, two electrodes are immersed in the solution in a beaker-type cell and power is supplied by a commercial battery. The choice of the electrode materials, solvents, and supporting electrolyte also play an important role, and specific choices might be needed for optimal

results. Finally, the redox process can be performed directly at the electrode surface or, in cases where the electron transfer is hindered in whatever fashion, indirect electrolysis strategies utilizing a redox catalyst (mediator) can be applied. For detailed introduction to the theory, instrumentation, and various direct and indirect electrochemical applications, the reader is directed to the several reviews and comprehensive textbooks that are available.^{2–14}

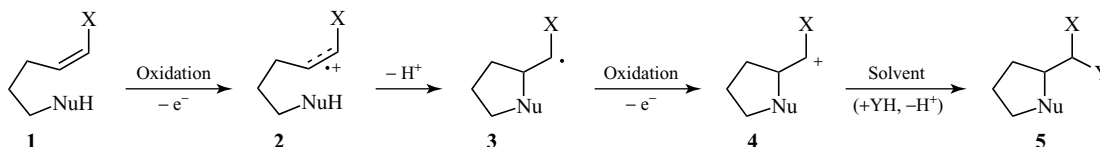
Nevertheless, electrochemical conversions have an enormous advantage in that the redox potential can be adjusted to the needs of the individual starting material so that even small differences in the redox potential of the functional groups can be differentiated. Accordingly, electron-rich materials can be converted into radical cations upon abstraction of an electron at the anode, while electron-deficient starting materials can be reduced at the cathode to the corresponding radical anions. Once these radical cation/anion intermediates are formed near the electrode surface, in the so-called Helmholtz layer, either a follow-up reaction will occur or in some cases the intermediates undergo further redox processes to generate the corresponding cations or anions, respectively. In this article, we focus on the chemistry associated with radical cations or radical anions, as well as neutral radical species. Of particular interest are those electrochemical transformations published in the time frame from circa 1997 until 2010 that have generated new carbon–carbon bonds or led to the introduction of functional groups.

2 ANODIC PROCESSES

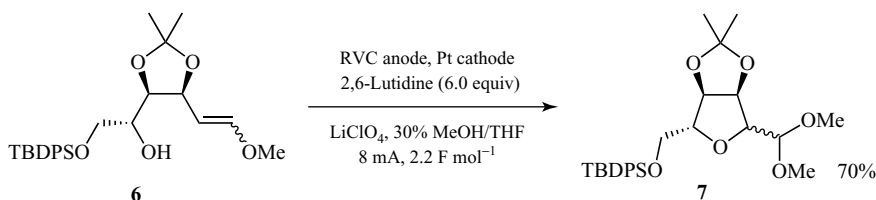
2.1 Intramolecular Anodic Coupling of Electron-Rich Double Bonds to Nucleophiles

Anodic electrochemical transformations have proven to be an effective method for the oxidation of electron-rich functional groups such as enol ethers **1**. Thereby, the reactivity of the enol ether **1** is altered and reactions are initiated under umpolung of the initial reactivity. The oxidation of the enol ether **1** by one-electron oxidation generates a radical cation intermediate such as **2**, which can be trapped with a nucleophile in an intermolecular fashion to form carbon–heteroatom bonds or carbon–carbon bonds (Scheme 1). This transformation affords cyclic intermediates after the bond formation process such as **3**, and a subsequent second oxidation step occurs to generate cationic intermediates such as **4** which are quenched by the solvent (YH) to obtain the final product **5**.

Such anodic processes have been initiated by the oxidation of enol ethers, N,O- or S,S-ketene acetals, and electron-rich aromatic rings. Simple olefins, enol ethers, allyl- and vinylsilanes, electron-rich aryl rings, alcohols, amides, and sulfonamides have been explored as internal nucleophiles for the formation of carbon–heteroatom and carbon–carbon bonds.^{15,16}



Scheme 1 Intramolecular cyclization by electrochemical umpolung of the starting material.



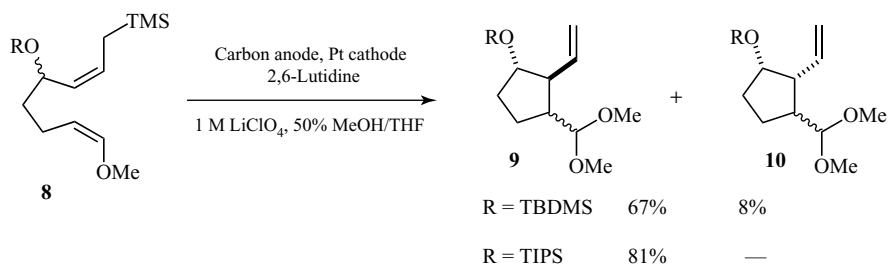
Scheme 2 Tetrahydrofuran synthesis by electrochemical oxidation of an alcohol bearing enol ether.

2.2 Oxidation of Enol Ethers

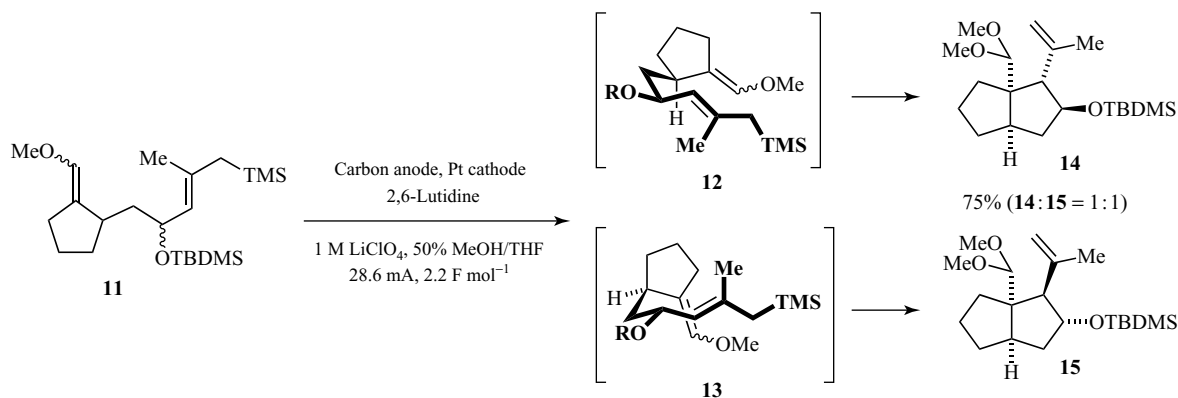
Recent applications of the electrochemical oxidation of enol ethers under current-controlled conditions to the corresponding radical cation intermediates have been reported by Moeller and coworkers. This versatile method was used for the synthesis of various carbocyclic systems either as studies in methodology or for the diversity-oriented synthesis of new carbon–carbon bonds. Various applications of electrochemical oxidation reactions utilizing enol ethers, as an example of an oxidizable electron-rich functionality, have been described as key steps in the synthesis of natural products. Out of the many applications, a selected example of electrochemical activation of an enol ethers is shown in Scheme 2.¹⁷ The electrochemical oxidation is performed on a reticulated vitreous carbon (RVC) electrode at relatively low current (8 mA), and a total amount of 2.2 F mol⁻¹ of electricity is passed through the solution.

The synthesis of C-glycosides was accomplished from enol ethers such as **6** in a current-controlled electrolysis to afford **7** in good yields as a mixture of diastereomers (Scheme 2). Nevertheless, the stereochemistry of the substrate and the choice of the protecting groups (PGs) applied play important roles, which have not been solved for all combinations.

The electrochemical oxidation of enol ethers was also applied in cases where an allyl silane was utilized to react as the electrophilic component.¹⁶ It became obvious that the choice of silyl PGs



Scheme 3 Cyclopentane synthesis by electrochemical oxidation of an allylsilane-bearing enol ether.



Scheme 4 Diastereoselectivity of the radical cation cyclization of polysubstituted starting materials.

on oxygen functionalities in **8** that do not directly react in the electrochemical conversion is crucial for the control of the products formed. In the case illustrated in Scheme 3, the diastereoselectivity is best controlled by a triisopropylsilyl (TIPS) PG to form **9** exclusively, while the *t*-butyldimethylsiloxy (TBDMS) PG led to the formation of the additional diastereomer **10**.

For the synthesis of bicyclic products such as **14** and **15**, the use of the racemic **11** led to the formation of only two of the possible four diastereomers. This stereocontrol is explained by reactive conformers **12** and **13**, which exhibit the lowest barrier for the desired cyclization via their corresponding radical cations (Scheme 4).¹⁸

Accordingly, the OTBDMS as well as the biologically important isopropenyl group were introduced with good diastereocontrol, as only the two trans isomers **14** and **15** could be detected.

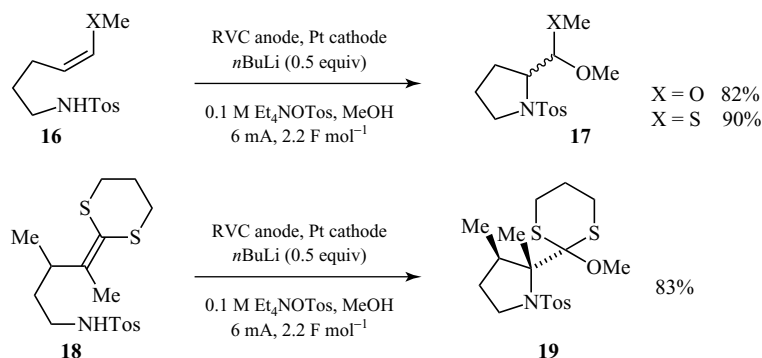
The Moeller group also reported the use of nitrogen-based functional groups as trapping agents for the intramolecular cyclization of appropriate alkenyl amines such as **16** and **18** (Scheme 5).

When the enol ether moieties in **16** or **18** were oxidized at low current densities, the cyclization led predominantly to the five-membered proline-type products such as **17** and **19**. Also, excellent results were obtained when thioenol ethers (X = S) were applied in this reaction under basic conditions.¹⁹

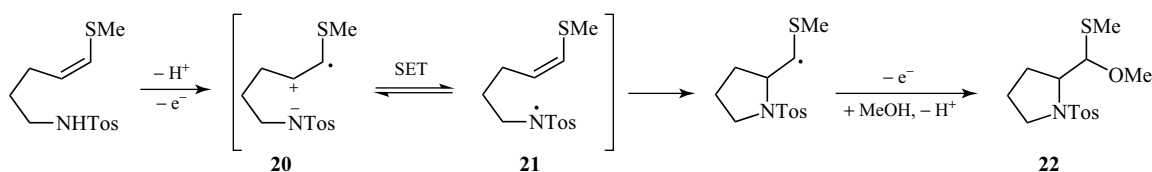
The deprotonation of the sulfonamides **16** and **18** proved to be of advantage for the cyclization process, reducing the tendency to eliminate methanol from the primary cyclization product but also enabling the equilibrium between **20** and **21** by single-electron transfer (SET) (Scheme 6), from which the 5-*endo*-trig-cyclization toward the product rationalizes the formation of the five-membered products **22**.

2.3 Oxidation of Ketene Dithio- and N,O-Acetals

The anodic oxidation of ketene dithioacetals was investigated by Moeller for the synthesis of new carbon–carbon bonds when two electron-rich olefins



Scheme 5 Pyrrolidine formation by electrochemical oxidation of an amine-bearing electron-rich olefins.



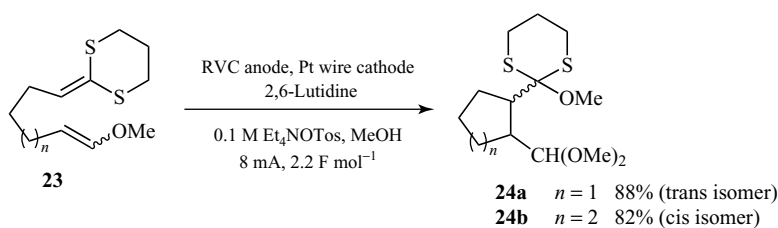
Scheme 6 Mechanism of the radical-cation-initiated cyclization of amine-bearing thioenol ether.

are reacted with each other. The redox potential is expected to be an important issue in these reactions. Electrochemical methods are well suited to discriminate between two functional groups that differ only marginally in their electronic nature. The potential is either controlled by applying an additional reference electrode (potentiostatic electrolysis), or the current density in galvanostatic electrolysis is set to a low value. In the latter case, the low current density at the working electrode will select the starting material (or the functional group), which has the lowest redox potential as long as the diffusion of the starting material is not the limiting factor.

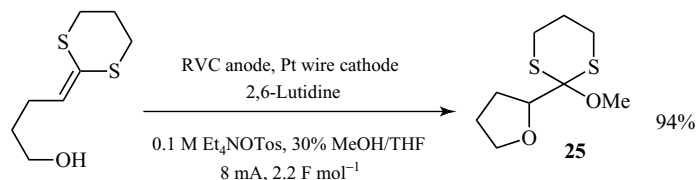
For this purpose, the two ketene dithioacetals **23** and **24** were synthesized and electrolyzed on an RVC anode at a constant current of

8.0 mA until 2.2 F mol^{-1} passed through the solution (Scheme 7).²⁰ The two reactions gave excellent results in terms of chemical yields, and the five- and six-membered rings were formed in the absence of the all-too-often-needed Thorpe–Ingold effect. It is interesting to note that the two reactions gave different types of diastereomers upon cyclization.

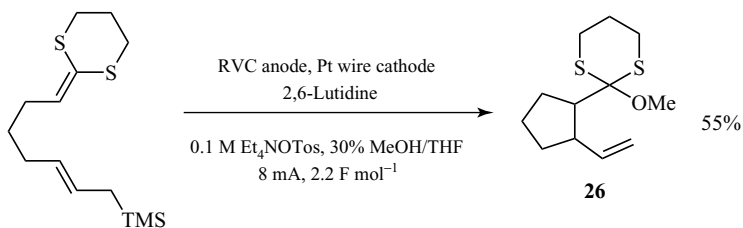
While the five-membered ring product **24a** gave the trans isomer, the cyclization to the cyclohexane derivative **24b** produced the cis isomer exclusively. This finding is in strong contrast to earlier reports concerning coupling reactions of two enol–ether-type double bonds.²¹ In these cases, the corresponding cyclization products were formed in a nearly 1:1 ratio of the cis/trans isomers. Moeller also reported the trapping of the radical cation generated from the oxidation of the



Scheme 7 Cyclization of a ketene dithio-acetal-bearing enol ether.



Scheme 8 Tetrahydrofuran synthesis of an alcohol-bearing ketene dithio-acetal.

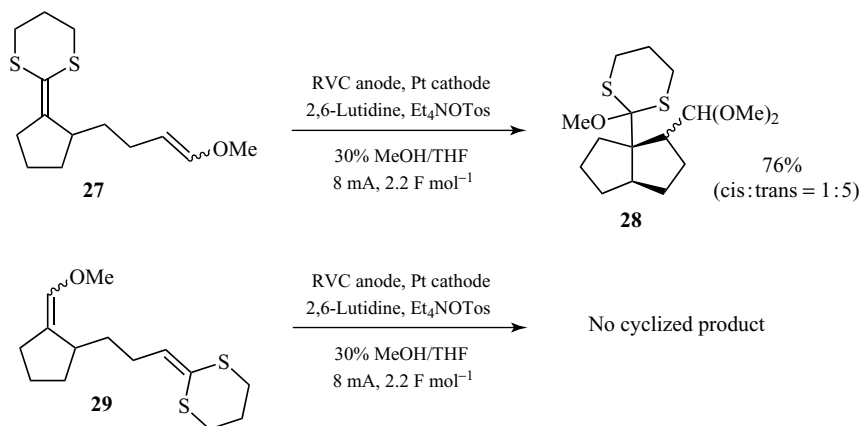


Scheme 9 Cyclopentane synthesis of an allylsilane-bearing ketene dithio-acetal.

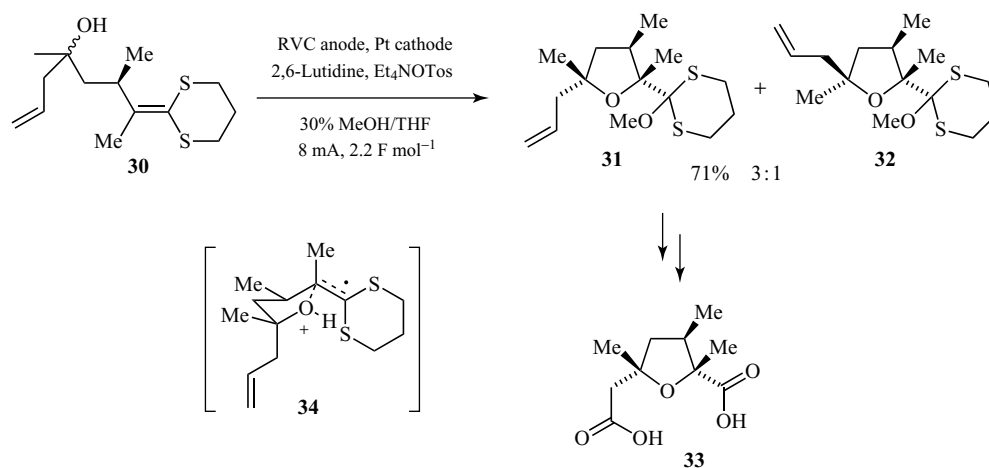
ketene dithioacetal subunit by oxygen nucleophiles. In these cases, tetrahydrofuran (THF) as well as tetrahydropyran derivatives²² were obtained in excellent yields and additional substituents were well accepted for the formation of the THF derivative **25** in excellent yields as a single product (Scheme 8).²⁰

In this context, the direct formation of lactones was realized when amides were utilized as nucleophilic groups in similar cyclization reactions.²³ In addition, an intramolecular cyclization utilizing an allyl silane functionality could be performed for the formation of a new carbon–carbon bond as well, and product **26** was generated in acceptable 55% yield as a mixture of diastereomers (Scheme 9).²⁰

In a very interesting cross-experiment, Moeller described the cyclization of the two ketene dithioacetals **27** and **29** (Scheme 10).²⁴ Ketene dithioacetal **27** gave the desired bicyclic product **28** with a good yield of 76% and an acceptable diastereoselectivity trans:cis = 5 : 1. The radical-type cyclization is not hindered by the steric bulkiness on the carbon bearing the radical functionality. On the other hand, the corresponding regioisomeric starting material **29** did not result in an oxidative cyclization. In this case, the steric hindrance of the internal carbon of the olefin being attacked by the radical has a strong effect on cyclization.



Scheme 10 Cross experiments for cyclization reactions of ketene dithio-acetal-bearing enol ethers.



Scheme 11 Diastereoselective formation of tetrahydrofurans for the synthesis of (+)-nemorensic acid.

Moeller also noted that these cyclization reactions were dependent on the nature of the trapping group. An alkene will react as a “radical-like” nucleophile with the radical cation. When alcohol nucleophiles are used, the observed behavior is different. In these cases, the radical cation intermediates originating either from the oxidation of a ketene dithioacetal or from the oxidation of an alkyl enol ether exhibit “cation-like” reactivity.

This observation eventually led to the design of a ketene dithioacetal starting material which was used for the synthesis of (+)-nemorensic acid (**33**). In this case, the starting material **30** was converted under oxidative conditions in an undivided cell at a constant current of 8.0 mA using 2.0 F mol⁻¹ (Scheme 11).²⁵

In the key step of the synthesis, the alcohol group trapped the radical cation intermediate **34**, while the allyl group in **30** did not react but remained available as a masked carboxylic acid functionality. The two diastereomers utilized for the electrochemical reaction were transformed with excellent stereocontrol via the transition state **34** to the desired products **31**, while **32** was formed from an analogous epimeric transition state. Finally, the natural product **33** was obtained from **31** in three more steps realizing the synthesis of (+)-nemorensic acid in only 11 steps, with the electrochemical conversion as key transformation.

Another interesting application concerning ketene N,O-acetals was the anodic oxidation reaction observed when an intramolecular allyl

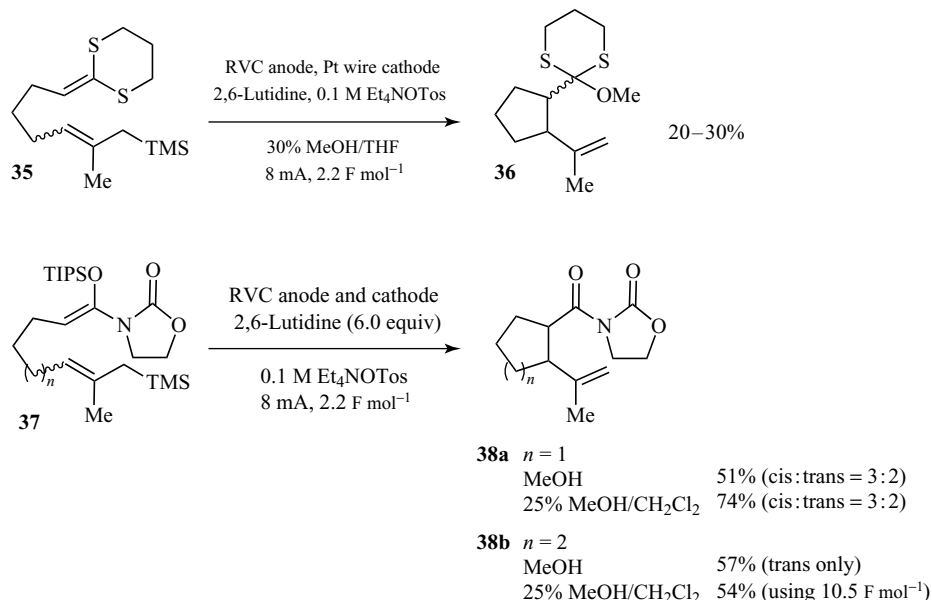
trimethylsilane subunit was utilized as the radical acceptor.²⁶ A comparison of different cyclization precursors led to the conclusion that the presence of a single additional methyl substituent such as in the starting material **35** decreased the yield dramatically compared to the pure allylic system so that only 20–30% of **36** could be obtained (Scheme 12). When ketene N,O-acetals such as **37** were applied, good yields of up to 74% for the similar cyclization product **38a** were obtained as a nearly 1 : 1 mixture of diastereomers. The corresponding product **38b** was generated exclusively as the trans isomer in a lower yield of 57%.

Although the diastereoselectivity of this process is only moderate at best for products of type **38a**, the possibility for further optimization using (chiral) modification of the oxazolidinone substituents seems possible, opening the way to controlling the absolute stereochemistry of cyclization products of this type.

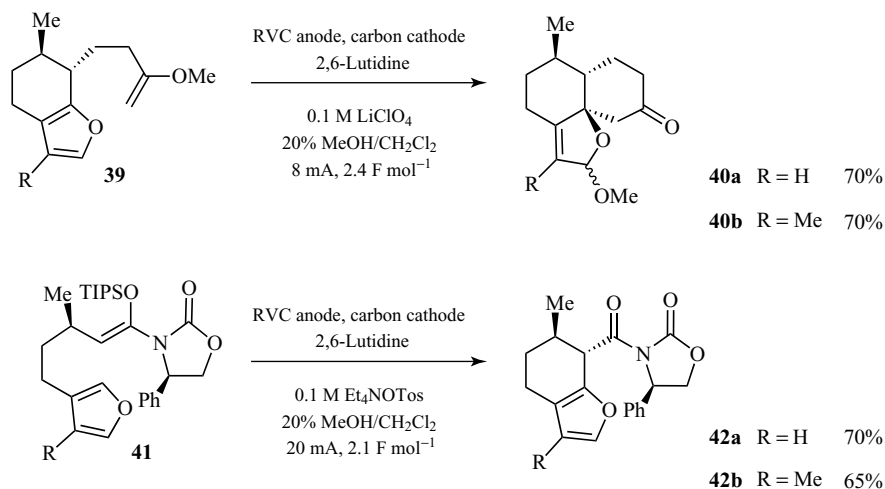
2.4 Oxidation of Electron-Rich Aromatic Rings

The electrochemical oxidation of electron-rich aromatic subunits can be used for the intramolecular cyclization of the intermediate radical cations. In particular, furan derivatives were utilized by Moeller and Wright for the synthesis of bicyclic and tricyclic derivatives.

In studies on the usefulness of this method, furan derivatives were investigated that were



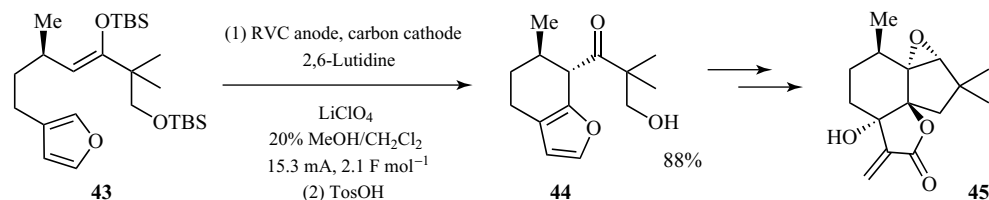
Scheme 12 Comparison between cyclizations of ketene dithio-acetal or ketene N,O-acetals in electrochemically initiated cyclizations.



Scheme 13 Electrochemically initiated cyclization of enol ether-bearing furan derivatives.

functionalized with enol ethers such as **39** as well as ketene N,O-acetals such as **41** to optimize the cyclization process (Scheme 13).^{27,28} Both enol ether functional groups are well suited to act as the radical acceptor, and the radical cation generated by the electrochemical oxidation of the furan subunit initiates the cyclization. The tricyclic derivatives **40a** and **40b**, as well as the bicyclic product **42**, are generated in good yields as single isomers.

The synthesis of the tricyclic product **40** generated by the anodic oxidation of **39** at low current densities is a promising example of a transformation toward the synthesis of complex molecules. These selected examples illustrate that the electrochemical oxidation of electron-rich aromatic rings under controlled conditions utilizing low current densities (<20 mA) is a well-suited method to initiate such reactions.



Scheme 14 Electrochemically initiated cyclization of enol ether-bearing furan derivatives for the synthesis of (–)-alliacol A.

The application of the anodic oxidation of enol ethers as the key step in natural products synthesis was exemplified in the synthesis of linalool²⁹ and (–)-alliacol A (**45**).^{30,31} For the synthesis of (–)-alliacol A, the electrochemical oxidation of the intermediate **43** (Scheme 14) was used for the formation of the six-membered ring in **44** found in the natural products. The product **44** was isolated in an excellent yield of 88% over two steps and, after a number of further steps, (–)-alliacol A **45** was obtained.

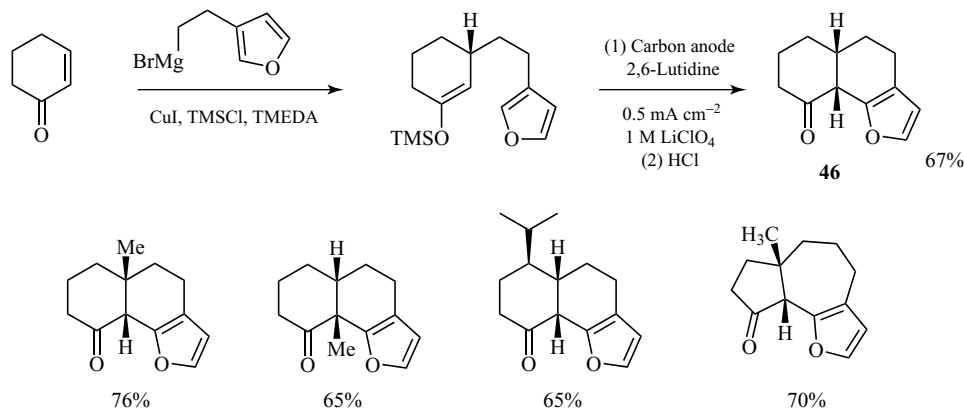
This application also illustrates that electrochemical methods are well suited for activating functional groups based only on their lowest oxidation potential once current-controlled methodologies are applied. Other functional groups are not affected, as the higher redox potentials required are not reached. Once the chemoselective activation of the furan has been realized, the intramolecular cyclization is the major reaction pathway to form the desired products.

The Wright group also applied furan derivatives for the synthesis of tricyclic products utilizing silyl enol ethers as radical acceptor functionalities.

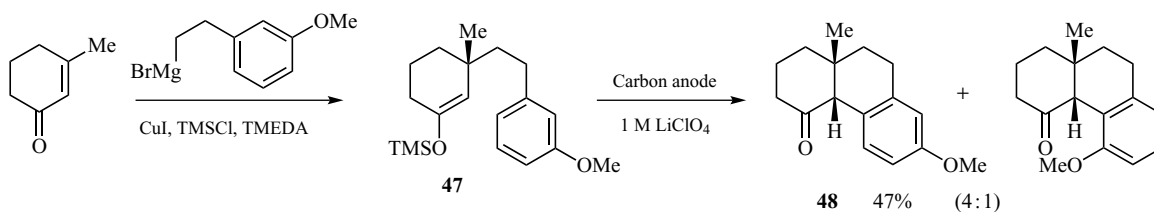
The two-step process consists of a copper-initiated 1,4-addition of a suitable Grignard reagent onto an α,β -unsaturated ketone (Scheme 15), followed by electrochemical cyclization and acidic workup to generate tricyclic products such as **46**.³² For this sequence, good yields of the desired products were also obtained when quarternary centers were formed and the ring size was altered depending on the α,β -unsaturated ketone or the Grignard reagent utilized, as shown in the additional examples.

Mechanistic studies revealed that the electrochemical transformation leads to the formation of the radical cation intermediate from the silyl enol ether functionality based on the lower redox potential of this group ($E_{1/2} = \sim 0.85$ V) compared to the furan ring system ($E_{1/2} = \sim 1.31$ V).

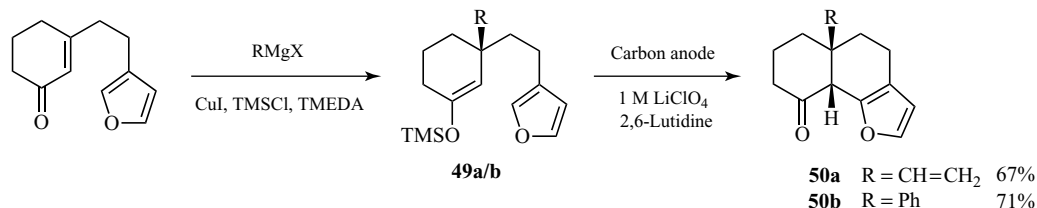
Interestingly, Wright also extended the application of the electrochemical generation of radical cations with the use of anisole-type starting materials. In a key investigation, **47** was generated as before by a copper-catalyzed 1,4-addition and then converted to product **48** by electrochemical oxidation in methanol (Scheme 16).³³



Scheme 15 Electrochemically initiated cyclization of enol ether-bearing furan derivatives for the synthesis of tricyclic products.



Scheme 16 Electrochemically initiated cyclization of enol ether-bearing anisole derivatives for the synthesis of tricyclic products.



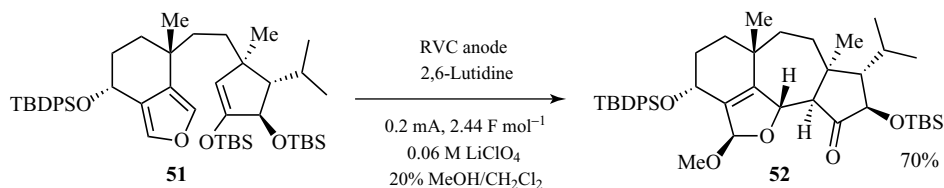
Scheme 17 Cyclization of enol ether-bearing furan derivatives for the synthesis of tricyclic products containing functionalized quaternary centers.

Also, more complex quaternary-carbon-bearing derivatives such as **50a/b** were obtained when the copper-catalyzed 1,4-addition was performed with furan derivatives such as **49a/b** (Scheme 17). The electrochemical generation of the radical cation led to the desired product of type **50** in good yield.

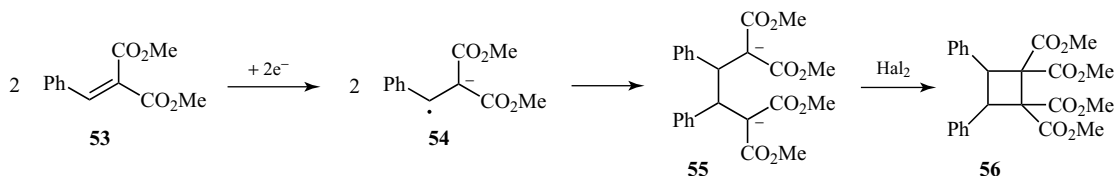
An application of this method on a somewhat more sophisticated level of molecular complexity was reported by Trauner for the assembly of the carbocyclic skeleton of the guanacastepenes.³⁴ The polyfunctionalized starting material **51** was utilized for the electrochemical key step of the reaction sequence to afford the desired intramolecular carbon–carbon bond formation (Scheme 18). The product **52** was isolated in 70% yield via a diastereoselective cyclization and an approach toward the natural product class of tetracyclic guanacastepene derivatives could be realized.

2.5 Synthesis of Four-Membered Rings

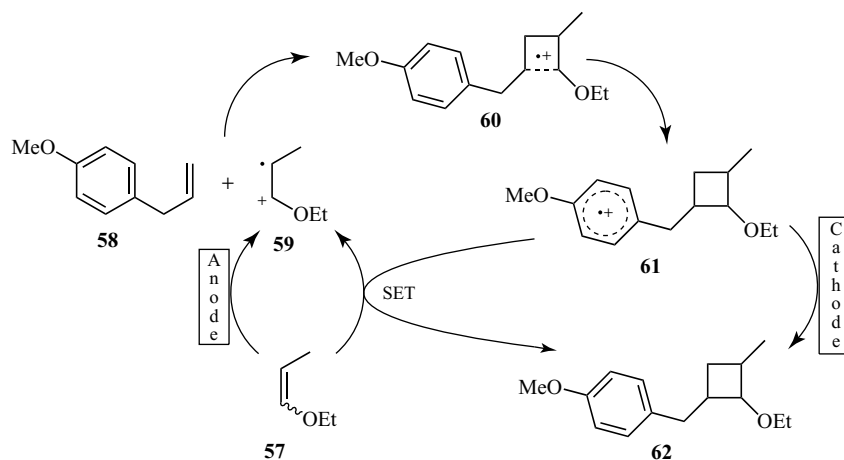
The electrochemically initiated formation of four-membered ring systems starting from alkylidenmalonates can be realized in an undivided cell in terms of a paired electrolysis where processes at both electrodes are used for the generation of the product.³⁵ In these reactions, the cathodic reduction of the alkylidenmalonate **53** generates the radical anion intermediates **54**, which undergo radical dimerization to form the dianion intermediate **55** (Scheme 19). From here, several reaction pathways are accessible, resulting in a mixture of the products formed. Nevertheless, when the electrolysis is performed in an undivided cell with sodium bromide or sodium iodide as the supporting electrolyte, anodic oxidation of the halide generates the corresponding Hal_2 , which reacts with the dianion leading to the formation of the cyclobutane derivatives of type **56**.



Scheme 18 Electrochemical transformation as key step in the synthesis of the guanacastepenes skeleton.



Scheme 19 Cyclobutane synthesis via a paired electrolysis of Knoevenagel adducts.



Scheme 20 Mechanism of the electrocatalytic intermolecular cyclobutane formation.

On the other hand, the formation of four-membered ring systems by electrochemical oxidation of electron-rich enol ethers was realized by Chiba in an intermolecular cross-cyclization using two different starting materials.³⁶ The enol ether **57** is electrochemically oxidized on the basis of the less positive redox potential compared to the allyl benzene derivative **58** (Scheme 20). The umpolung of the reactivity of the enol ether radical cation **59** allows the reaction with the allyl benzene derivative to proceed in a regioselective fashion leading to intermediate **60**. This intermediate reacts as an oxidizing agent on the aromatic substituent to form the more stable radical cation **61** for the formation of the four-membered ring system. The back-electron transfer leading to the final product **62** takes place either on the cathode in an undivided cell or in homogeneous solution utilizing the enol ether starting material **57** as electron donor. Thereby, an electrocatalytic process can be realized in which the process is not stoichiometric in the current passed through the solution so that only a catalytic amount of electricity is sufficient to achieve complete

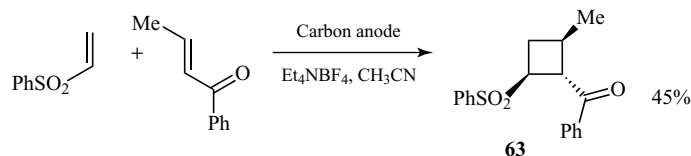
conversion of the starting materials under ideal circumstances.

Similar processes have been utilized in the past for the formation of four-membered ring systems with phenyl vinyl sulfones as starting materials in terms of a homo-cyclization.^{37,38} Recently, Felton described the cross-cyclization of phenyl vinyl sulfone in the presence of α,β -unsaturated ketones for the regio- and diastereoselective formation of cyclobutane derivatives such as **63** in moderate yields of up to 45% along with a number of side products (Scheme 21).³⁹

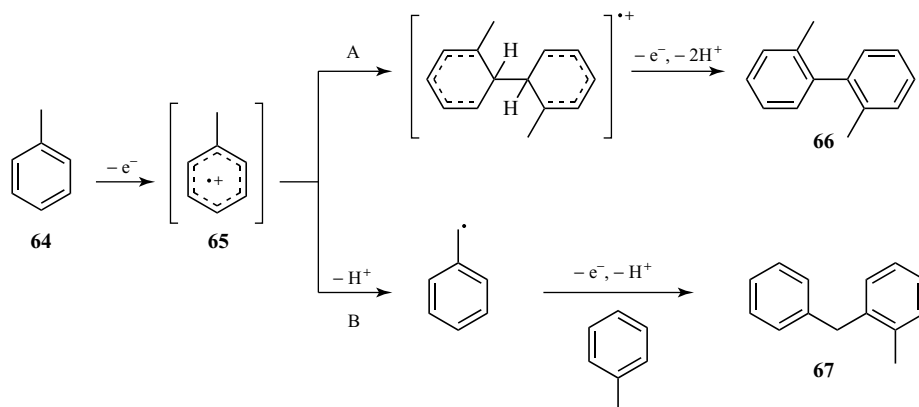
Nevertheless, in combination with a suitable second starting material, similar inter- and intramolecular cyclization reactions initiated by electrochemical oxidation of double bonds seem to be worth investigating in the future.

2.6 Synthesis of Biarylcompounds

Anodically generated radical cations of alkyl-substituted arenes such as **64** can follow two different reaction pathways.⁴⁰ Biaryl **66** is formed



Scheme 21 Intermolecular formation of a polyfunctionalized cyclobutane derivative.



Scheme 22 Reaction pathways of the anodically generated radical cation derived from alkylbenzenes.

when the radical cation **65** reacts with the starting compound (Scheme 22, path **A**), whereas deprotonation leads to a benzyl radical which undergoes an electrophilic aromatic substitution after being reoxidized to the cation generating a diphenylmethane compound **67** (path **B**). A major factor influencing this selectivity is the choice of solvent since, in nucleophilic solvents, the biaryl is generated as the main product, whereas the electrolysis in nonnucleophilic and therefore less basic solvents leads to the side-chain reaction forming diphenylmethanes of type **67**. The latter conversion is synthetically more valuable and therefore applied in industrial processes. Additional by-products, quinone-derivatives for example, can occur depending on the reaction medium. Therefore, the anodic coupling of alkyl-substituted benzenes is not the effective method for the synthesis of biaryl compounds compared to the well-established transition-metal-mediated coupling reactions.

Works of Nyberg^{41–43} in the early 1970s showed that the homo-coupling products of alkyl-substituted benzenes such as **68** and **69** can be obtained in moderate to good yields using carbon or platinum electrodes and a tetrafluoroborate as the supporting

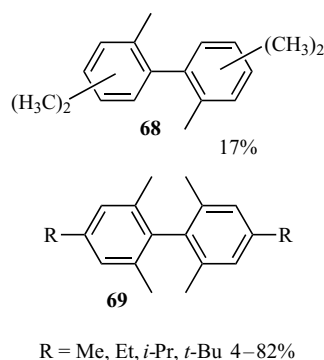
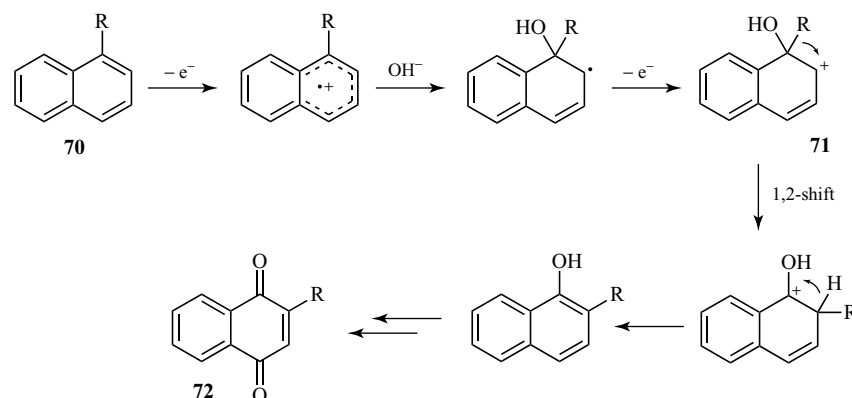


Figure 1 Biaryls formed via anodic oxidation according to the procedure of Nyberg.

electrolyte (Figure 1). The solvents utilized for these conversions are acetonitrile or nitromethane.

The electrolysis of naphthalene and alkylnaphthalenes such as **70** in acetone–water leads to binaphthyls under similar conditions when the substrates are not substituted in 1-position; otherwise, the respective naphthoquinone **72** is formed via further oxidation of the radical intermediate to the cation **71** and a 1,2-shift of the alkyl-substituent in 1-position (Scheme 23).^{44,45}



Scheme 23 Formation of naphthoquinones after electrolysis of 1-alkyl-substituted naphthalenes.

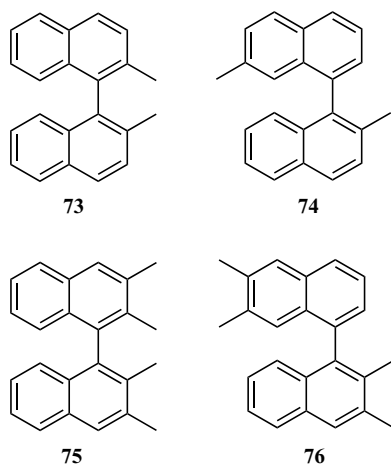


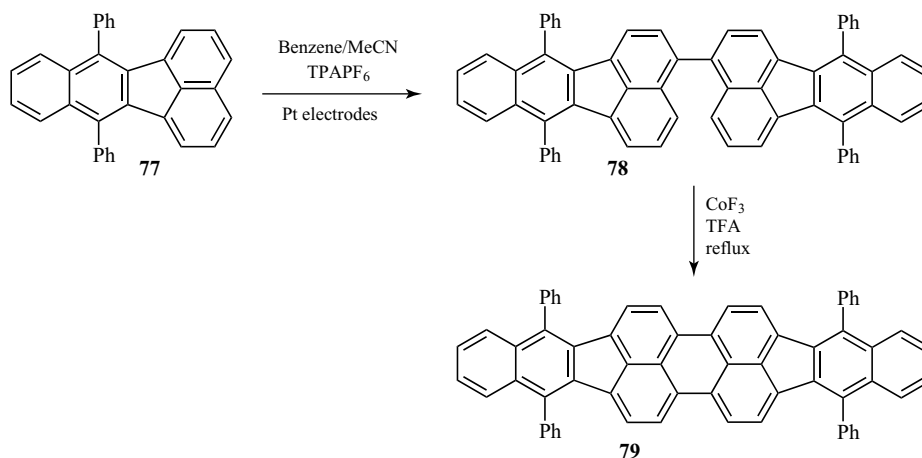
Figure 2 Structures determined by NMR of the isolated binaphthyls (no yield given).

The conversion of 2-methylnaphthalene leads to four regioisomers of the binaphthyl, which were isolated in a 20:10:1.5:1 ratio as detected by gas chromatography-mass spectrometry (GC-MS). The structures of the two major isomers **73/74** and **75/76** obtained from the conversions of 2-methylnaphthalene and 2,3-dimethylnaphthalene were resolved using nuclear magnetic resonance (NMR) techniques (Figure 2). Since a preparative separation of the other isomers was not possible, their probable structures were derived from molecular orbital calculations whereby the most reactive positions of the substrate were determined.

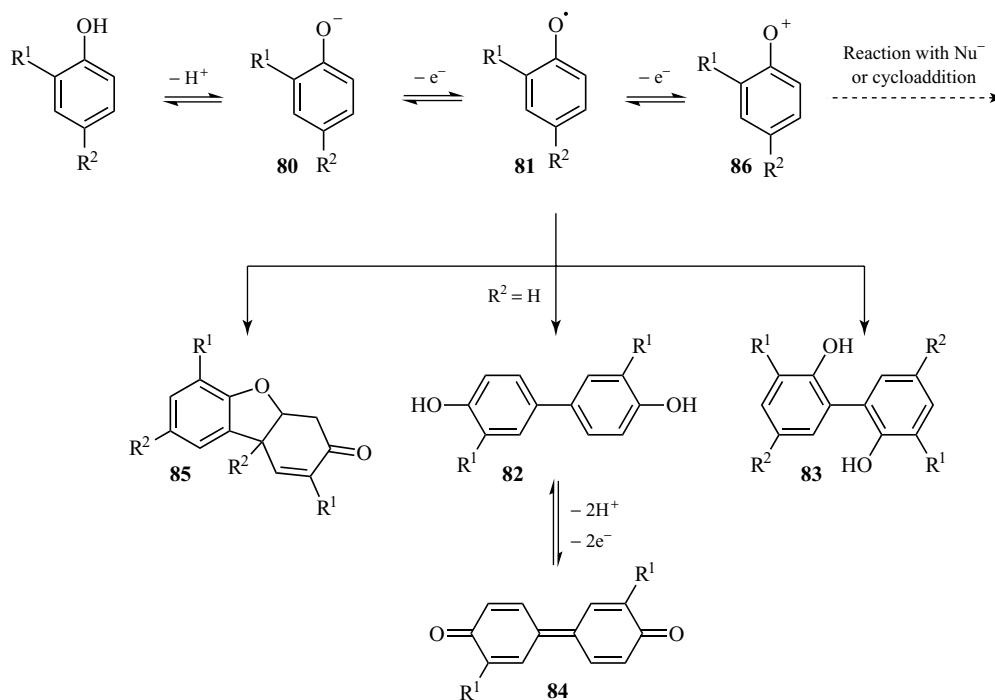
The bulk electrolysis of fluoranthene **77** toward the perylene derivative **78** was accomplished by

Bard⁴⁶ to investigate the electrochemical properties and chemoluminescence of the radical cation generated from **77**. The process affords the formation of two carbon-carbon bonds of which the first one is intermolecular and the second one intramolecular. It was observed by means of cyclovoltammetry that the intramolecular bond formation is reversible and occurs very slowly; therefore, the direct synthesis of the perylene **79** was not performed electrochemically in preparative scales. The biaryl compound **78** was obtained in 24% yield and the second bond formation is afforded by a chemical oxidation agent (Scheme 24).

Phenol and its derivatives represent appropriate substrates for electrochemical conversions because of the electron-donating and therefore radical-stabilizing nature of the hydroxyl substituent. The anodic coupling is mostly carried out under basic conditions to obtain phenolate **80** as an intermediate, which is then oxidized to the phenoxy radical **81** (Scheme 25).⁴⁰ Common bases for this purpose are alkali hydroxides, Et₄NOH, or 2,6-lutidine. The phenoxy radicals form dimers either by carbon-carbon or carbon-oxygen bond formation leading to a variety of isomers when the substrate is an unsubstituted phenol. The main isomer is normally the para-para product **82**; but when this position is blocked by a substituent, the coupling reaction takes place at the ortho position to form product **83** (Scheme 25).⁴⁰ Under convenient conditions, further oxidation to a diphenoketone species **84** takes place; therefore the desired biaryl compound **82** must be regenerated via a subsequent reduction step.



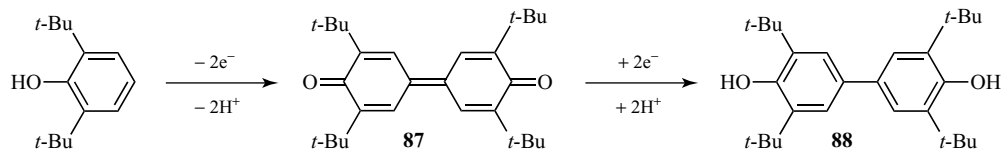
Scheme 24 Synthesis of a perylene derivative by electrolysis and chemical oxidation of fluoranthene.



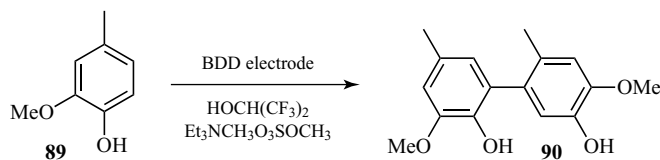
Scheme 25 Reaction pathways of the phenoxy radical.

The ortho–para coupling is followed by an intramolecular Michael addition, generating the Pummerer ketone **85**. When the radical recombination toward the coupling products is slow, the phenoxy radical is further oxidized to the cation **86**, which can react with a nucleophile or form cycloaddition products.

The selectivity between carbon–carbon and carbon–oxygen coupling of the phenoxy radical is determined by the steric and electronic properties of the substituents.⁵ Investigation of the oxidation of phenols by Nonhebel⁴⁷ suggests that the minimization of repulsion between the oxygen atoms of the combining radicals plays an important role



Scheme 26 Anodic oxidation of 2,6-di-*tert*-butylphenol.



Scheme 27 Anodic homo-coupling of 4-methylguaiaicol.

for the regioselectivity. When this minimization is not possible because of bulky substituents, the carbon–oxygen coupling represents the favored pathway.

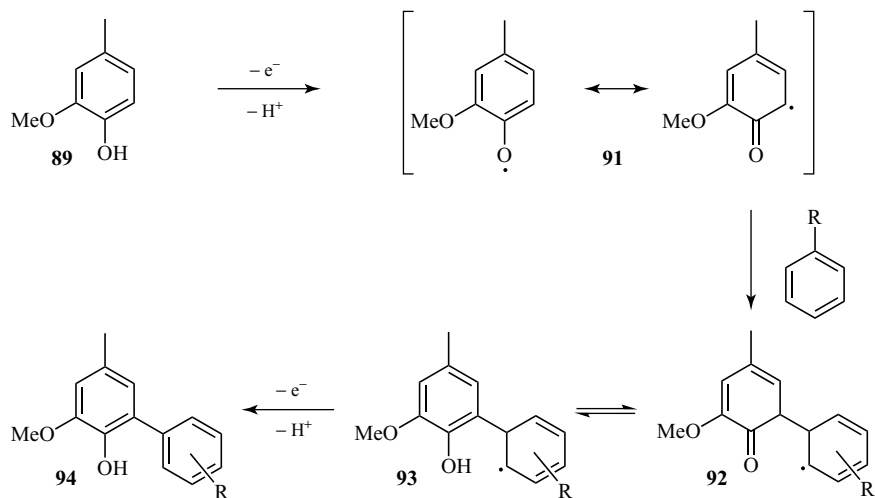
The homo-coupling of 2,6-di-*tert*-butylphenol with LiClO₄ as electrolyte in MeOH in an undivided cell (Scheme 26) was investigated by Schäfer⁴⁸ and Torii *et al.*⁴⁹ and led to diphenoquinone **87** as the major product.

For the synthesis of the desired biphenol **88** in excellent yields, the electrolysis was performed via subsequent reduction of the initially formed diphenoquinone **87** by changing the current direction in a divided cell. Another solution is a paired electrolysis consisting of the oxidation of the starting material

in the anode cell and the simultaneous reduction of the generated diphenoquinone in the cathode cell.

An unusual anodic coupling of a substituted phenol was found by Waldvogel: oxidation of 4-methylguaiaicol (**89**) employing boron-doped diamond (BDD) electrodes led to the ortho–meta coupled product **90** instead of the expected ortho coupling (Scheme 27).⁵⁰

The electrolysis was performed in hexafluoroisopropanol whose specific role has not yet been established, but in the absence of hexafluoroisopropanol the conversion does not proceed. However, the fluorinated alcohol is capable of stabilizing radicals because of its nonnucleophilic and protic nature. The reaction requires no additional base, and



Scheme 28 Mechanism of the anodic cross-coupling.

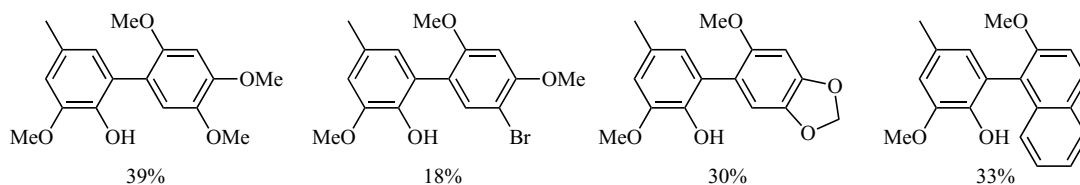
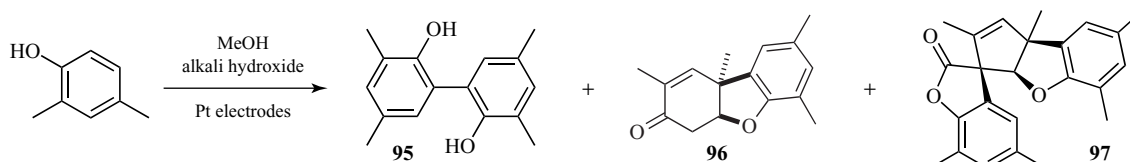


Figure 3 Hetero-coupling products of 4-methylguaiaicol and arylethers.



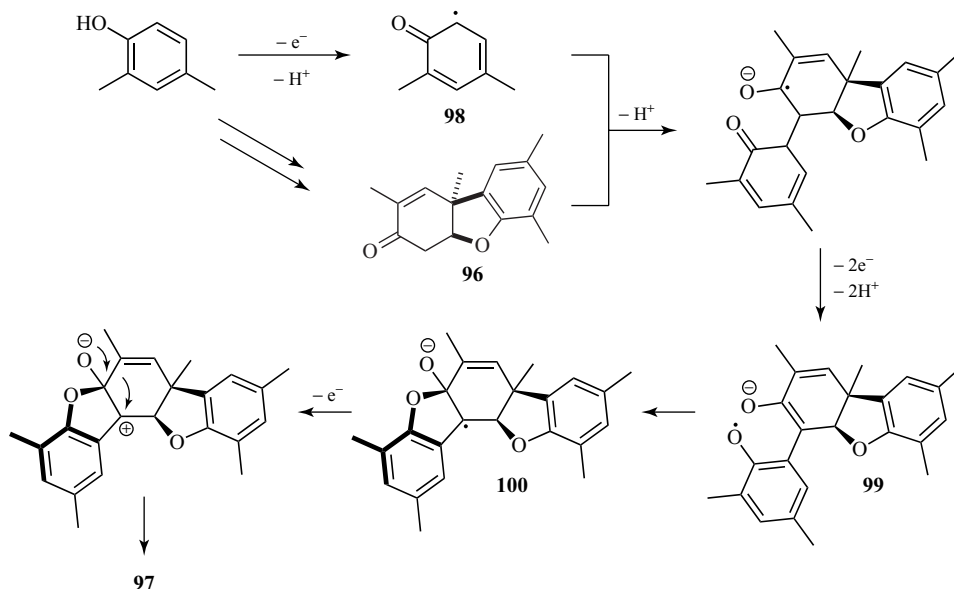
Scheme 29 Products of the anodic oxidation of 4,6-dimethylphenol.

generates no phenolate prior to the electron transfer at the anode. After this oxidation of **89**, the acidity of the phenol species is increased; thus deprotonation occurs immediately to the radical **91** (Scheme 28).

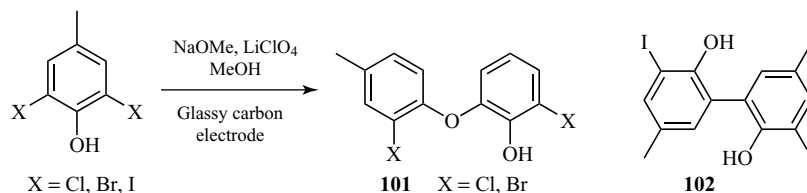
The following electrophilic attack takes place at the most electron-rich position of the coupling partner to form **92**. Tautomerization to **93** and a further oxidation step afford the desired product such as **94**. The reaction can also be performed as a cross-coupling of phenol **89** with several arylethers in moderate yields (Figure 3).

When 4,6-dimethylphenol was exposed to anodic oxidation by Waldvogel, the pentacyclic spirolactone **97** was generated as a single diastereomer alongside the biaryl coupling product **95** and the Pummerer ketone **96** (Scheme 29).⁵¹ The spirolactone **97** represents a trimer of the starting material formed via three dehydrodimerization steps.

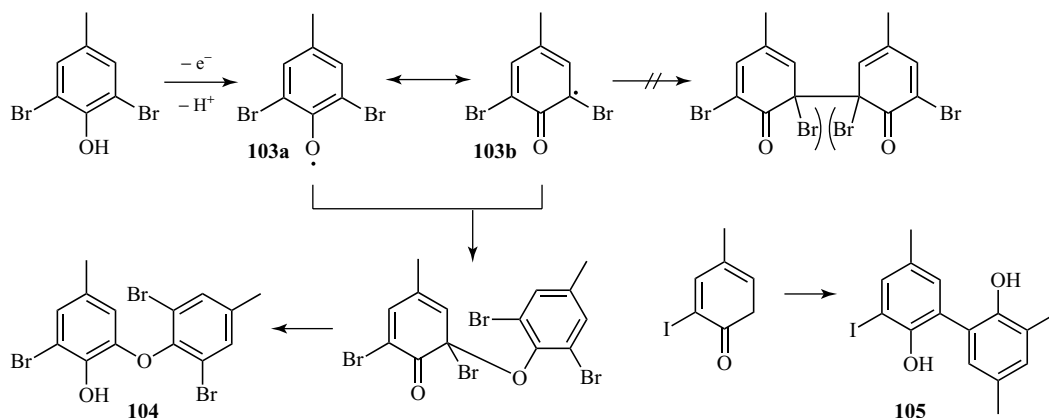
As the reaction is performed in basic media, the formation of **97** begins with an electrophilic attack of the phenoxy radical **98** on the enolate of the Pummerer ketone **96** (Scheme 30). Further oxidation



Scheme 30 Proposed mechanism of spirolactone formation.



Scheme 31 Electrolysis of 2,6-dihalogenated phenols.



Scheme 32 Mechanism of the anodic coupling of 2,6-dihalogenated phenols.

generates the radical anion **99**, which undergoes cyclization to intermediate **100**. Another SET is followed by a Meerwein rearrangement, leading to spirolactone **97**.

The anodic oxidation of ortho–ortho' dihalogenated phenols accomplished by Nishiyama⁵² generates the ortho-substituted diarylether (**101**) or the biaryl compound (**102**) depending on the halogen substituent (Scheme 31). While the biaryls are obtained from diiodophenols, the analog chlorine and bromine compounds provide the diarylethers, which represent the building blocks for the isodityrosine class natural products. In case of mono-halogenated phenols, the reaction leads to the same products, but the selectivity is independent of the type of halogen atoms. The steric demand of the adjacent substituents is the only factor of consequence.⁵³

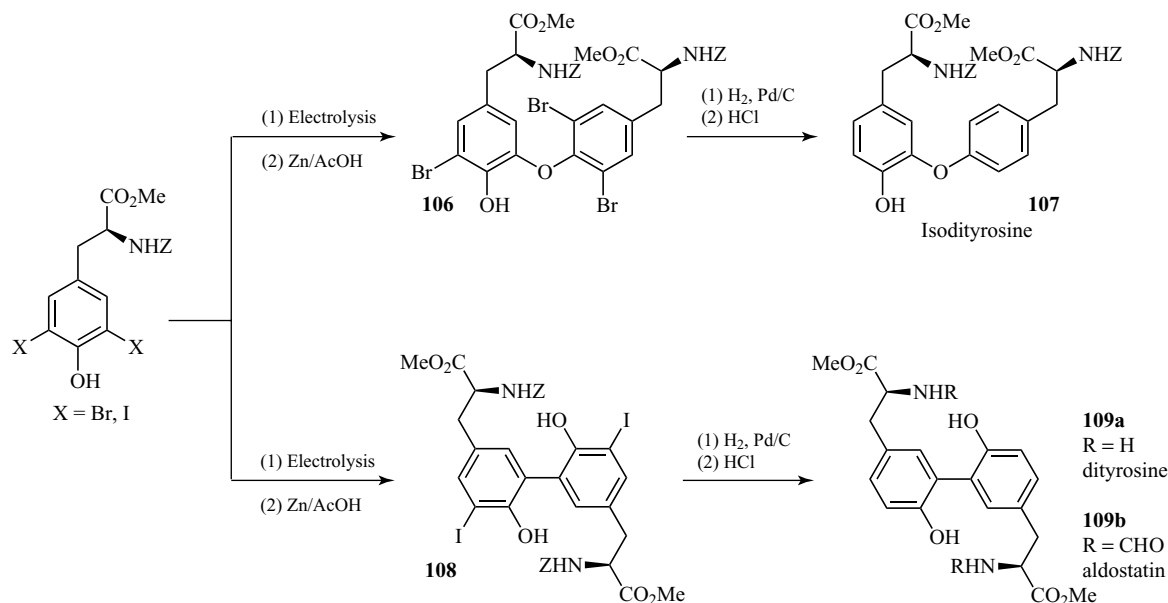
The oxidation of the dihalogenated phenol initially leads to a phenoxy radical with the unpaired electron localized either at the oxygen atom (**103a**) or one of the halogen-substituted carbons (**103b**) (Scheme 32). According to density functional theory (DFT) studies, the oxygen-localized radical resonance structure is always preferred, but the

preference is, in agreement with the experimental results, higher for the dichloro and dibromo system than for the diiodo system.⁵²

A homo-coupling of the bromine-substituted carbon-localized radical **103b** is in any case improbable because of the repulsion of the bromine atoms; therefore, the carbon–oxygen coupling pathway toward the diarylether **104** is favored. In the case of iodine, the biaryl product **105** is formed after cleavage of one halogen substituent via a nonradical mechanism.

Starting from halogenated L-tyrosine derivatives, the diarylether coupling product of the dibromo derivative **106** was obtained in 45% yield and could be converted into isodityrosine (**107**) in two steps (Scheme 33).^{54,55} By changing the halogen substituents to iodine, the same anodic oxidation created the biaryl compound **108** in 28% yield, a precursor of dityrosine **109a**, and its *N*-formylated derivative aldostatin **109b** which is an aldose reductase inhibitor.⁵²

The electrooxidative coupling of arylothers to biaryl compounds such as **111** occurs in combination of two radical cations and is more selective than the coupling of the corresponding



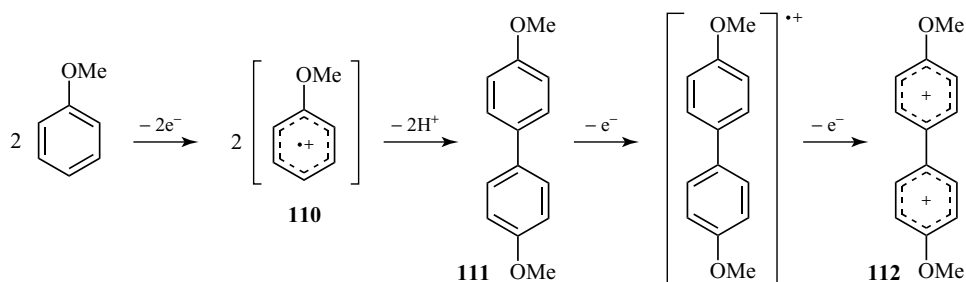
Scheme 33 Application of the coupling of 2,6-dihalogenated phenols for the syntheses of dityrosine-class natural products.

phenols because of the protected hydroxyl functionality which makes the side reaction toward diarylethers impossible (Scheme 34). Furthermore, the *ortho* coupling and quinone by-products are less readily formed. However, the initially formed radical cations **110** are highly sensitive to the attack of nucleophiles present in the reaction medium; hence water-free conditions are required. The conversions are usually performed in dichloromethane (DCM) or acetonitrile in combination with trifluoroacetic acid (TFA) to lower the nucleophilicity. The over-oxidized dicationic biaryl species **112** is more stable under acid conditions, thus avoiding further reactions to unwanted by-products.

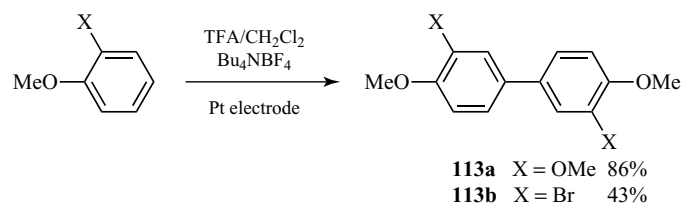
A frequently used electrolyte is Bu₄NBF₄ as in the synthesis of biaryls such as **113a** starting from 1,2-dimethoxybenzene by Parker (Scheme 35). The respective coupling of *ortho*-bromanisole to **113b** was accomplished under the same conditions.⁵⁶

A methoxy-substituted triphenylene derivative **114** was obtained in 60% yield by mixed electrolysis of anisole and veratrol (Scheme 36).⁵⁷

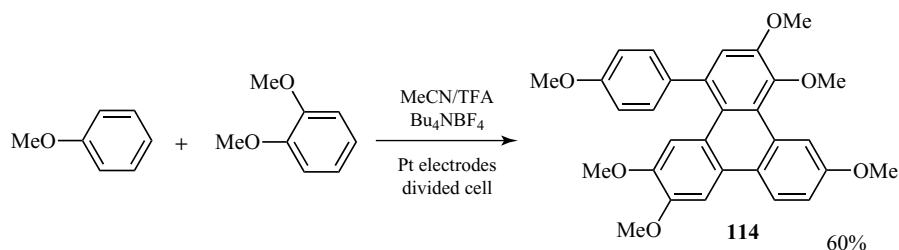
Functionalized triphenylene cores, which represent receptors for the binding of alkylated oxopurines⁵⁸ such as caffeine, were synthesized by Waldvogel under similar conditions (Scheme 37).⁵⁹ The coupling of chiral spiroketals derived from catechol affords two diastereomers of the triphenylene



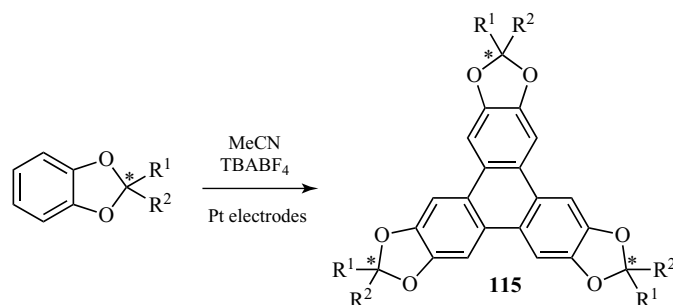
Scheme 34 Biaryl synthesis via anodic coupling of arylenes.



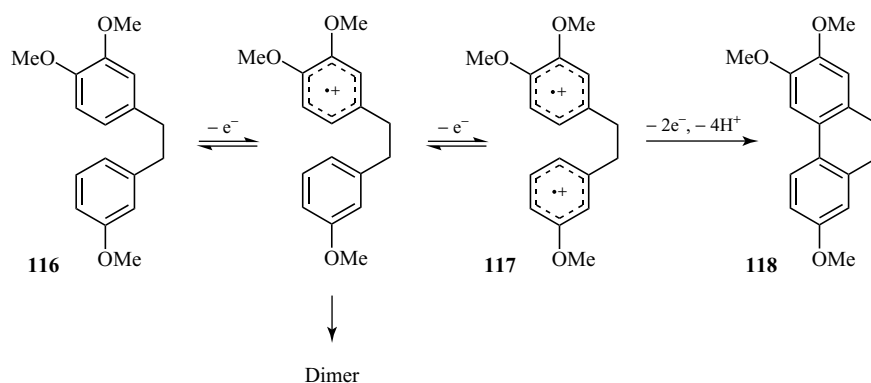
Scheme 35 Conversion of arylethers.



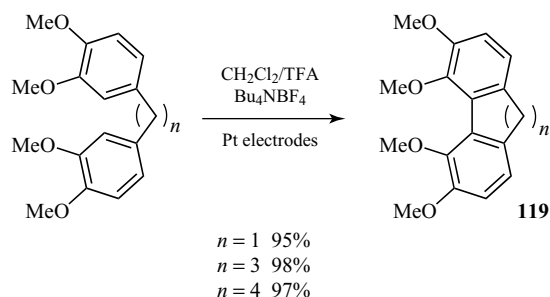
Scheme 36 Synthesis of a triphenylene core by electrolysis of anisole and veratrol.



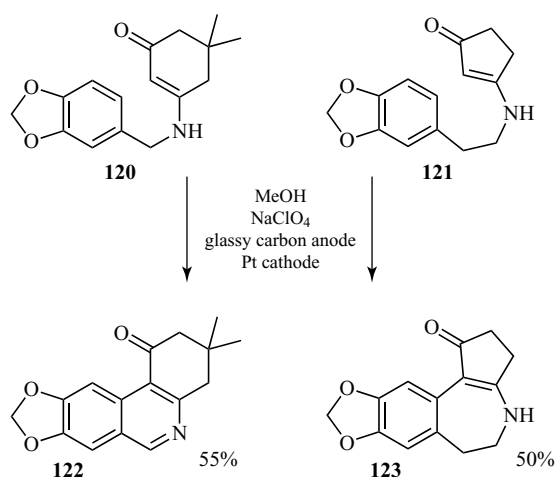
Scheme 37 Coupling of chiral spiroketals toward functionalized triphenylene cores.



Scheme 38 Formation of a methoxylated phenanthrene.



Scheme 39 Intramolecular coupling of methoxylated diphenylalkanes.



Scheme 40 Synthesis of isoquinolines and benzazepines.

product **115**. These electron-rich donors are able to host electron-deficient guest molecules showing C_3 symmetry.⁶⁰ An intramolecular electrochemical coupling reaction for the synthesis of alkyl-bridged biphenyls of type **116** was accomplished by Parker (Scheme 38).^{61–63} The formation of a diradical

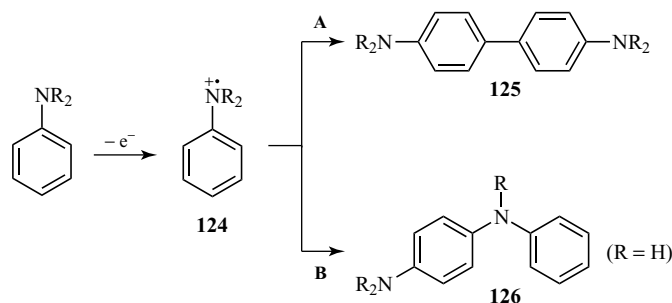
species **117** is necessary for this conversion to proceed toward the intramolecular product **118**; otherwise, the dimer of the substrate will be formed.

The six-membered ring resulting from the diphenylethane **116** is further oxidized to the corresponding phenanthrene **118** at higher potentials (Scheme 38).⁶¹ Under typical conditions, five-, seven-, and eight-membered rings (**119**) derived from methoxylated diphenylalkenes were obtained in excellent yields (Scheme 39).

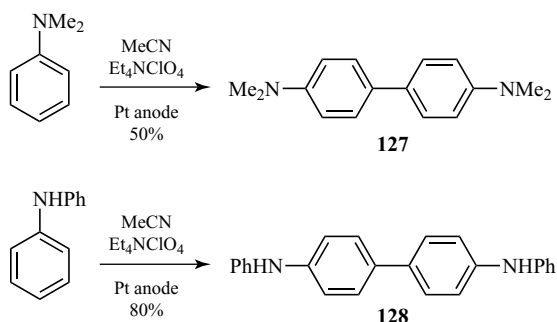
Isoquinolines and benzazepines of types **122** and **123** were obtained via intramolecular cyclization at the anode by Schäfer (Scheme 40).⁶⁴ The conversion of the alkyl-linked aryl enaminones **120/121** was performed in MeOH with NaClO_4 as the supporting electrolyte. The products **122/123** could be isolated in good yields and represent building blocks in the syntheses of alkaloid natural products.

The electrochemical reaction of arylamines toward biaryl compounds of type **125** proceeds in analogy to the conversion of arylethers starting with the generation of a radical cation **124** (Scheme 41). The synthesis of the benzidines **125** resulting from carbon–carbon coupling (path A) is accompanied by the formation of diphenylamines **126** (path B) when utilizing primary or secondary arylamines.

The selectivity strongly depends on steric factors since the biaryl product of type **125** is favored in the presence of bulky alkyl substituents R, but the product ratio is also determined by substrate concentration, current density, and pH of the solution.⁶⁵ In dilute solutions at high current densities and low pH values, the benzidine compound is the major product, whereas the opposite conditions predominantly lead to the diphenylamine. The electrolysis is usually carried out in acetonitrile with Et_4NClO_4 as the supporting electrolyte.⁴⁰ Under these conditions, the



Scheme 41 Electrochemical conversion of dialkylanilines.



Scheme 42 Homo-coupling of aniline derivatives toward biaryl compounds.

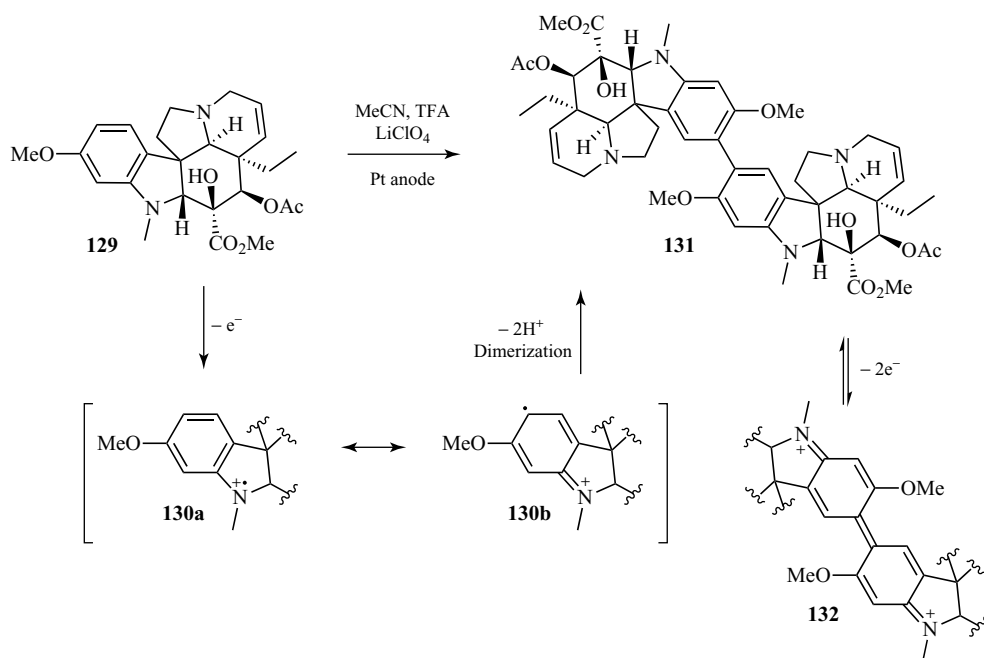
homo-coupling of *N,N*-dimethylaniline was accomplished by Hand and Nelson⁶⁶ in moderate to good yields to produce **127**, while the respective coupling of diphenylamine yielding 80% of benzidine **128** was performed by Cauquis (Scheme 42).⁶⁷

An oxidation–reduction sequence for the synthesis of 10,10'-bisvindoline (**131**) was presented by Tabakovic (Scheme 43).⁶⁸ The synthesis was carried out in a divided cell in MeCN with LiClO₄ and additional TFA in the anode cell, where at first the bis-indole alkaloid vindoline **129** was oxidized

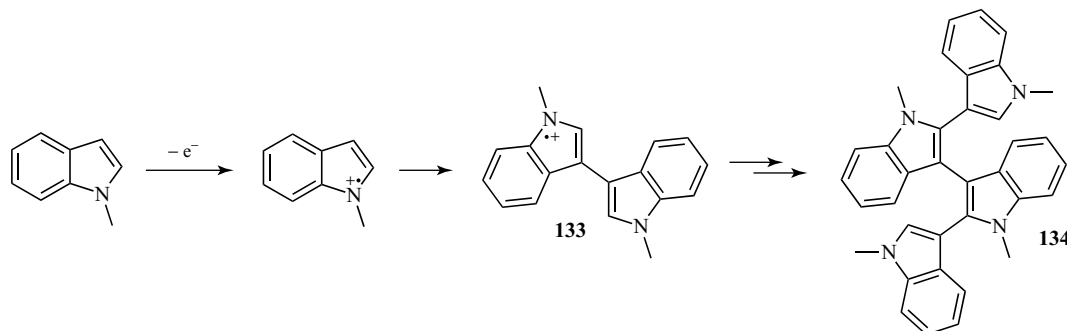
to the radical cation **130a/b**. This intermediate is stabilized by several resonance structures and dimerizes to the product **131**. On account of further oxidation to the dication **132**, changing the current direction after full conversion is required to obtain the desired product in 60% yield.

The application of unsubstituted indoles in anodic oxidation leads to polymers linked at 2 and 3 positions. Polyindoles represent electroconductive materials, which have evoked interest in the field of sensors. Investigations by Berlin *et al.*⁶⁹ have shown the initial formation of a 3,3'-coupled dimer **133** for the oxidation of 1-methylindole in acetonitrile. Further electrolysis generates the tetramer **134** (Scheme 44).

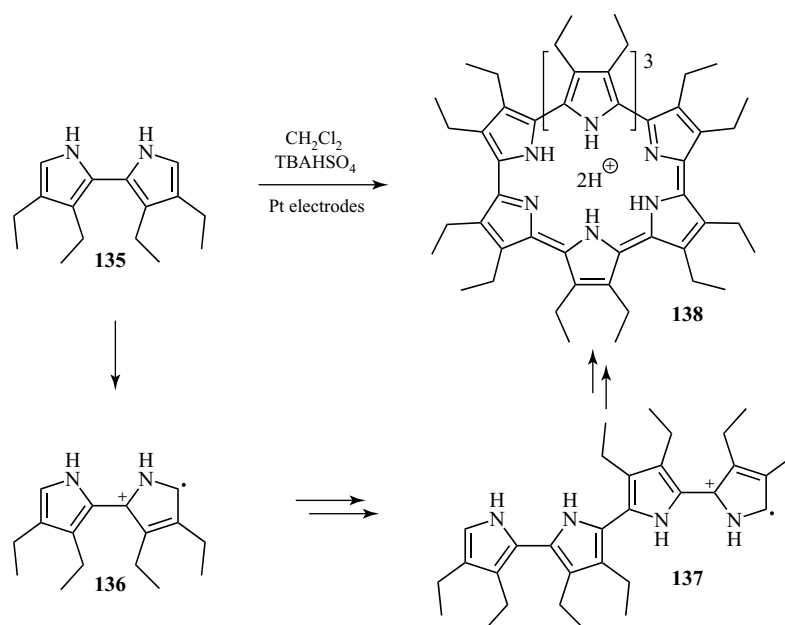
Sessler recently succeeded in synthesizing cyclo[8]pyrrole **138** electrochemically from tetraethyldipyrrole **135** (Scheme 45).⁷⁰ They found that the conversion strongly depends on the size of counter anion of the ammonium salt applied as the supporting electrolyte. The yield ranges from 0% with tetrabutylammoniumfluoride (TBAF) and almost 70% with tetrabutylammoniumdihydrogensulfate (TBAHSO₄). This is explained by templating effects of the anion during the polypyrrole formation, which leads to stabilization of the



Scheme 43 Dimerization of vindoline.



Scheme 44 Electrochemical generation of an indole tetramer.



Scheme 45 Synthesis of cyclo[8]pyrrole.

linear intermediates such as **136** and **137**. However, when the anion is too basic, deprotonation might occur leading to side-product formation.

The conversion starts with the anodic generation of a radical cation (**136**), which undergoes dimerization to **137** after being deprotonated. Further oxidation and deprotonation leads to the tetramer and its cyclization to cyclo[8]pyrrole **138**.

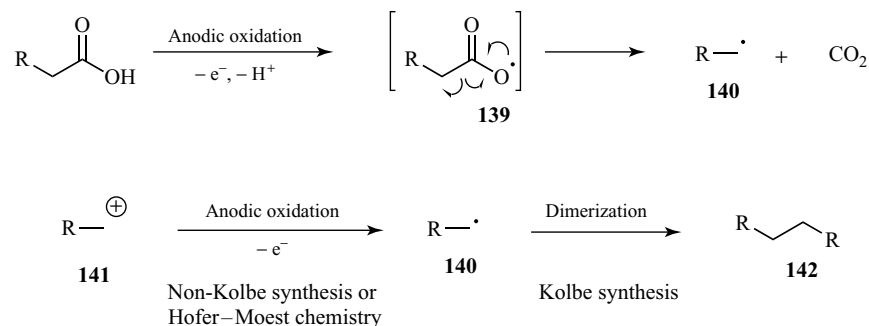
2.7 Kolbe Electrolysis

The dimerization of two sp^3 -carbon-centered radicals generated by electrochemical one-electron

oxidation of the homologous carboxylic acid is generally known as *Kolbe synthesis* (Scheme 46).

The short-lived intermediate acyloxy radicals **139** rapidly decarboxylate, leading to aliphatic radicals of type **140**. If two free radicals combine, the desired Kolbe dimer is obtained. The most commonly encountered side reaction results from a second oxidation process, resulting in the formation of the corresponding carbocation **141**, which, being itself an unstable intermediate, generally reacts with any present nucleophile. This process is known as *non-Kolbe synthesis* or the *Hofer–Moest reaction*.

The conditions leading to the preference of Kolbe synthesis over Hofer–Moest chemistry are well

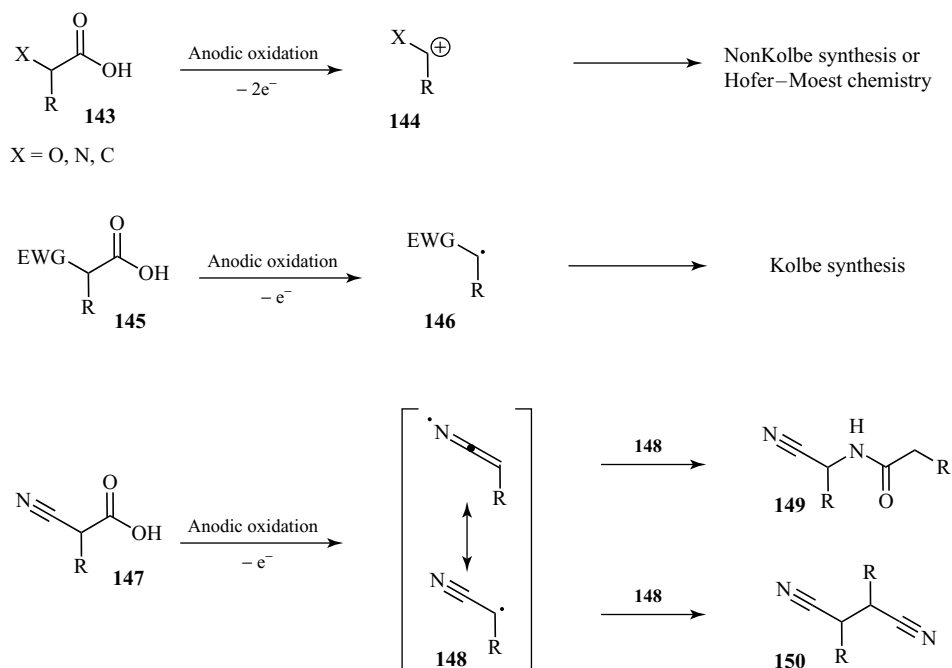


Scheme 46 Electrochemical generation of acyloxy radicals **139** with subsequent decarboxylation giving sp^3 carbon radicals **140** and their reactions.

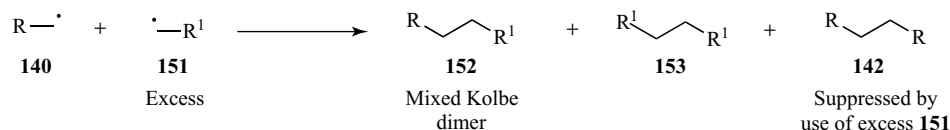
understood: polar/protic solvents (mainly methanol), platinum anodic electrode, weakly acidic pH (easily achieved by the addition of up to 30 mol% of alkali alkoxides, thus regulating pH and generating the supporting electrolytes *in situ*), and high current densities are the conditions commonly used.

The success of the Kolbe dimerization depends strongly on the substrate applied. Substituents in α -position, which stabilize cations, lead to Hofer–Moest products via **144** (Scheme 47). As

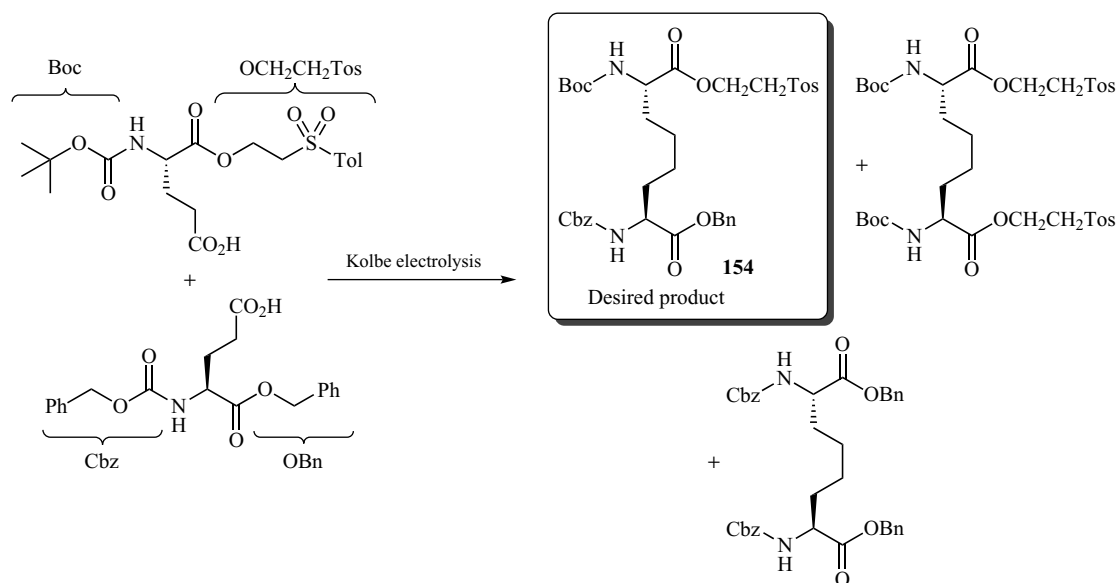
such, tertiary (and to a lesser extent secondary) carboxylic as well as α -hydroxy or α -amino acids are generally not convertible to the required radical species **140**. Electron-withdrawing substituents in the α -position, on the other hand, strongly favor the formation of radical species **146** and thus lead to the desired dimeric Kolbe products. Notable exceptions are α -nitrilo acids, which give radical **148** upon oxidation. Dimerization can proceed through both of the shown mesomeric forms, leading to a



Scheme 47 Effect of the substrate substitution pattern on the outcome of the electrolysis of carboxylic acids (EWG: electron-withdrawing group).



Scheme 48 Reaction of two different substrates under Kolbe conditions.



Scheme 49 Example of separable mixtures of dimers of orthogonally protected diaminodicarboxylic acids based on the applied protecting groups.

mixture of products **149** (Ritter-type reactivity) and **150**.

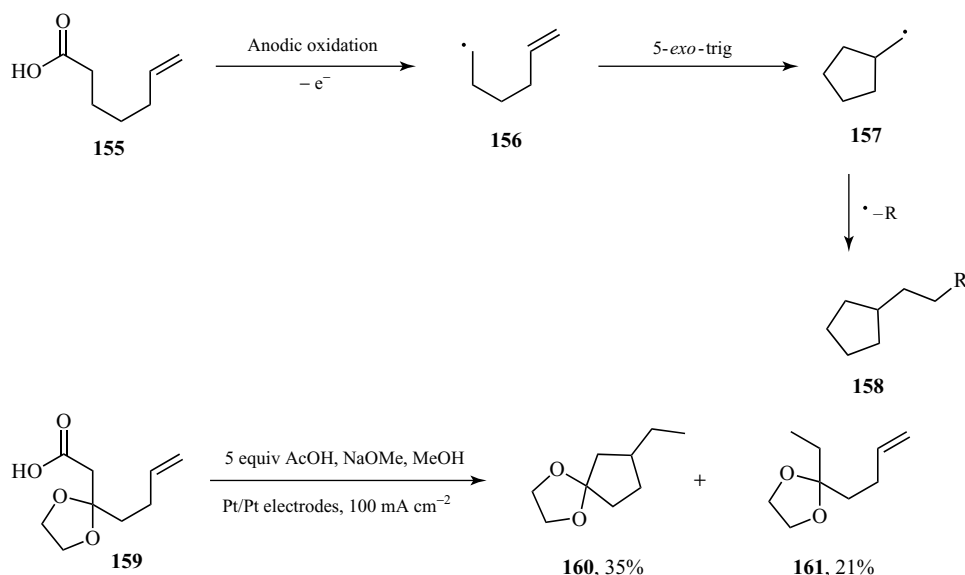
Yields for Kolbe dimerizations of substrates with hindering α -substituents are generally below 25–30%, although some new approaches offer the possibility of improvement (sono-emulsions for example).⁷¹

The rather indiscriminating reactivity pattern of the radical intermediates **140** and **151** leads to statistical mixtures of products (**152**, **153**, and **142**) when two different acids are applied (Scheme 48). Unless the acids in question are of greatly different polarity and/or molecular structure, separation of these mixtures is usually not readily attainable. However, when one of the acids (usually the less expensive one) is used in excess, the formation of one of the symmetrical dimers (**142** in Scheme 48) is suppressed, greatly simplifying the purification of the desired unsymmetrical mixed Kolbe dimer. Some work has been carried out utilizing differently

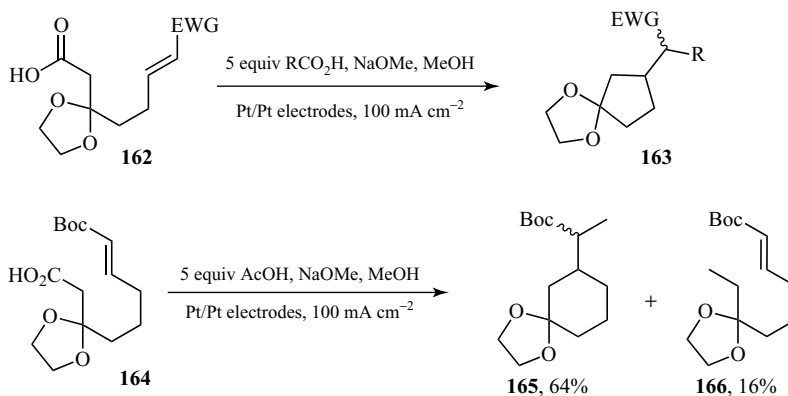
protected glutamic and aspartic acids in the synthesis of orthogonally protected diaminodicarboxylic acids where both starting materials are present in 1 : 1 ratio (Scheme 49).⁷²

While no solution to the low yields of this scenario is presented (12–16% of the desired mixed dimers **154** are obtained), utilizing Boc (*tert*-butoxycarbonyl)/EtTos (ethyl tolyl sulfone) on one glutamic acid and Cbz (carboxybenzyl)/Bn (benzyl) on the other generally leads to mixtures that are separable by column chromatography based on the greatly different polarity of the protected diaminodicarboxylic acids (Scheme 49).

The applicability of the Kolbe reaction in the formation of numerous substance classes (1, ω -diesters, long-chain hydrocarbons, etc.)⁷³ and natural products^{74–76} has a long and proven track record, which has been discussed elsewhere. Two recent works, however, have extended the range of applicability of this venerable reaction.



Scheme 50 Radical cyclization initiated by Kolbe electrolysis.



Scheme 51 Effect of an electron-withdrawing group (EWG) on the radical cyclization of ϵ -unsaturated carboxylic acids.

Building on the pioneering work of Schäfer^{77–79} regarding the radical cyclization of ϵ -(**155**, **159** in Scheme 50) and ζ -unsaturated carboxylic acids to five- and six-membered rings, respectively, Lebreux has shown that the yield of the cyclization product is greatly increased, compared to the almost 1 : 1 ratio of cyclized (**160**) to linear (**161**) product obtained for a terminal olefin, when the double bond is electron deficient (Scheme 50).⁸⁰

Both the 5-*exo*-trig and 6-*exo*-trig cyclizations, leading to cyclopentanes (**163**) and hexanes (**165**), readily occur under these conditions (Scheme 51), although the 6-*exo*-trig cyclization does appear to

be somewhat slower, as a small amount of linear product **166** was obtained.

The nature of the electron-withdrawing group (EWG) is not unimportant: unbranched α,β -unsaturated esters smoothly give the product in excellent yield (**167**, Figure 4), while α -methyl unsaturated esters already give a mixture of cyclized (**170**) and cyclization/Hofer–Moest tandem product derived from an intermediate presumably analogous to **157**. Nitriles predominantly lead to **168** and, while no mention of alternative products is made, it appears plausible that side reactions deriving from radical intermediates of type **148** might play

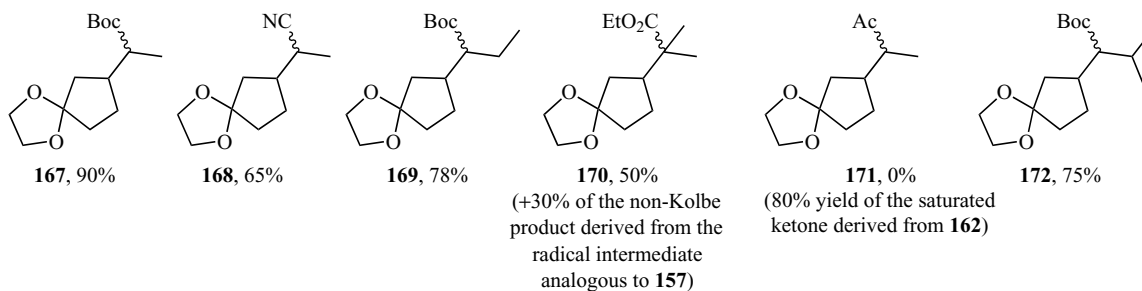
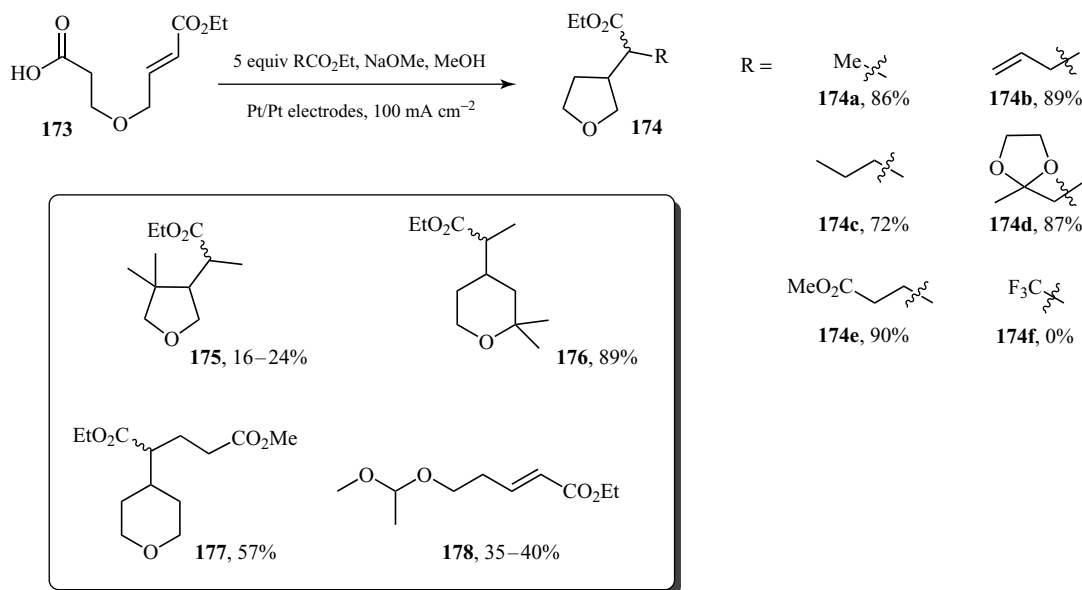


Figure 4 Products obtained from the 5-*exo*-trig cyclization presented in Scheme 51.



Scheme 52 Synthesis of tetrahydrofuran and tetrahydropyran derivatives via electrochemically initiated radical cyclizations.

a role in the lower yield. Unsaturated ketones do not appear to be substrates in this conversion, as the cathodic reduction of the α,β -double bond completely dominates (**171**, Figure 4).

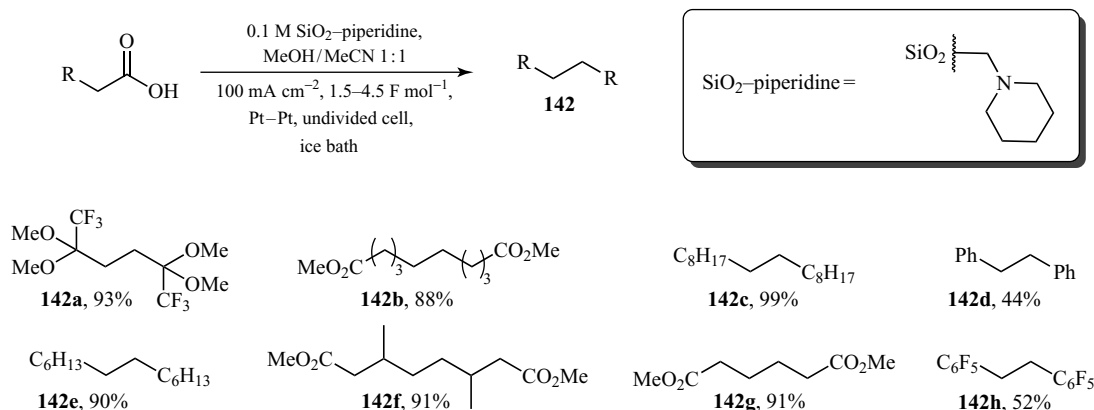
The application of electron-deficient olefins and the universal use of the Thorpe–Ingold effect enable the reported increase in yields and selectivities with respect to the desired cyclization reactions.

Besides acetic acid, propanoic and isobutyric acids were also applied as co-acids, both leading to the desired products in good yields (**169** and **172** respectively, Figure 4).

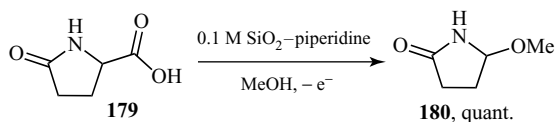
Ethers of type **173** could also be applied (Scheme 52), permitting the generation of THF derivatives with a wide range of functionalities derived from various co-acids (**174a–e**). Only the

electron-poor trifluoroacetic acid proved to be unreactive (**174f**). Products of the type **175** were obtained only in poor yields, presumably because of steric congestion of the intermediate radical, as no further products were reported. Tetrahydropyran derivatives are accessible in excellent yields (**176**) when a gem-dimethyl substitution pattern is applied. Without the dimethyl moiety, the obtained yield is reduced (**177**), coupled with the generation of a further linear product **178** possibly originating in a rearrangement of either a radical or carbocationic intermediate.

The classical application of the Kolbe reaction is the dimerization of primary carboxylic acids leading to the decarboxylated dimer (refer to Scheme 46). While the reaction generally proceeds smoothly,



Scheme 53 Kolbe dimerization of primary aliphatic carboxylic acids utilizing SiO₂ gel-supported piperidine.



Scheme 54 Influence of α -heteroatoms on the outcome of the electrolysis of carboxylic acids.

yields of significantly lower than 50% are the norm.

Recent work by Fuchigami has increased the yield that can be expected for the dimerization.⁸¹ This was achieved by the application of silica-gel-bound piperidine as the base, with the resulting ammonium carboxylate pair serving as the supporting electrolyte, in methanol/acetonitrile 1:1. Interestingly, no Ritter-type side reactions derived from the attack by the generated radicals on the nitrile functionality of the co-solvent were reported.

Using this new methodology, excellent to quantitative yields were obtained in the cases that favor generation of the radical (**140**) over the cationic (**141**) intermediate (Scheme 53). Purification was reported to be greatly simplified: filtration and removal of the solvent were usually the only tasks required to allow isolation of pure product. The silica-bound piperidine proved to be recyclable; up to 10 cycles were reported without loss of activity.

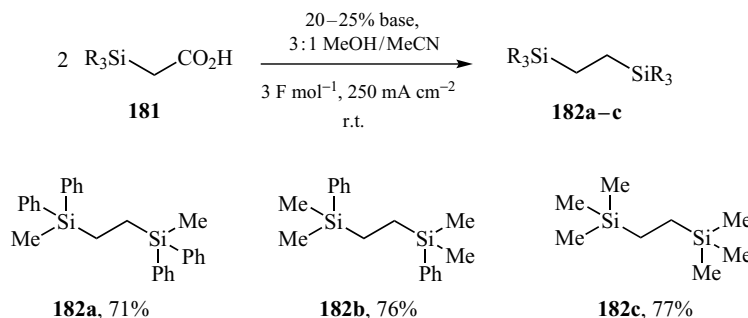
The general limits of the Kolbe reaction do, however, still apply. Benzylic radical intermediates, generated from 2-aryl acetic acids, lead to the formation of a significant amount of Hofer–Moest products and thus lower yields of the desired dimer (**142d** and **142h**). The dimerization yields are

nevertheless still higher for these substrates than usually obtained when using the original procedure. Following this trend, the same authors have also reported that heteroatoms in α -position as in **179** to the newly formed radical intermediate lead exclusively to the generation of the carbocationic species, so that non-Kolbe products such as **180** are the only species observed (Scheme 54).⁸²

The higher yields obtainable with the silica-bound piperidine bring the yield into synthetically interesting ranges. Should the mixed Kolbe reaction be equally amenable to this strategy, it stands to reason that renewed attention will be directed at this venerable transformation.

Shtelman and Becker recently reported the successful synthesis of 1,2-bissilyl ethanes (**182a–c**, Scheme 55) from the corresponding α -silyl carboxylic acids (**181**, Scheme 55).⁸³ Part of the interest for this project was derived from the uncertain influence of the α -silyl group on the outcome of the Kolbe reaction. The authors note that competing electronic influences of the Si–C bonds (α/β -Si effect) might lead to unexpected results for these α -silyl acids. Should the cationic intermediate be preferred, substantially lower yields are to be expected. The results indicate that radical formation is indeed the preferred pathway, as good yields are obtained, after optimization, for the three examined silyl groups (Scheme 55).

It was found that the standard Kolbe conditions did not lead to successful conversion of the starting materials. When the amount of base (the preferred base was 3 N KOH) applied was increased to 20%, the yield responded favorably, leading the

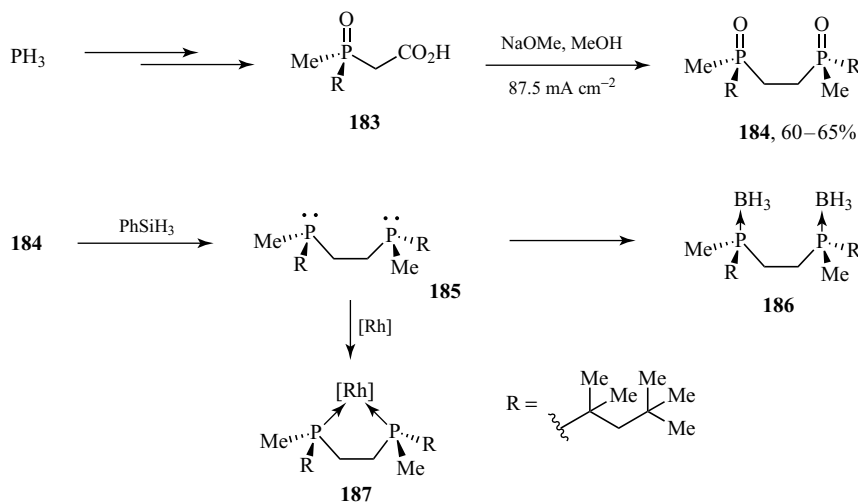


Scheme 55 Electrochemical dimerization of α -silyl acetic acids.

authors to the conclusion that the weaker pK_a of the α -silyl acetic acids (5.22 vs 4.75) was to blame for the initial failure. Higher current densities (200–250 mA cm^{-2}), room temperature, and a 3 : 1 MeOH/MeCN mixture were further identified as optimal parameters. Electricity consumptions of over 3 F mol^{-1} were also found to be detrimental.

Kolbe electrolysis has also been used by Sugiyama and Nohira to generate P-chiral bisphosphine compounds via the intermediate P-chiral phosphinoyl carboxylic acids (Scheme 56).^{84,85} Starting from phosphine, the key racemic phosphinoyl carboxylic acid intermediate is obtained after several steps. Optical resolution by fractional crystallization using (–)-(S)-1-phenylethylamine as the resolving agent gave the desired chiral compounds (**183**). Standard Kolbe conditions permitted the synthesis of

the P-chiral bisphosphine oxides (**184**) in 60–65%, isolated yield from which the bisphosphines (**185**) were liberated by reduction with phenyl silane. The expected side products of the Kolbe reaction account for the nonquantitative yield and could be isolated, showing varying amounts of Hofer–Moest, disproportionation (where possible), and esterification products. The absolute configuration was confirmed by conversion of **185** into bisphosphine–borane complexes (**186**) and by comparing with available literature for optical rotation values. The bisphosphino ethane **185** was used as a chiral ligand, with rhodium giving chiral complexes of type **187**. This complex was tested in the hydrogenation of α -(acylamino)acrylic derivatives. The corresponding saturated compounds showed good to excellent enantiomeric excesses, proving the worth of



Scheme 56 Generation of P-chiral bisphosphino ligands with Kolbe electrolysis as the key step.

this type of P-chiral chelating ligand in asymmetric catalysis. Higher homologs of the bisphosphino compounds are also accessible.

2.8 Aminoxyl Radical-Mediated Reactions

The electrochemical generation of radicals from various precursor molecules permits the rapid and selective functionalization or defunctionalization of molecular scaffolds. Many of these processes involve radical species only transiently or as noncritical intermediates. While these reactions are in and of themselves fascinating, they do not fall under the scope of this brief overview and as such we point to the original publications themselves for those interested in further information.^{86–98}

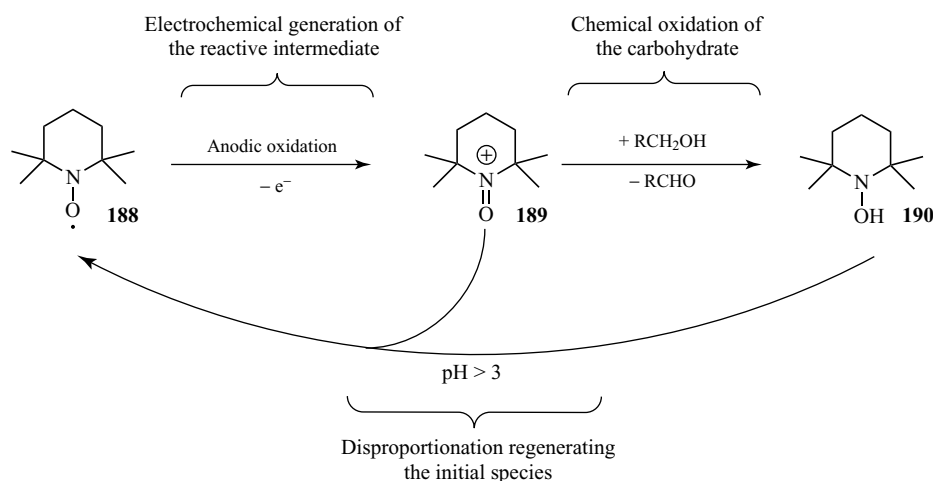
One of these fields of work which should nonetheless be highlighted is the regeneration of reactive intermediates in the catalytic application of stable N,O radical species (see **Nitroxides in Synthetic Radical Chemistry**). This approach underlines the synthetic utility of radical chemistry in general and the unique opportunities afforded by the appropriate use of electrochemistry. TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, **188**) is the most prominent of this class of stable radicals and numerous uses are known; stoichiometric quantities of this species are often required, but the addition of an oxidant to regenerate the active species **189** and thus allow catalytic turnover with regard to

TEMPO are also common. In this context, Schäfer has applied catalytic amounts of TEMPO as a mediator in the selective electrochemical oxidation of carbohydrates to the respective uronic acids.^{99,100}

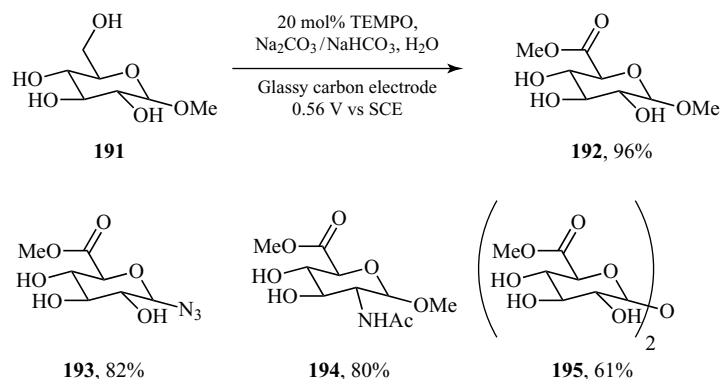
TEMPO is electrochemically converted to the actual chemical oxidant: the nitrosonium cation **189**. After the target oxidation itself is carried out, hydroxylamine **190** reacts with another equivalent of **189** to regenerate TEMPO itself, thus closing the catalytic cycle. The electrochemically generated species (**189**) is not just the key oxidant but also crucial for the regeneration of the catalyst. A wide range of carbohydrates such as **191** were reacted under the reported reaction conditions, a small excerpt of which (**192–195**) is shown in Scheme 58.

A range of functionalities is tolerated, and in general the yields are good to excellent. The nitrosonium cation **189** can evidently discriminate handily between the primary and secondary hydroxy functionalities, thus permitting selective oxidation. One of the key limitations of this method is that the anomeric center must be protected.

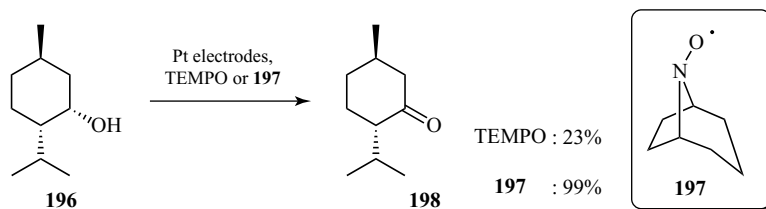
Demizu *et al.* carried out further tests with different stable *N*-oxyl radicals, here azabi- and tricyclic systems, which owe their stability to Bredt's rule.¹⁰¹ The nitrosonium cations (equivalent to **189**, Scheme 57) were successfully applied in the oxidation of primary and secondary alcohols to aldehydes and ketones. In many cases, such as the oxidation of menthol (**196**) to **198** mediated by **197** in Scheme 59, the alternative *N*-oxyl radicals lead to significantly higher yields than TEMPO.



Scheme 57 Role of TEMPO in the electrochemical oxidation of carbohydrates.



Scheme 58 Examples of the uronic acids accessible via the TEMPO-mediated electrochemical oxidation of carbohydrates.



Scheme 59 Electrochemical oxidation of menthol mediated by azabicyclic *N*-oxyl radical **197**.

2.9 Halide-Mediated Reactions

The opening of carbocycles and subsequent derivatization of the thus obtained radical intermediates is a strategy that shows promise. Royer's group has published work on the anodic oxidation of *N*-cyanomethyloxazolidines of type **199** (Scheme 60). They have observed that, in the presence of halogenides (Cl^- and Br^-), which are presumed to act as mediators in the course of the reaction as well as the halogenating agents, a gem-dihalogenated product **200** is observed, while in the presence of water products of type **201** are obtained.¹⁰²

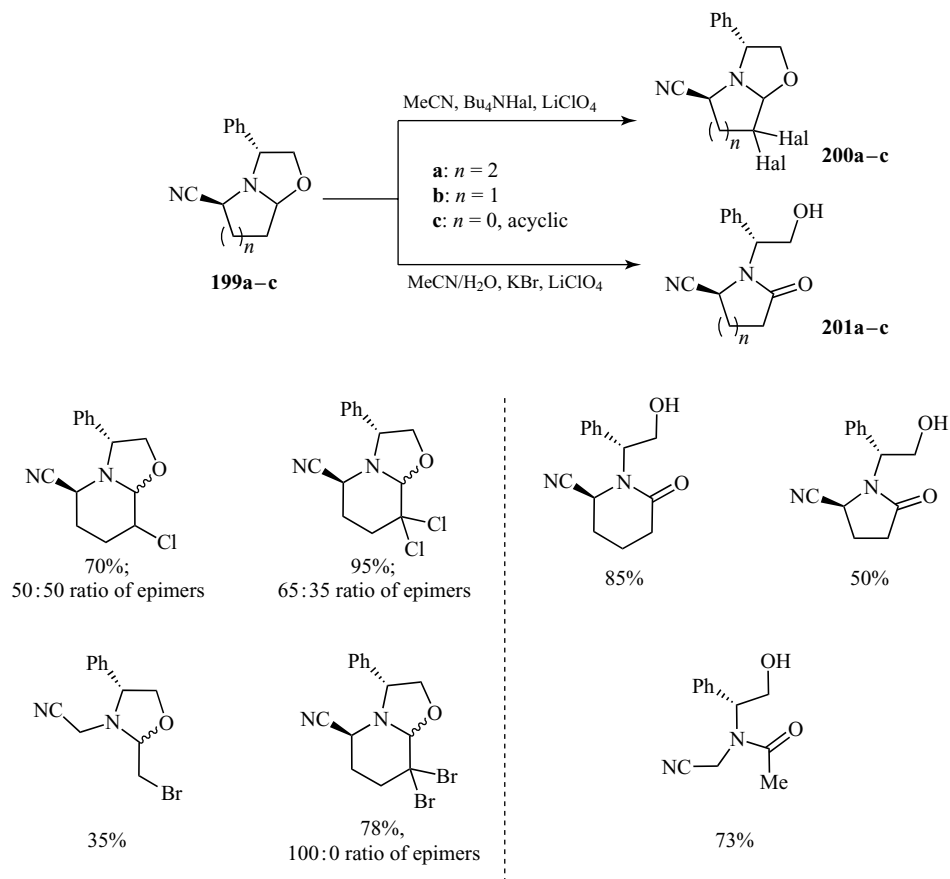
A general feature of these reactions is that the presence of at least traces of bromide is essential to obtain high yields and rates of reaction. The authors provide mechanistic evidence pointing toward the crucial role of the trihalogenide anions, which are generated *in situ* following electrochemical oxidation of the simple halogenides to the elemental halogens, for successful conversion of the starting material (Scheme 61). The proposed hypothesis argues that tribromide is the superior electron transfer agent and thus critical to the success of

the conversion of **202** to **207**. The bromination is believed to proceed from **204a/b** to the iminium cation **205**, which is then in equilibrium with the bicyclic intermediate **206**. Repetition of this sequence leads to the dihalogenated product **207**. Fluoride was not able to mediate the oxidation, in accordance with its high oxidation potential. The use of iodide was not reported.

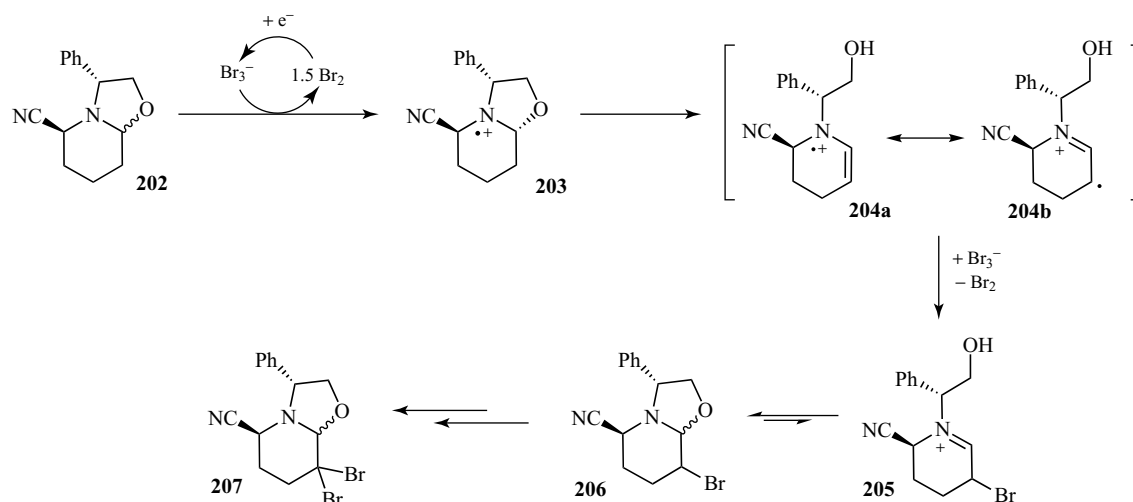
When vinyl ethers are added and lithium perchlorate is used as the supporting electrolyte, the result is the expansion of the ring system to the cyclization product **208** (Scheme 62).¹⁰³ A similar mechanism is postulated, with the addition of the unsaturated ether to intermediate **209** as the key step.

2.10 Functional Group Exchange Reactions

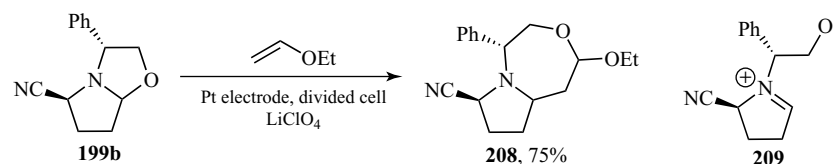
Le Gall presented a case where the selective fragmentation of an electrochemically generated radical was exploited to deliver a valuable compound. They report that, upon anodic oxidation of *N*-substituted α -silyl piperidines of type **210** in the presence of a cyanide source, exclusive exchange of the silyl group for cyanide to generate products of type **211** is observed.¹⁰⁴



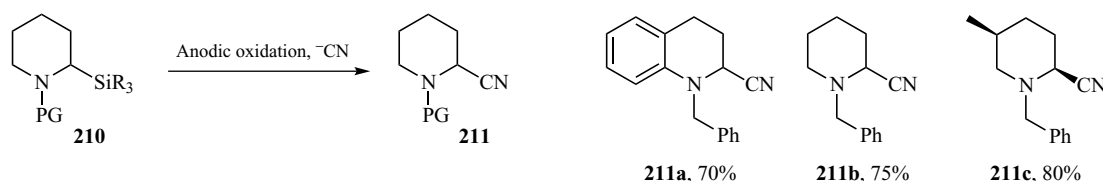
Scheme 60 Electrochemical functionalization of oxazolidines **199a-c**.



Scheme 61 Postulated mechanism for the electrochemical functionalization of **202**.



Scheme 62 Electrochemical ring expansion of oxazolidines with vinyl ethers.



Scheme 63 Exchange of silyl for nitrile functionality in piperidine derivatives (PG: protecting group).

The mechanism is postulated to proceed via a preliminary N-centered radical cation derived from **210**, which leads to exclusive fragmentation of the α -C–Si bond. This generates a secondary C-centered radical which is subjected to a second oxidation step leading to an intermediate iminium ion, which is then attacked by cyanide to yield the α -nitrile amine products of type **211**. The nitrile group always assumes an axial orientation in the piperidine ring. The authors offer an explanation based on the stereoelectronics of the intermediate iminium cation. The rationale is broadly identical with the concept of an anomeric effect as derived from carbohydrate chemistry.

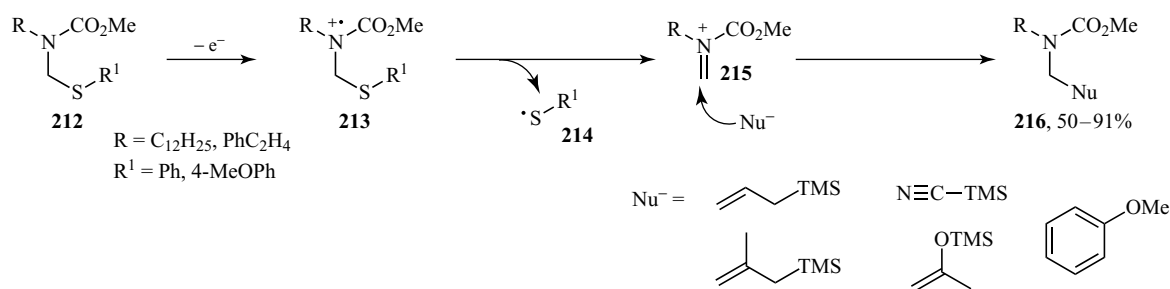
A common problem when subjecting tertiary or secondary amines to anodic oxidation is the lack of specificity with respect to which the α -bond fragments to generate the iminium cation. A novel solution was presented by Yoshida's group.¹⁰⁵ They determined that the C–S bond of a N,S-acetal (**212**) functions as an electrochemically activated breaking

point (Scheme 64). The thus-derived iminium cation **215** can be subsequently derivatized by nucleophilic attack to yield product **216**.

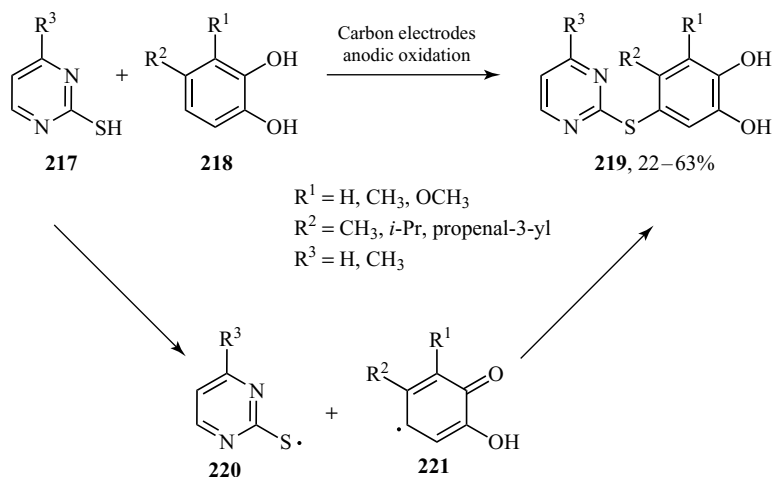
The first step is the oxidation of the carbamate nitrogen in **212** to generate the radical cation **213**. Despite a second α -position being available for fragmentation, the α -C–S bond is selectively cleaved, freeing an S-centered radical **214** (which reacts with a second equivalent to generate a disulfide) and the electrophilic iminium cation **215**. Various carbon nucleophiles were tested, and good to excellent yields of the corresponding products of type **216** were reported.

2.11 Coupling Reactions Initiated by Anodic Oxidation

The coupling of substituted catechols (**218**) and aromatic thiols (**217**) via electrochemical oxidation of both substrates was achieved by Becker



Scheme 64 Electrochemical functionalization of α -thio carbamates with carbon nucleophiles.



Scheme 65 Oxidative electrochemical formation of thioethers.

(Scheme 65).¹⁰⁶ While the desired thioethers of type **219** were obtained in poor to acceptable yields, the products do show a relatively high degree of functionality and are reported as intermediates of interest for materials and biological applications.

Although the mechanism of this transformation has not yet been elucidated, the authors speculate that the coupling might take place via the reaction of two separate electrochemically generated radical intermediates, **220** and **221**, which then combine to give the product upon re-aromatization.

3 CATHODIC PROCESSES

3.1 Cyclizations Induced by Reduction of Carbonyl Groups

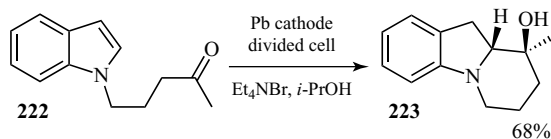
The reduction of carbonyl groups by SmI_2 is a very versatile method for the initiation of cyclization reactions of suitable starting materials utilizing 2 equiv of the reducing agent (see **Organic Synthesis Using Samarium Diiodide**). In order to reduce waste and to be able to continuously adjust the redox potential for each individual starting material, electrochemical reduction would be the method of choice. Recent applications in such cyclization reactions have been reported by Kise for the generation of mono- and bicyclic products starting from ketones and oximes. As acceptor

functionalities, imides,¹⁰⁷ indole derivatives,¹⁰⁸ and esters,¹⁰⁹ were used.

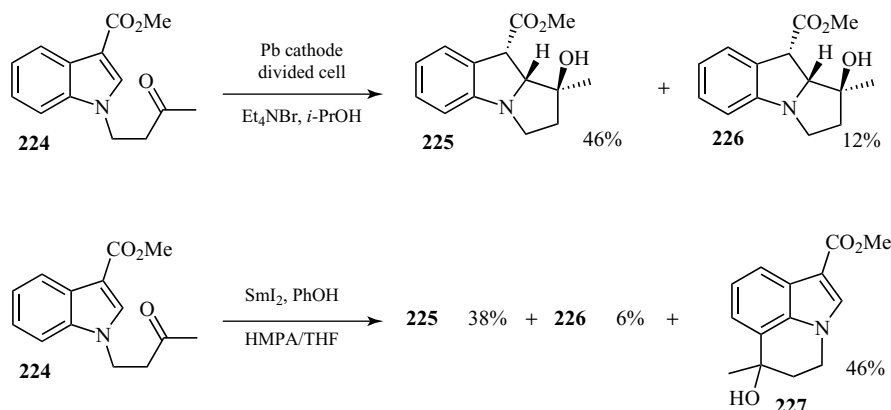
Of particular interest are those reactions that involve heteroaromatic scaffolds such as the indole derivative shown in Scheme 66.¹⁰⁸ The electrochemically initiated reaction of indole derivative **222** generates the tricyclic product **223** in good yield of 68% in an undivided cell (divided cell; 65% yield), which is comparable to the yield obtained for the chemical method utilizing SmI_2 as reductant (73%).

The electrochemical method allows the formation of the product **225** in moderate yield (46%) with three adjacent chiral carbon atoms with reasonable diastereoselectivity (Scheme 23). Interestingly, the corresponding SmI_2 -initiated reaction from **224** led to a different distribution of products. In this case, **225** was generated alongside 6% of **226**, but the tricyclic derivative **227** was also isolated and identified as yet another cyclization product.

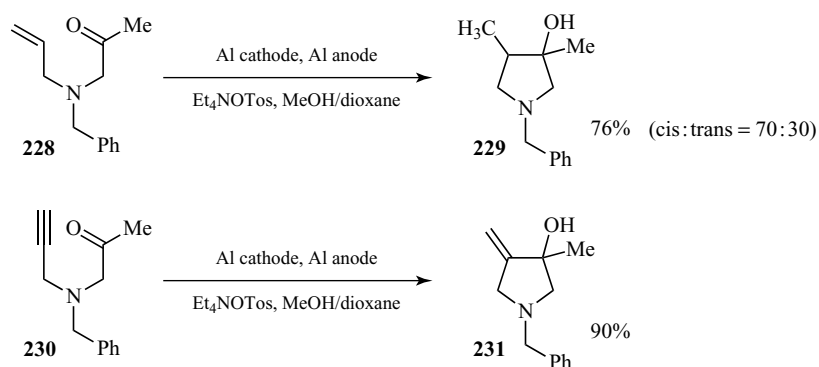
In the case of the ester-functionalized starting material **224**, cyclic voltammetry indicated that the reduction is more likely to proceed at the



Scheme 66 Reductive cyclization of a ketone-bearing indole derivative.



Scheme 67 Comparison of the electrochemical and chemical reductive cyclization of a ketone-containing indole derivative.



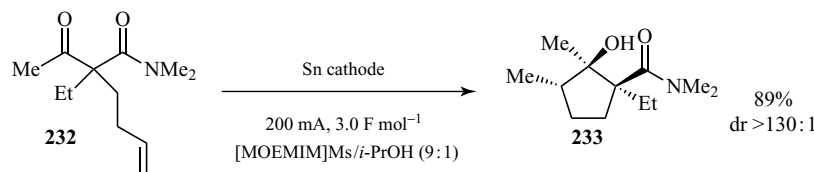
Scheme 68 Reductive cyclization of a ketone-bearing alkene and alkyne derivative.

α,β -unsaturated subunit rather than at the keto functionality as in **222**. Accordingly, the reduction of the two starting materials generates radical anions at different functional groups based on the redox potential. The chemical reducing agent SmI_2 generated a mixture of products in the presence of hexamethylphosphoramide (HMPA) as cosolvent, while, in the absence of HMPA product **225** was formed in 73% yield.

Nonconjugated enones and ynones were applied by Nishiguchi for the synthesis of functionalized five- and six-membered carbo-, sulfur- and nitrogen-containing heterocycles.¹¹⁰ The electrolysis was conducted with aluminum electrodes, and the application of enones such as **228** gave the desired products **229** in moderate to good yields (Scheme 68), whereas the electrolysis of the ynone **230** gave the corresponding cyclic allylic alcohol derivatives of type **231** in good to excellent yields.

The application of ionic liquids such as 1-methoxyethyl-3-methylimidazolium mesylate (MOEMIM) as solvent and electrolyte, together with isopropanol as proton donor, was reported by Yadav in the electrochemical reduction of β -ketoesters and β -ketoamides such as **232** (Scheme 69).¹¹¹ In these cases, the β -dicarbonyl groups were substituted with an alkyl group and a 1-butenyl substituent at the α -position to suppress the formation of enolates. Accordingly, the polysubstituted products such as **233** were formed in good to excellent yields, in good to exclusive diastereoselectivities, and with excellent regioselectivities.

The electrochemical reduction of carbon–carbon double bonds can be easily achieved when electron-deficient double bonds are used as starting materials. Accordingly, educts of the Knoevenagel type have a long track of successful applications in



Scheme 69 Reductive cyclization of an alkenyl substituted 1,3-diketone in an ionic liquid.

such reactions. In the presence of *in situ* accessible nucleophiles (such as malonates), two successive carbon–carbon bond formations can be realized in a one-step procedure. Thereby, cyclopropanations of Knoevenagel-type starting materials can be realized.^{35, 112–120} The reactions are performed in alcoholic solvents utilizing a halide source as the electrochemical mediator, and, therefore, from a mechanistic point of view, such reactions are most likely initiated by an electroreductively generated alkoxide base that deprotonates the malonate-type starting material and the oxidation of the halide, initiating ionic follow-up reactions with the Knoevenagel-type materials applied.

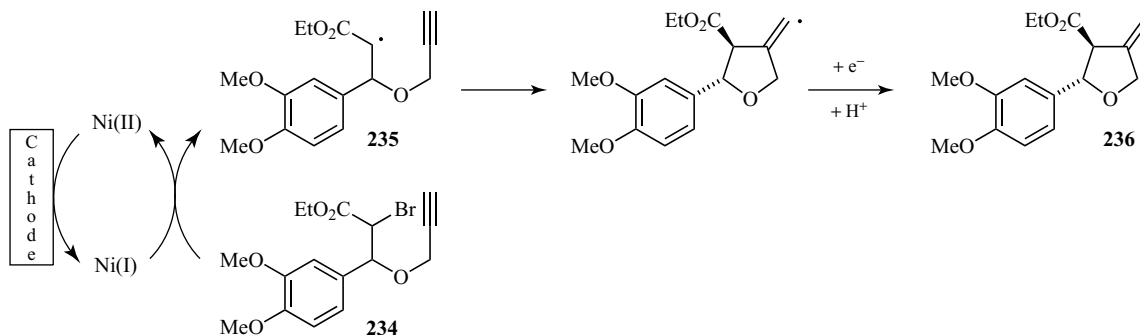
3.2 Nickel-Mediated Reduction of Alkylhalides

Another type of functional group that is well suited for electrochemical reductions under mild conditions are alkylbromide or alkyl iodide derivatives. Being adjacent to ester functionalities, the radical anions such as **235** are stabilized and lead to cyclization reactions with unsaturated groups along the chain (Scheme 70). The electrochemical reduction of such starting materials (e.g., **234**) can be performed directly at the cathode surface with only

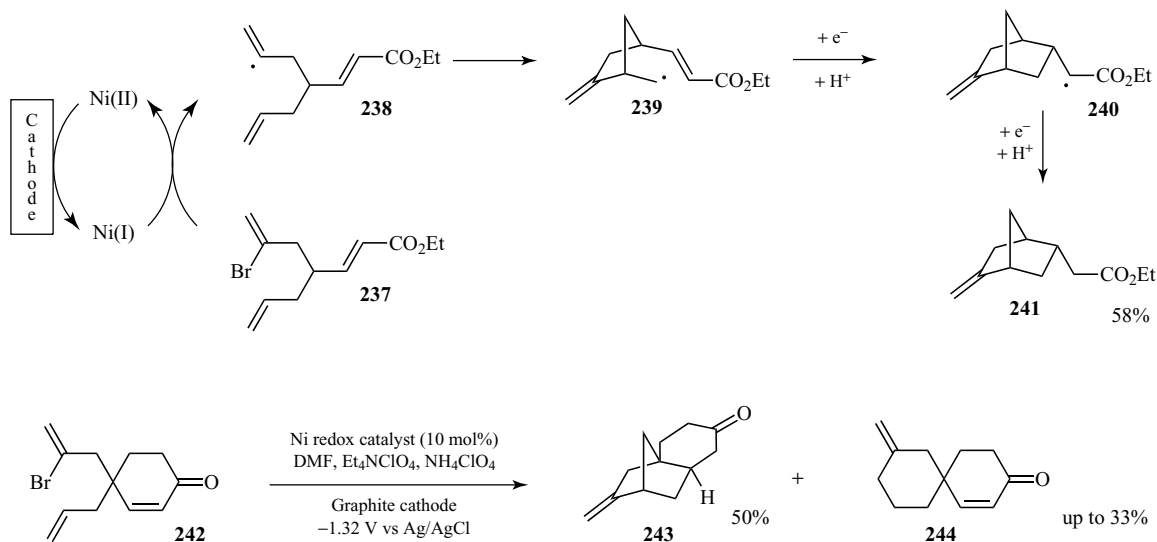
moderate success,¹²¹ or indirectly utilizing nickel complexes acting as mediators.^{122–125} In these latter cases, the desired cyclization product **236** could be obtained in up to quantitative yield, depending on the nickel complex used as the redox catalyst or the substituents present in the starting material.

Consecutive tandem cyclizations have been described by Toyota for the synthesis of norbornene-type structures utilizing vinylbromides such as **237** as starting material under nickel redox catalysis (Scheme 71).¹²⁶ The tandem cyclization reaction via intermediates **238/239** and **240** led predominantly to the endo-substituted norbornene product **241** in moderate yield. Alongside the norbornene products (**243**) formed from bisallyl-modified cyclic enones (**242**), spiro-bicyclic products such as **244** could also be obtained in moderate yield.

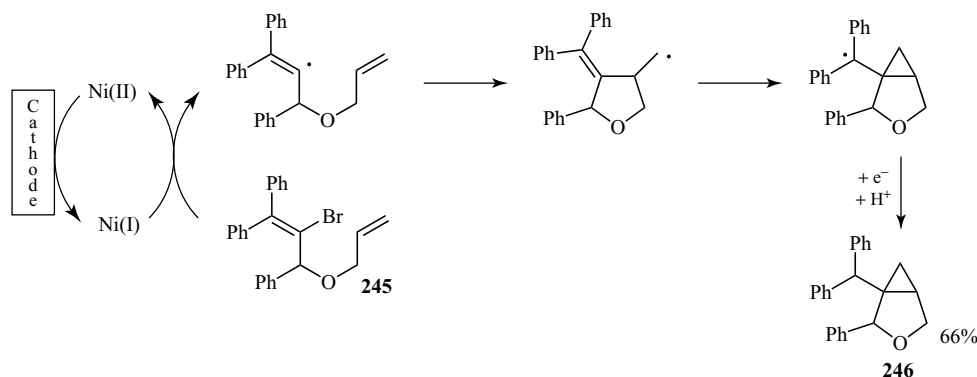
On the other hand, when additional double bonds were not present as in **245**, the formation of bicyclic compounds such as **246** via a tandem cyclization reaction sequence initiated by the reductive carbon–bromine bond cleavage was observed (Scheme 72).¹²⁷ In these cases, the Thorpe–Ingold effect seems to have promoted the cyclization; only the appropriately substituted carbocycles or furan- and pyrrolidine-derivatives were investigated.



Scheme 70 Mechanism of the indirect electrochemical nickel-mediated reductive cyclization of a halide-bearing alkyne.



Scheme 71 Mechanism of the indirect electrochemical nickel-mediated reductive tandem cyclization of a halide-bearing polyene.



Scheme 72 Mechanism of the indirect electrochemical nickel-mediated cyclopropane formation from a halide-bearing alkene.

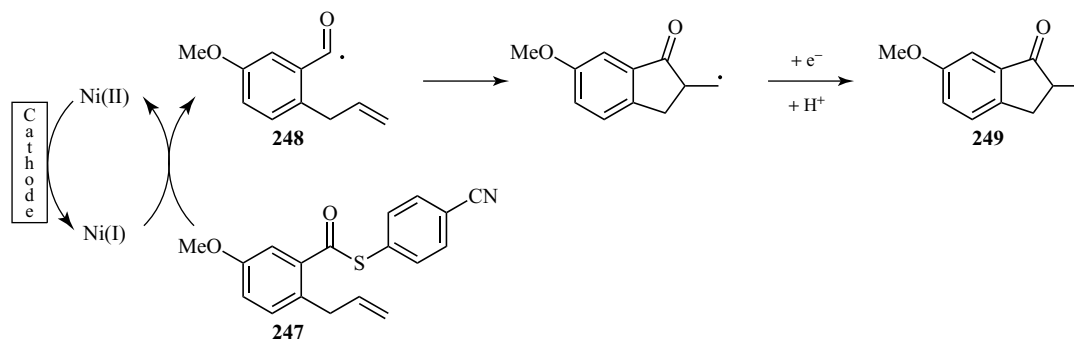
Nickel catalysts were also used for the cleavage of the carbon–sulfur bond in thioesters, as was described by Ozaki. In these cases, the thioester functionality in **247** is easily cleaved under reductive conditions. Interestingly, this procedure can be used for the generation of the sulfur-centered radical for the synthesis of sulfur-containing heterocycles¹²⁸ as well as for the generation of acyl radicals (**248**) as shown in Scheme 73. In the latter case, the acyl radical **248** led to the formation of the corresponding ketones **249** upon intramolecular addition to a double bond and further reduction and protonation.^{129,130}

In this context, the further reduction of the sulfur-centered radical to the thiolate anion was

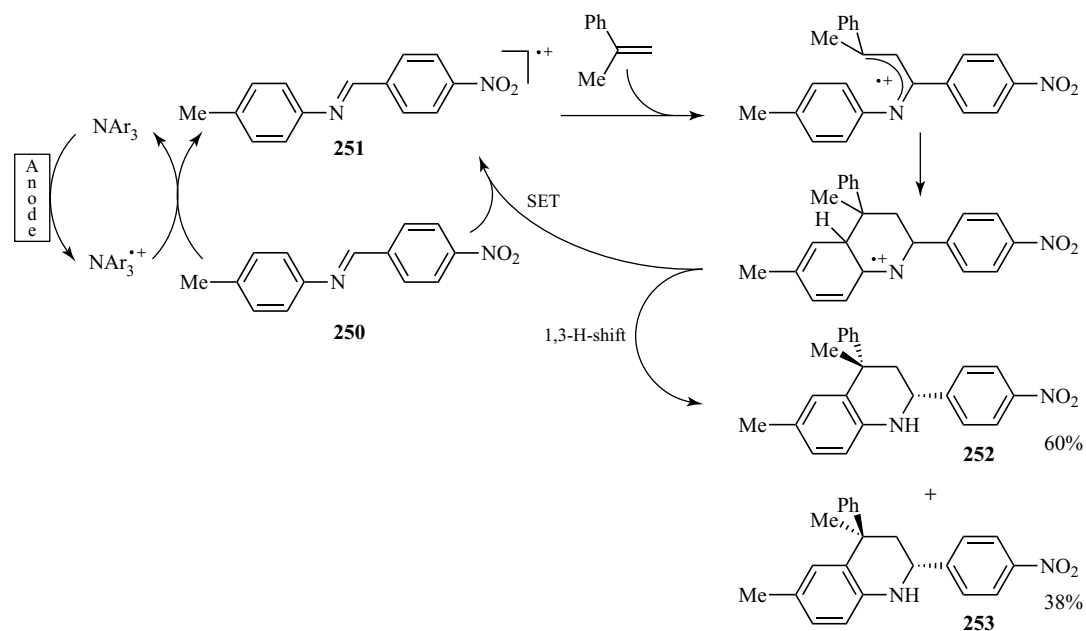
utilized by Ozaki for the nucleophilic ring-opening reaction of epoxides to generate 5,7-membered bicyclic sulfur-containing heterocycles in an intramolecular fashion.¹³¹

Although the application of organic electron-transfer reagents of the triarylamine type is an oxidative indirect electrochemical-initiated reaction, the methodology fits well into the context of indirect electrochemical reactions. Accordingly, triarylamines can be utilized for the electron-transfer-initiated Povarov reaction of aromatic imines with styrene derivatives and dihydrofuran via radical cation intermediates of type **251** (Scheme 74).¹³²

The reaction is very dependent on the redox potentials of the starting material **250** and the



Scheme 73 Mechanism of the indirect electrochemical nickel-mediated thioester cleavage for the synthesis of a ketone.



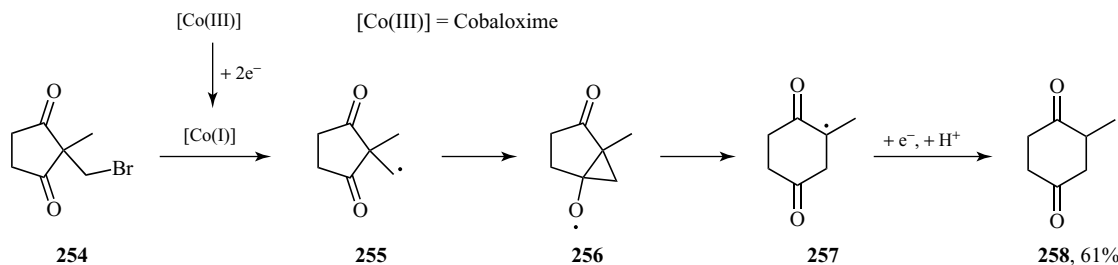
Scheme 74 Mechanism of the indirect electrochemical triarylamine-mediated, oxidatively induced Povarov cyclization.

styrene derivative applied. The reaction takes place only when the oxidation potential of the dienophile is appreciably lower than that of the hetero-diene **250**. Nevertheless, when the redox potentials are well chosen, the *cis* product **252** and the *trans*-configured product **253** are formed in excellent combined yield.

Inokuchi reported a cobalt-mediated method leading to cyclohexane-1,4-diones (**258**) in moderate to acceptable yields from cyclopentane-1,3-diones (**254**).¹³³ Cobaloxime was used as the cobalt source, and the electrochemical generation of a cobalt(I) species permitted the abstraction of

bromine from the substrate **254** leading to the primary radical **255** (Scheme 75). The ring-expanded cyclohexane-1,4-dione **258** is thought to result from a formal 1,2-acyl shift (**255** to **257**) via cyclopropane **256** and subsequent reduction to an enolate and protonation.

A further cobalt-mediated transformation of styrene to cyclopropyl benzene has been presented.¹³⁴ An electrochemical reduction of vitamin B₁₂ (a naturally occurring cobalt–corrin complex) was carried out to generate the reactive Co(I) complex. This reacts with DCM, leading to the chloromethyl radical, which adds to styrene. The benzylic



Scheme 75 Cobalt-mediated ring expansion of cyclopentane-1,3-diones.

radical thus generated is postulated to be further reduced, and the resulting anion should attack the chlorine-bearing carbon intramolecularly. The desired product cyclopropyl benzene was obtained in quantitative yields. No other substrates were examined, but the work does however hint at the tantalizing prospect of combining biologically derived or inspired molecules with synthetic electrochemistry.

3.3 Coupling Reactions Initiated by Reduction of Ketones

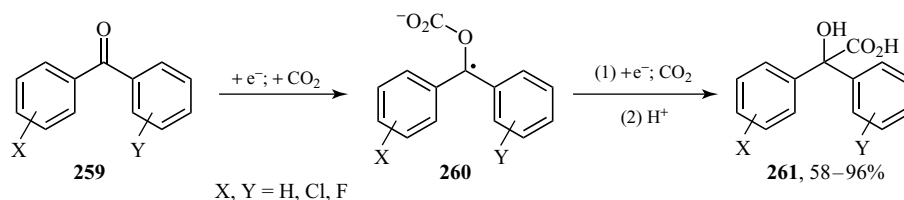
Radical anions generated via cathodic reduction processes are also viable synthetic intermediates. Gennaro and coworkers examined the reactions of radical anions **260** derived from the benzophenone and its halogenated derivatives **259** with CO_2 to afford α -hydroxy carboxylic acids such as **261** (Scheme 76).¹³⁵

Yields of the target α -hydroxy carboxylic acids were generally good to excellent; only in two cases did the yield fall below 80%. The main focus was however on the elucidation of the mechanistic aspects of this transformations. The author's proposed mechanism is outlined in Scheme 76. The reaction is initiated by the reduction of the ketone

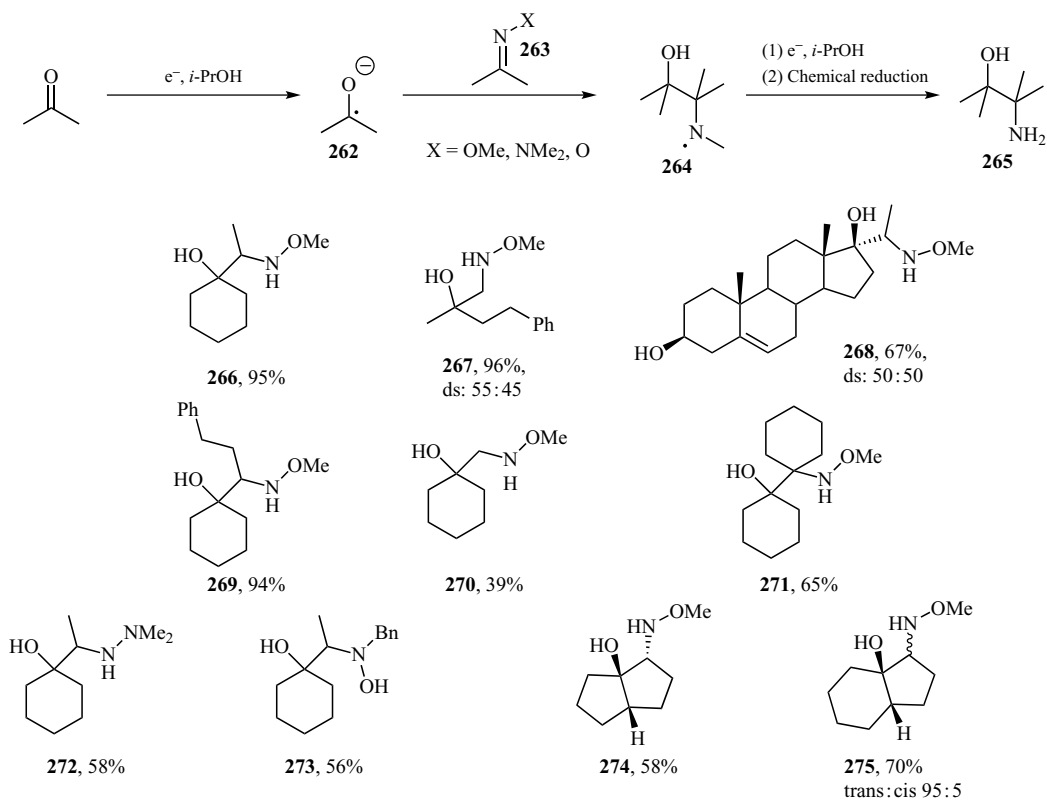
259 to the respective ketyl anion radicals, which capture CO_2 , leading to formation of the carbonate **260**. A further reduction step leads to a carbanionic intermediate, which itself nucleophilically attacks CO_2 giving a carbonate/carboxylate intermediate that is transformed to the final α -hydroxy carboxylic acid **261** after acid workup freeing the alcohol functionality by hydrolysis of the carbonate moiety. The key to obtaining high yields, as reported, is deemed to be the presence of CO_2 , as the intermediate ketyl radical anions suffer fragmentation of the C–X/Y bonds, precluding the formation of halogenated α -hydroxy carboxylic acids of type **261**.

A relatively early report of the reductive coupling of ketones and imine-type compounds was provided by Shono *et al.*¹³⁶ Under cathodic conditions, the ketone was reduced to a ketyl radical anion (**262**) which then reacted with the imine derivative (oximes, hydrazones, and nitrones are reported as viable reaction partners) to form the α -amino alcohol compound after chemical reduction (Scheme 77). A wide variety of ketones and nitrogen-containing compounds were reacted, and some examples are presented in Scheme 77 (**266–275**).

Cyclic and acyclic ketones and oximes are suitable substrates for this conversion, with yields



Scheme 76 Reactions of halogenated benzophenones with CO_2 under reductive conditions.



Scheme 77 Reductive coupling of ketones with oximes, hydrazones, and nitrones.

generally in the good to excellent range (see compounds **266**, **267**, **269–271**). More complex ketones also react satisfactorily, as shown by the reaction of a steroidal ketone leading to **268**. Hydrazone and nitron derivatives also lead to the respective β -amino alcohol precursors **272** and **273**, although the yields are lower than in the reactions with the oxime compounds. Intramolecular cyclizations are also amenable to this methodology, as exemplified by **275**. Yields and selectivities for the cyclizations are satisfactory to good.

Initial efforts have been reported that combine many of the optimization parameters specific to electrochemical systems, thus enabling new synergistic possibilities of reaction activation. An interesting application of triple activation was reported by Compton, who applied photoactivation, ultrasound emulsification, and electrochemistry to permit a reaction previously not readily attainable.¹³⁷

3.4 Defunctionalization

Defunctionalization of aryl and alkyl halides has been reported by several groups with two broad trends being recognizable: direct defunctionalization through direct electron transfer and subsequent C–Hal bond cleavage; or activation of transition metals or complexes thereof, which then carry out the defunctionalization chemistry. Both the direct defunctionalization at various electrode materials^{138–140} and the transition-metal-mediated defunctionalization have been examined from a primarily mechanistic viewpoint, but no particular effort with a methodological/synthetic focus has been reported.^{141–144}

4 CONCLUSIONS

The generation of neutral as well as charged radical species can be performed by electrochemical

methods, as shown by many applications in the past and present. The usefulness of electrochemistry for the initiation of relevant organic transformations has been demonstrated in basic transformations such as the formation of carbon–carbon bonds as well as the formation and the cleavage of carbon–heteroatom bonds.

The use of the anode and cathode as mass-free redox reagents will always be of considerable interest in terms of effectiveness and environmental compatibility. Nevertheless, electrochemical methods are still considered as complicated and difficult to master. The examples outlined in this article illustrate that the allocation of time and resources required initially is not futile, as the pay off is most rewarding.

While fundamental questions are still being addressed, evermore sophisticated applications are being and have been developed and applied to the selective activation of functional groups in increasingly complex starting materials. The fact that research groups are willing to apply electrochemical redox processes in the synthesis of complex molecules and do so with success is a remarkable confirmation of the utility of these transformations and a sign of how far this field has developed.

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Radical Chemistry by Using Flow Microreactor Technology

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1 INTRODUCTION

Since the nineteenth century, the glass flask (batch reactor) has been a familiar tool used by chemists to carry out chemical reactions. Radical reactions, which generally require heat and/or light, are no exception. However, rapidly evolving microreaction technology based on tiny microchannels, typically tens to hundreds of micrometers wide and deep, has attracted increased interest because of its high potential as a reaction apparatus ideal for chemical reactions.^{1–11} A microreaction system allows the chemical reactions to take place in a very narrow space. However, when coupled with a continuous flow system, it can serve as a production tool for synthetic organic chemistry and even for the chemical manufacturing industry. The primary advantage of such a system over conventional batch reactors is the very large surface-to-volume ratios for the microchannels. As illustrated in Figure 1, tiny microchannels allow not only efficient mixing of substrates and reagents but also very rapid heat, light, and mass transfer through the walls, which potentially affects the time, yield, and selectivity of the reactions (Figure 1). In this article, the focus is on the recent advances in radical reactions using microreaction technology, with an emphasis on the ways chemical devices can contribute to better results in ordinary synthetic radical reactions.¹²

2 THERMALLY INDUCED RADICAL REACTION

Of the wide variety of radical reactions, group 14 metal hydride-mediated radical reactions are the most widely used in organic synthesis (see **Silanes as Reducing Reagents in Radical Chemistry and Tin Hydrides and Functional Group Transformations**).^{13,14} The typical reaction time found in the literature for tributyltin hydride-mediated reactions in a batch flask reaction ranges from 10 minutes to hours. Ryu and coworkers examined the tributyltin hydride-mediated radical reaction of organic halides using a stainless steel microflow reactor.¹⁵ They found that the superior thermal efficiency inherent in tiny channels allowed for the rapid execution of the tin hydride-mediated radical reduction of bromoalkanes in less than 5 minutes. Importantly, they pointed out that 2,2'-azobisisobutyronitrile (AIBN), a slowly decomposing initiator, which is frequently used in batch reactions, is not an ideal initiator in a microflow reactor, when shorter reaction time is intended. Indeed, on using radical initiators that decompose more quickly, such as V-65 and V-70, the reductions took place within 1 minute to give the reduced product in high yields (Scheme 1).

Ryu and coworkers applied the high-speed radical reaction to the gram-scale synthesis of a

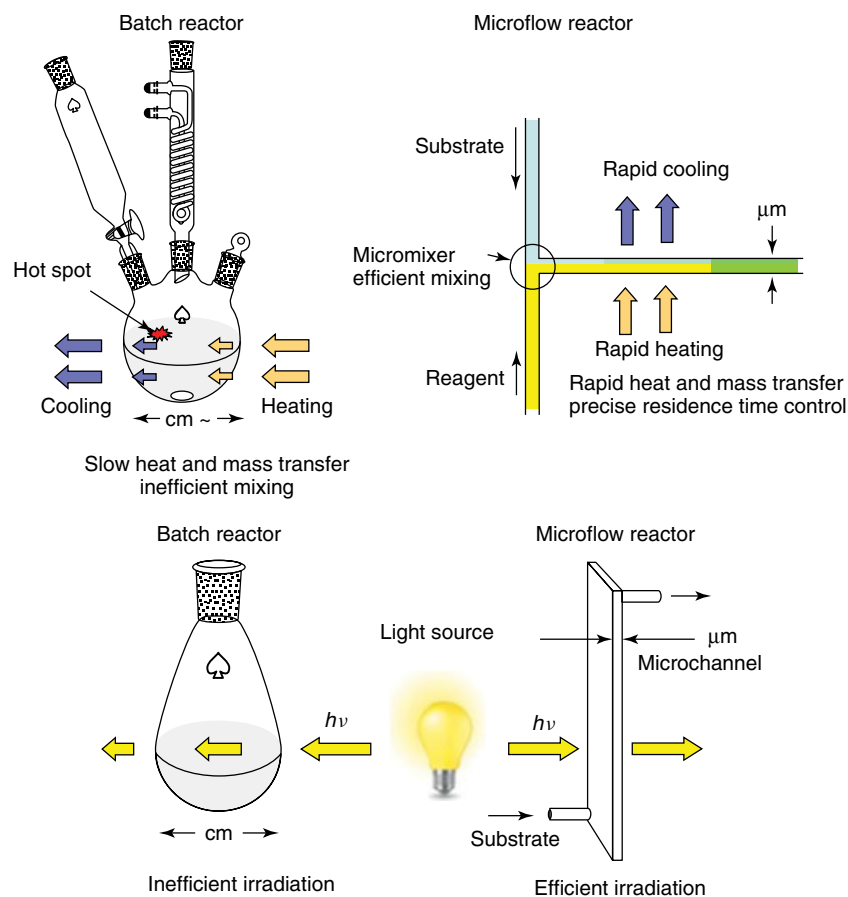


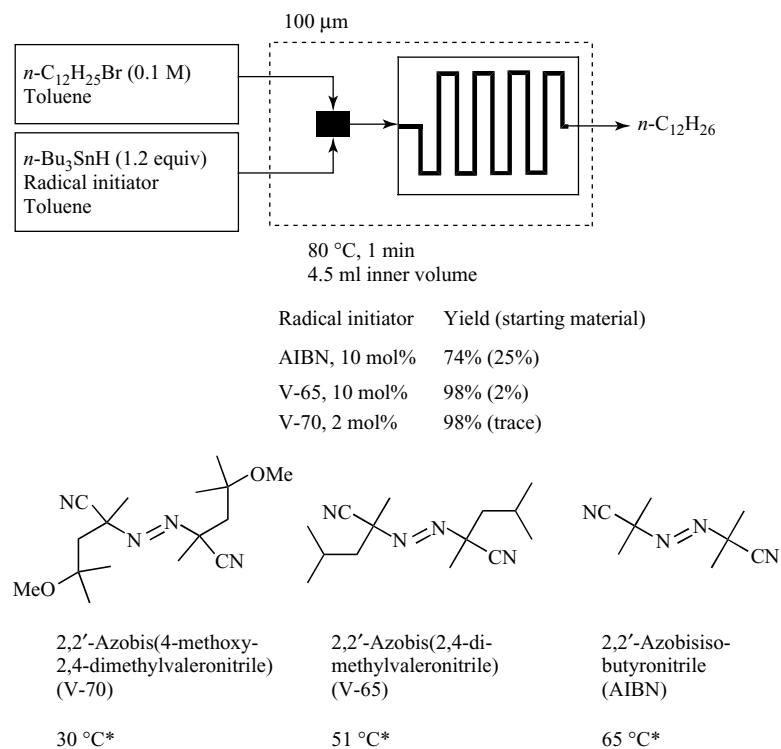
Figure 1 Thermal- and photoreactions using batch and microflow reactors.

tetrahydrofuran (THF) derivative,¹⁶ which is a key intermediate for the synthesis of furofuran lignans, using a microflow system consisting of two micromixers (MiChS type- α) and a stainless steel tube reactor connected serially (Scheme 2).¹⁵ Radical cyclization took place with 1-minute residence time to give the desired methylene tetrahydrofuran. Continuous operation for 185 minutes gave 7.6 g of THF derivative without any problem (Scheme 2).

Seeberger and coworkers reported the tris(trimethylsilyl)silane (TTMSS)-mediated radical reduction¹⁴ of alkyl halides and alcohol-derived thiocarbonyl derivatives (Barton–McCombie deoxygenations)¹⁷ using a Syrris glass microreactor with a 1.0-ml heated retention unit connected with a back pressure regulator (BPR), which enabled the reaction to occur at a temperature higher than the

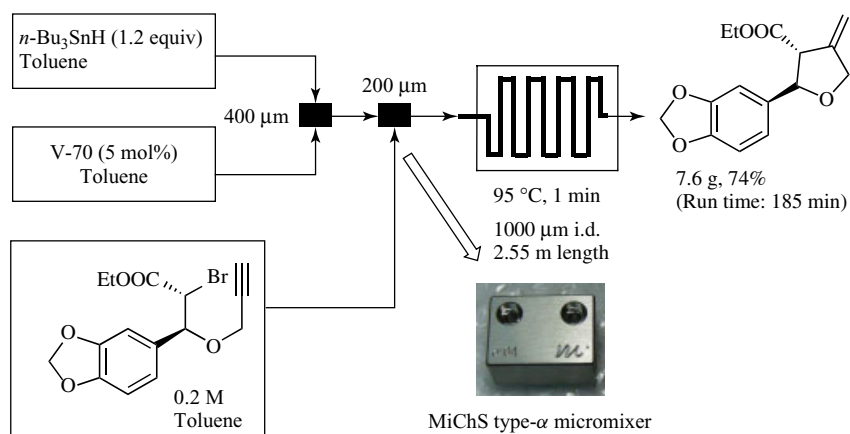
boiling point of a solvent.¹⁸ The BPR also works to suppress undesirable plug flow caused by N_2 generated from the radical initiator. The deoxygenation of a xanthate derived from D-galactose proceeded to give 6-deoxy-D-galactose in high yield with a 5-minute residence time (Scheme 3). They also reported that the hydrosilylation of terminal alkynes¹⁹ was faster for a microflow process. For example, a hydrosilylation reaction using the microreactor proceeded with a 5-minute residence time to give vinylsilane in good yields (Scheme 3).

Kim and coworkers developed monolithic and flexible polyimide (PI) film microreactors, which can be easily fabricated by photoablating a PI film.²⁰ The PI film microreactors are durable for many organic solvents, such as toluene, *N,N*-dimethylformamide (DMF), and



*Ten hours half-life decomposition temperature

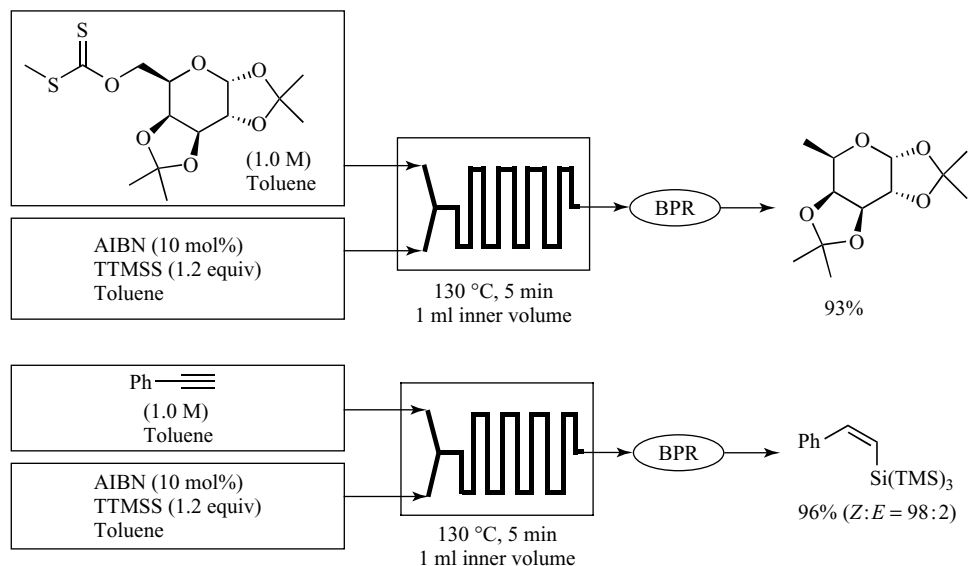
Scheme 1 Tributyltin hydride-mediated radical reduction.



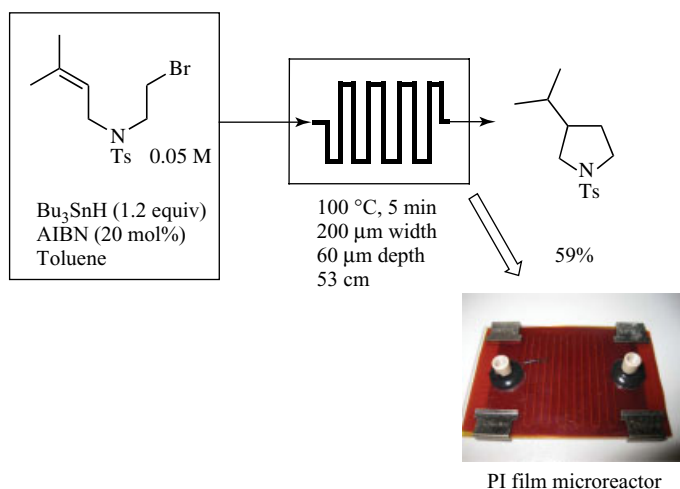
Scheme 2 Gram-scale synthesis of a key intermediate for the synthesis of furofuran lignans.

dimethyl sulfoxide (DMSO), highly acidic conditions (2 N H_2SO_4), and reasonably high temperatures (up to 100 °C). Tributyltin hydride-mediated radical reduction and radical cyclization proceeded smoothly

with the use of a PI film reactor. In the example shown in Scheme 4, the radical cyclization product was obtained in 59% yield with 5-minute residence time at 100 °C (Scheme 4).



Scheme 3 TTMSS-mediated Barton–McCombie deoxygenation and hydrosilylation of terminal alkynes.



Scheme 4 Tributyltin hydride-mediated radical cyclization using PI-film microreactor.

Microreactor technology can be employed for gas–liquid biphasic reactions, which include radical carbonylation reactions requiring high CO gas pressure.^{21–23} Ryu and coworkers reported radical carbonylation of alkyl halides in a microflow system that is durable under pressurized carbon monoxide gas.²⁴ The microflow system consisting of a micromixer and a tube reactor, both made of stainless steel, was employed. The system was connected to a BPR to regulate and maintain

the reactor system under gas pressure. Carbon monoxide was fed into a micromixer in a controlled manner through a mass flow controller and mixed with a solution containing a substrate, a radical initiator, and a radical mediator, which was fed by a pressure-durable syringe pump (Figures 2 and 3). Using this gas/liquid flow system, radical formylation of alkyl halides proceeded well to give aldehydes in good yields (Scheme 5). Tributyltin hydride-mediated cascade carbonylation reactions

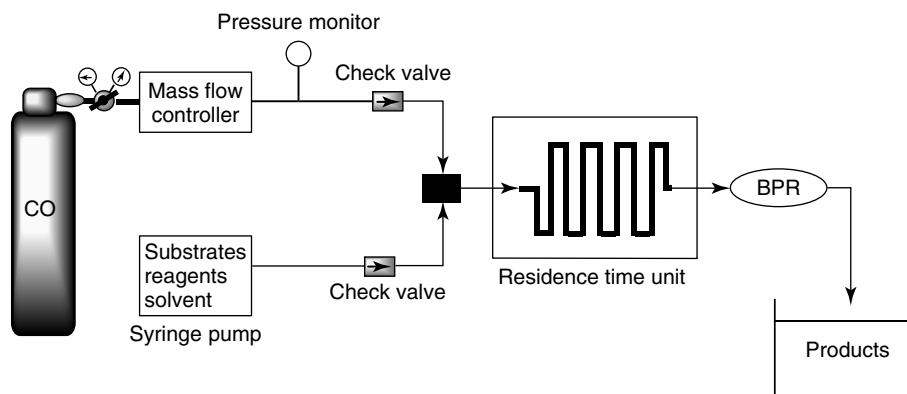


Figure 2 Microflow system available for radical carbonylation using pressurized CO.



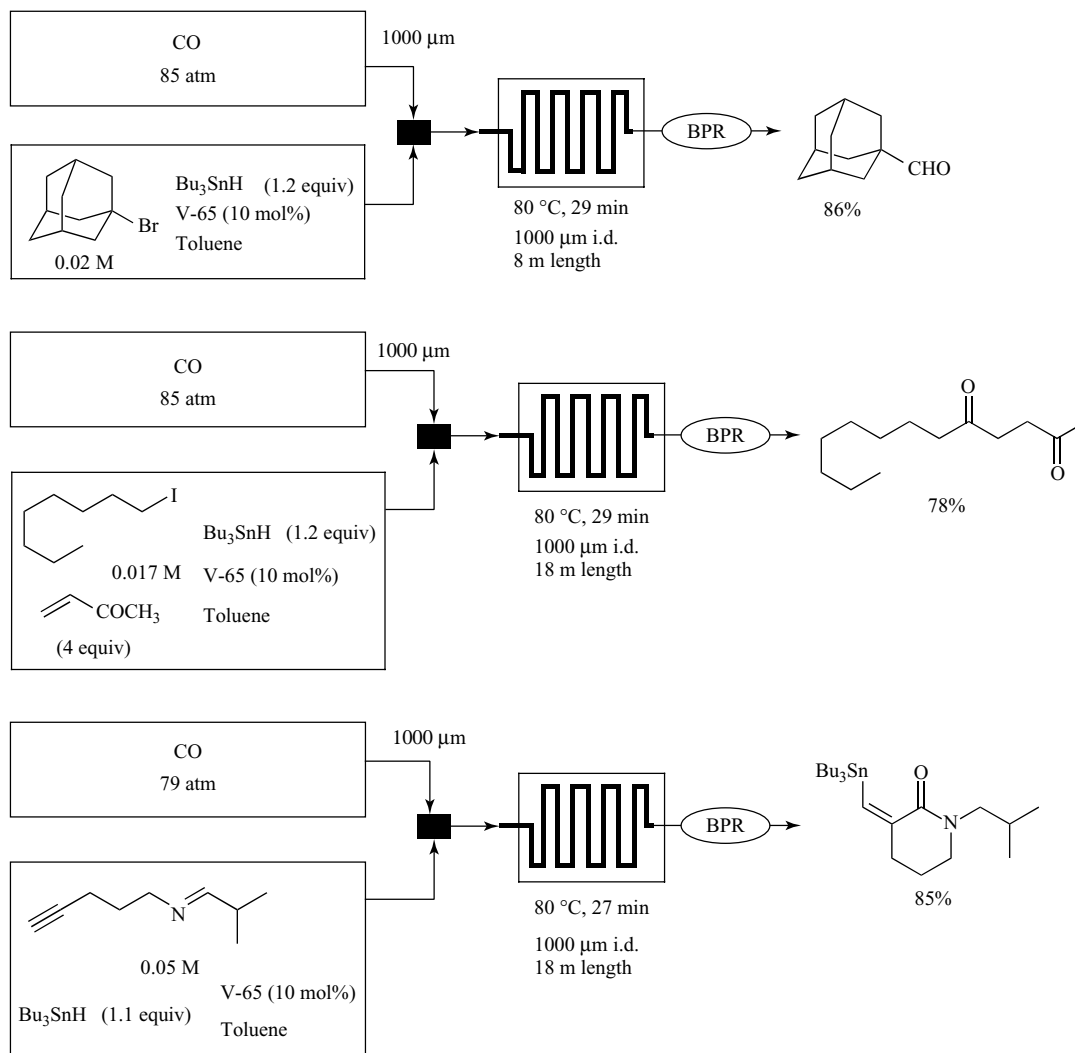
Figure 3 Mass flow control unit for carbonylation under pressurized conditions.

leading to unsymmetrical ketones²⁵ and lactams^{26,27} were also carried out successfully using a similar microflow system.

Studer and coworkers reported on the addition of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-malonate to alkenes under heated conditions using a conventional batch reactor.^{28,29} They found that microwave irradiation effectively accelerated this thermally induced radical reaction.³⁰ However, the formation of an undesirable decarboxylation product, formed by further thermal decomposition, was not suppressed in either batch method. The Studer group and the Ryu group jointly circumvented such a side-reaction issue by the use of a microflow system.³¹ In the microflow system, a carboaminoxylation product was obtained in high yield without suffering from the formation of a

decarboxylated product, which was supposed to be derived by the thermally induced second reaction (Scheme 6). An improved product selectivity may result from the digital-like on/off switching of heating and cooling available in a microflow reaction.

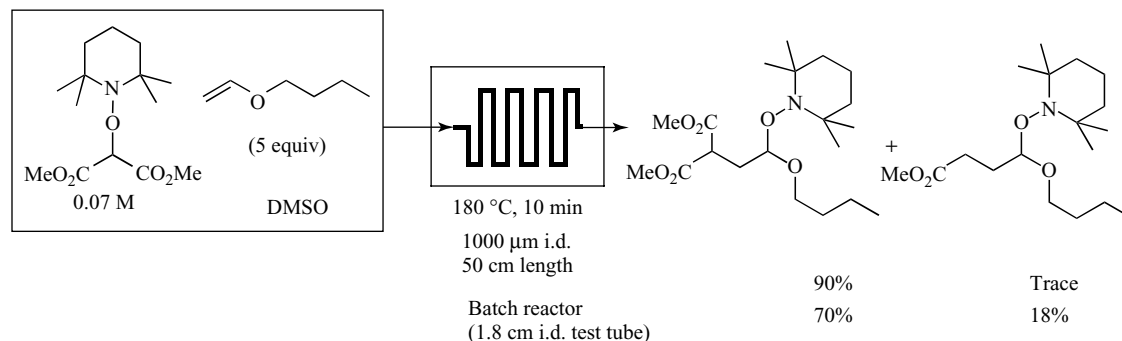
Free radical polymerization is a method used widely to obtain polymers on an industrial scale, irrespective of the nature of radical polymerization (noncontrolled or living, see **Fundamentals of Controlled/Living Radical Polymerization and Radical Polymerization in Industry**). Free radical polymerization is potentially exothermic because of the fact that a σ -bond is formed at the cost of a π -bond, and, therefore, precise temperature control is required to obtain controlled polymers. Iwasaki and Yoshida³² reported free radical polymerization of butyl acrylate, benzyl methacrylate, methyl methacrylate, vinyl benzoate, and styrene using AIBN as a radical initiator. They observed that during the polymerization of butyl acrylate, benzyl methacrylate, and methyl methacrylate using microreactors, the polydispersity index (PDI, M_w/M_n) was much smaller than that obtained with a conventional macro batch reactor (Scheme 7), while no appreciable effect of the microreactor on PDI was observed for the polymerization of vinyl benzoate and styrene. Yoshida and coworkers also reported an example of large-scale production for poly(methyl methacrylate) (PMMA). Using microtube reactors of varied inner diameters (i.d. = 500 μ m, 1950 mm $\times$ 8 + i.d. = 500 μ m, 1950 mm $\times$ 8 + i.d. = 1000 μ m, 1950 mm $\times$ 8, total reactor volume = 18.4 ml), 4 kg of PMMA was synthesized by continuous operation for 1 week.³³



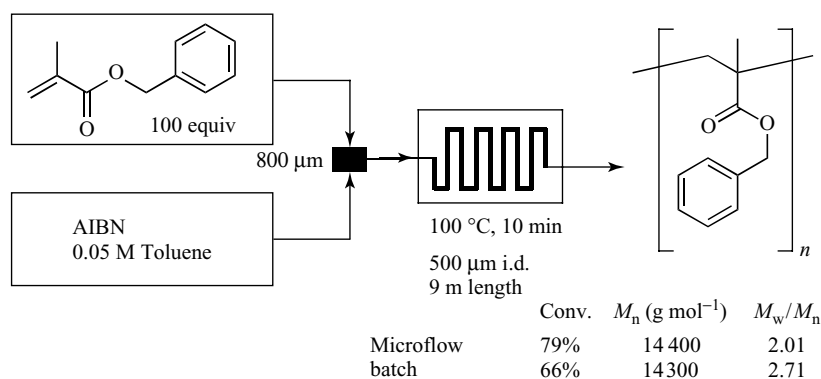
Scheme 5 Radical carbonylation in a microflow system.

Atom transfer radical polymerization (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**) of 2-hydroxypropyl methacrylate using a microreactor with $500\text{ }\mu\text{m} \times 600\text{ }\mu\text{m}$ microchannel was recently reported by Beers and coauthors.³⁴ Polymerization proceeded with 92% conversion and 1.21 PDI with a 2-hour residence time (Scheme 8). They also reported the synthesis of block copolymer poly(ethylene oxide)-*block*-2-hydroxypropyl methacrylate using bromo-substituted poly(ethylene oxide) as an initiator.³⁵

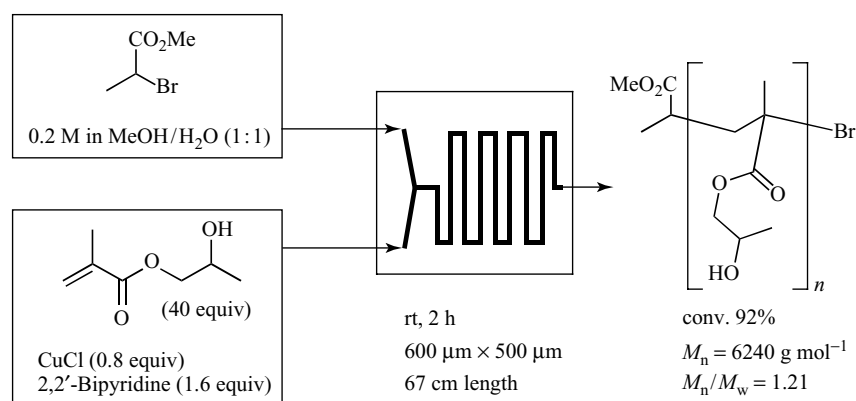
Serra and coworkers reported nitroxide-mediated radical polymerization (see **Nitroxide-Mediated Polymerization and its Applications**) of styrene and *n*-butyl acrylate using a microflow system.³⁶ Using 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane as a radical initiator, a polymer with 1.20 PDI was obtained in 45% conversion with 100-minute residence time at $140\text{ }^{\circ}\text{C}$ (Scheme 9). The result was comparable to that obtained with a batch reactor. They also reported the synthesis of a poly(*n*-butyl acrylate)-*block*-poly(styrene) copolymer using serially connected microreactors.³⁷



Scheme 6 Radical carboaminoxilation of alkenes in a microflow system.



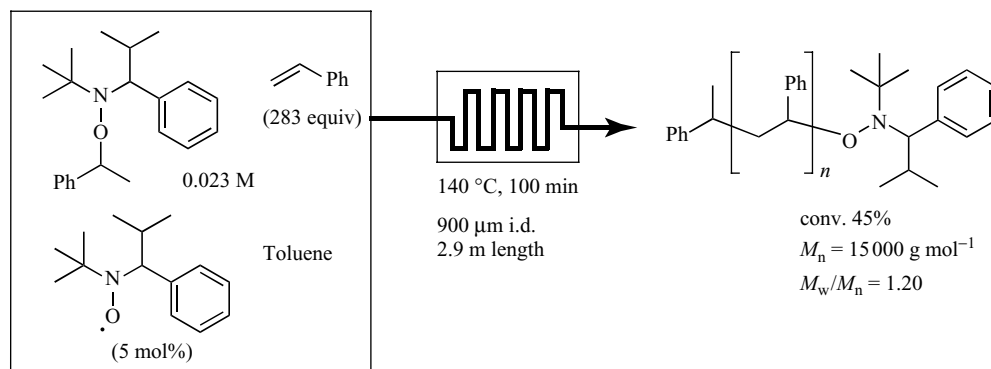
Scheme 7 Radical polymerization of benzyl methacrylate in a microflow system.



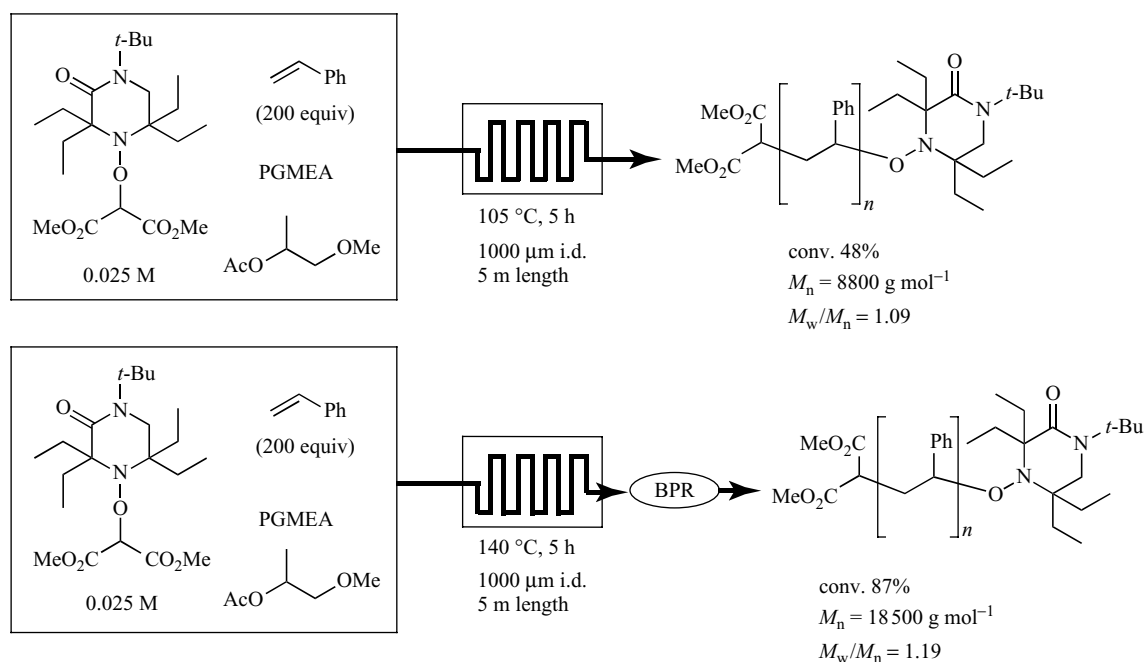
Scheme 8 Atom transfer radical polymerization in a microflow system.

The nitroxide-mediated living radical polymerization of styrene, which used a microflow reactor, was studied jointly by Studer and Ryu groups. They used nitroxyl-malonate as an initiator and propylene glycol-1-monomethyl ether-2-acetate (PGMEA) as a solvent to prevent the clogging

in the microchannels (Scheme 10). Polystyrene (PS) with 1.09 PDI was obtained in 48% conversion with a 5-hour residence time at 105 °C (Scheme 10).³⁸ Reaction at higher temperature using BPR gave PS with 87% conversion and 1.19 PDI.



Scheme 9 Nitroxide-mediated radical polymerization in a microflow system.

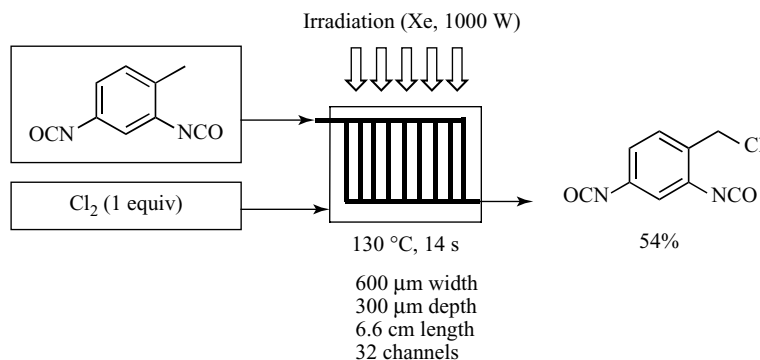


Scheme 10 Radical polymerization using nitroxyl-malonate in a microflow system.

3 PHOTOINDUCED RADICAL REACTIONS

Microreactors are also useful for photochemical reactions (see **Synthetic Radical Photochemistry**), since very thin channels allow efficient photo-irradiation (Figure 1).^{39,40} Since light strength attenuates exponentially with increasing optical path length according to the Lambert–Beer law ($\log(I_0/I) = \epsilon cl$), reactions run in microflow systems would be expected to terminate in considerably short irradiation time. This has tempted

chemists to use microreactors for selective radical halogenation reactions.⁴¹ Photoinduced radical chlorination of toluene-2,4-diisocyanate using a falling-film microreactor supplied by IMM (Institut für Mikrotechnik in Mainz) with a quartz window (600- μm width, 300- μm depth, 6.6-cm length, and 32 parallel channels) and a 1000-W Xe lamp was reported by Jähnisch and coauthors.⁴² Side-chain chlorinated product 1-chloromethyl-2,4-diisocyanatobenzene was obtained in 54% yield with a 14-second residence time (Scheme 11). With

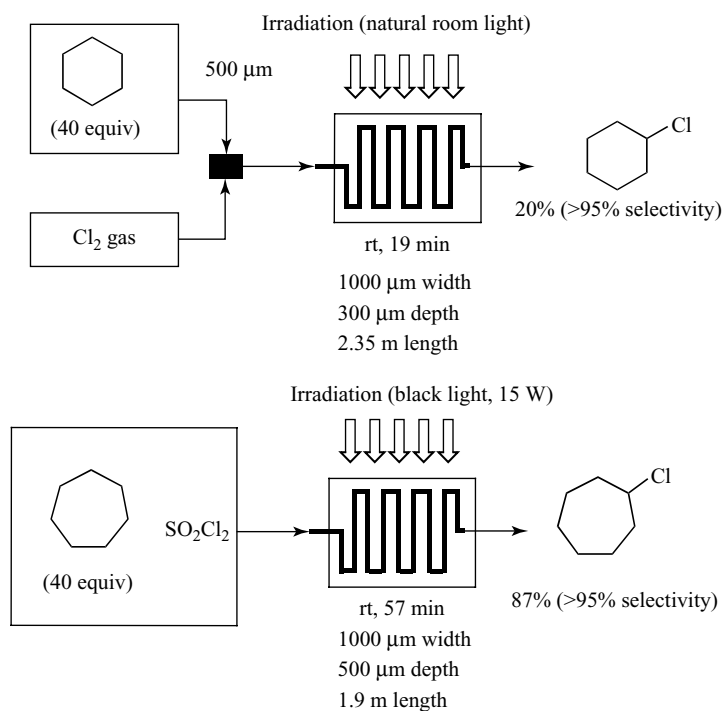


Scheme 11 Photoinduced radical chlorination using Cl_2 in a microflow system.

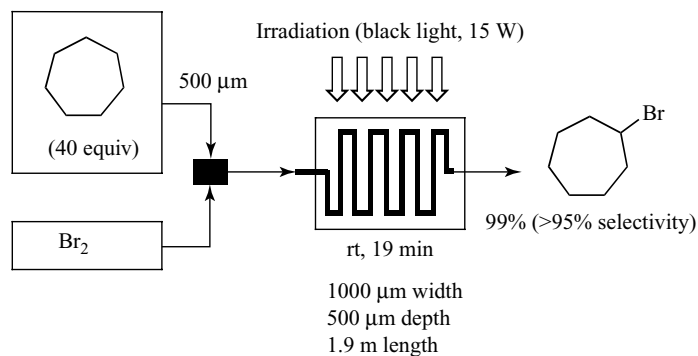
a longer residence time, the system suffered from the formation of unidentified byproducts.

The Ryu group demonstrated microflow photo-chlorination of cycloalkanes, using chlorine gas or sulfonyl chloride as a chlorination reagent.⁴³ Photo-chlorination of cyclohexane with chlorine gas was carried out using DNS (Dainippon Screen Mfg. Co. Ltd.) photo-microreactor composed of photo-etched stainless steel microchannel (1000-μm

width, 300-μm depth, and 2.35-m length) with covered Pyrex glass. On exposure to natural light, chlorocyclohexane was obtained in 20% yield with high selectivity for single chlorination (>95%; Scheme 12). Irradiation using a 15-W black light (peak wavelength: 352 nm) was effective for chlorination of cycloalkanes, especially when sulfonyl chloride was used as a chlorinating reagent.⁴³ For example, the reaction of cycloheptane



Scheme 12 Photoinduced chlorination of cycloalkanes using Cl_2 or SO_2Cl_2 as a chlorine source in a microflow system.



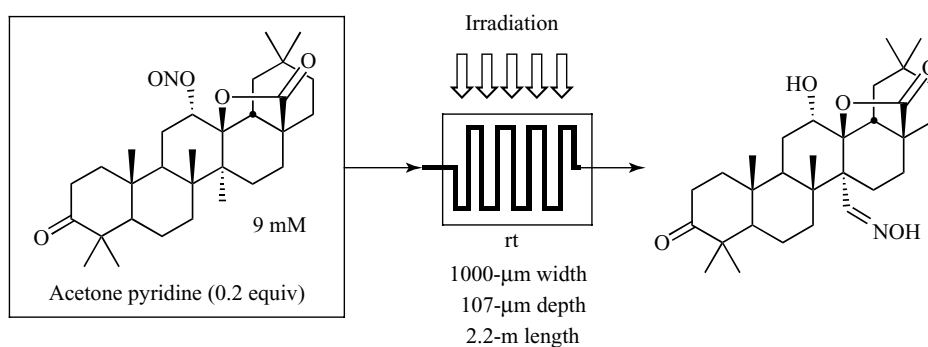
Scheme 13 Photoinduced radical bromination of cycloalkanes.

with SO_2Cl_2 using a Mikroglas Dwell Device as a photo-microreactor gave mono-chlorinated cycloheptane in 87% yield with high single selectivity (>95%; Scheme 12). The use of BPR was effective in suppressing the disordered stream because of the evolution of SO_2 gas. Photoinduced radical bromination of cycloalkanes also worked well when 15-W black light and Mikroglas photo-microreactor were used. For example, bromination of cycloheptane with Br_2 proceeded smoothly to give the mono-brominated product in almost quantitative yield (Scheme 13).⁴⁴

Ryu and coworkers also reported a photo-induced Barton reaction, using the DNS photo-microreactor.^{45,46} A key intermediate

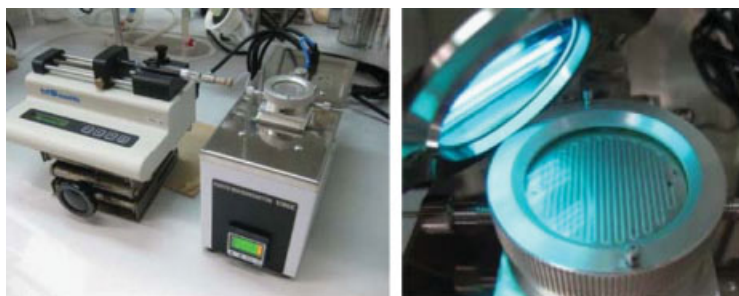
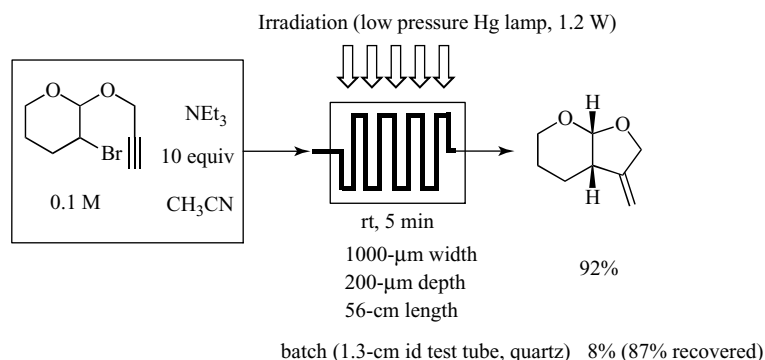
for the synthesis of myriceric acid A,⁴⁷ an endothelin receptor antagonist, was obtained using the DNS photo-microreactor. When a photo-microreactor is combined with a compact light source, such as a black light (15 W, peak wavelength: 352 nm) and a UV-LED (1.7 W, peak wavelength: 365 nm), an energy-saving photo-microreaction system is created (Scheme 14).

The photoinduced cyclization of bromoalkynes with triethylamine, originally developed by Cossy *et al.*,^{48,49} provides an attractive radical cyclization process, which does not require group 14 metal hydrides as a hydrogen source. The Ryu group investigated the microflow version of the Cossy reaction using a YMC photo-microreactor



Light source	Glass cover	Residence time (min)	Yield (%)	Wh	Yield/Wh
300 W Hg lamp	soda lime	6	56	30	1.89
15 W black light	Pyrex	12	71	3	23.7
17 W UV-LED	Pyrex	12	70	0.34	206

Scheme 14 Photoinduced Barton reaction using a photo-microreactor combined with an energy-saving, compact light source.

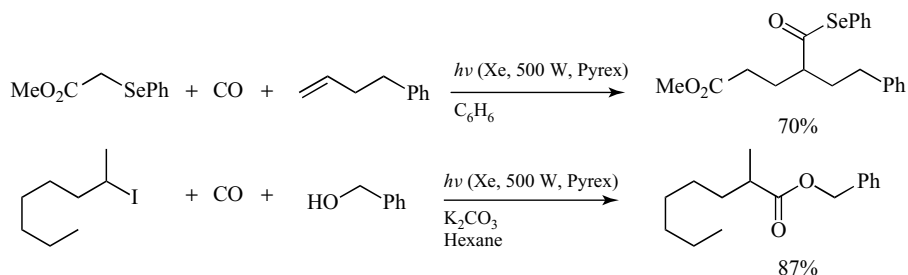


Scheme 15 Photoinduced radical cyclization using a photo-microreactor equipped with a low-pressure mercury lamp.

(KeyChem-Lumino) equipped with a 1.2-W low-pressure mercury lamp (254 nm).⁵⁰ The reaction using the microreactor system gave a cyclization product with a remarkably shortened reaction time of 5 minutes, compared with that of the batch reaction system (Scheme 15). It should be noted that there is a patent for which researchers at GlaxoSmithKline investigated a similar Cossy-type photo radical cyclization.⁵¹ Although a major part of the patent describes a batch reaction, interestingly they noted that a flow photo-reaction is also effective.

4 PHOTO-CARBONYLATION: BATCH TO STOPPED FLOW

Photoinduced atom and group transfer carbonylations provide useful methods to obtain basic carbonyl compounds, such as aliphatic carboxylic acid esters, amides, and seleno esters with incorporation of CO (Scheme 16).^{52–56} For these photoinduced radical carbonylations, a special photo-reaction device, a pressure durable stainless steel autoclave having two quartz windows for irradiation, was employed. Figure 4 shows a



Scheme 16 Photoinduced atom and group transfer radical carbonylation.



Figure 4 Taiatsu Techno's autoclave available for photo-irradiation reaction.

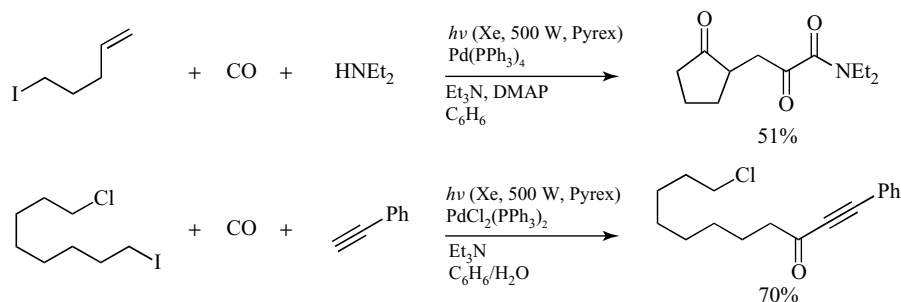
picture of Taiatsu Techno's autoclave available for photo-carbonylation, which was originally designed by Miyashita for the purpose of methane functionalization under photolysis.⁵⁷

One drawback of atom transfer carbonylation was the slow reaction with primary iodoalkanes owing to the relatively low efficiency of iodine atom transfer compared with secondary and tertiary iodoalkanes. However, the Ryu group found that the iodine atom transfer carbonylation of iodoalkanes is markedly accelerated by the addition of transition metal complexes, such as $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Mn}_2(\text{CO})_{10}$.^{58,59} This led to the development of a variety of multicomponent reactions with incorporation of CO.^{60,61} Some of the examples are shown in Scheme 17. Thus, cyclizative multiple

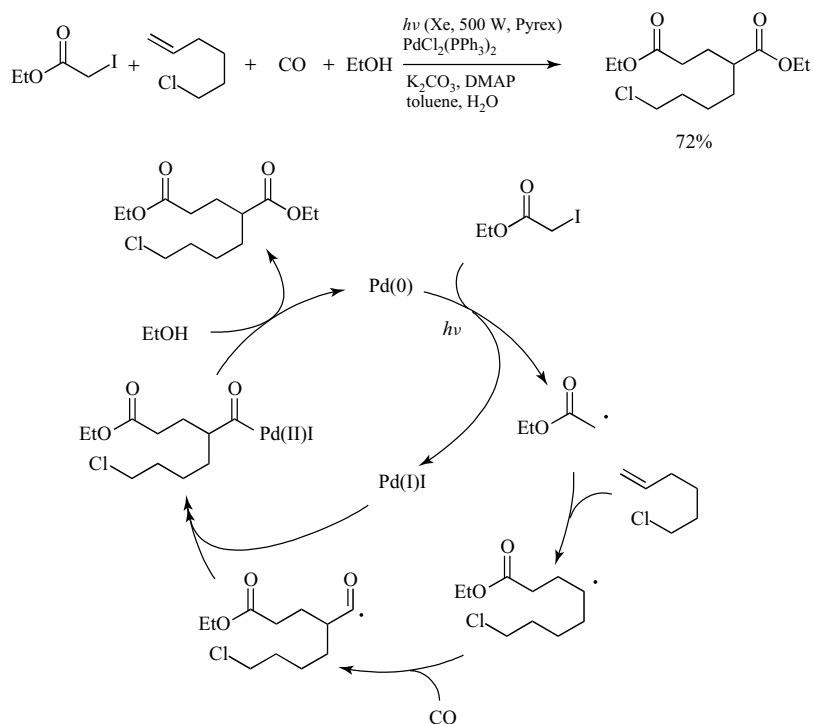
carbonylation of alkenyl iodides proceeded to give diketone amides under irradiation conditions in the presence of Pd catalyst.⁵⁸ Acetylenic ketones were obtained by the $h\nu/\text{Pd}$ -induced three-component coupling reaction of alkyl iodides, CO, and terminal alkynes.⁶⁰ Four-component coupling reaction of α -substituted iodoalkanes, alkenes, CO, and alcohols also proceeded well to give functionalized esters (Scheme 18).⁶¹ Pd is required in these cases not only for radical initiation⁶² but also for the formation of acylpalladium complexes in the end, which facilitated the total reaction schemes. Thus, radical and transition metal cooperation function well, which lead to the success of these multicomponent carbonylation reactions.

Photoinduced carbonylation has been recently extended to include efficient C–H carbonylation.²¹ Thus, photo-catalytic radical carbonylation of alkanes with electron-deficient alkenes using tetrakis(tetrabutylammonium) decatungstate as a catalyst gave unsymmetrical ketones in good yields (Scheme 19).⁶³ Here, photo-excited decatungstate abstracts hydrogen from alkanes to form alkyl radicals, which is then added to CO and electron-deficient alkenes consecutively. The reduced form of the photocatalyst ($\text{H}^+\text{W}_{10}\text{O}_{32}^{5-}$) delivers a hydrogen atom to the resulting radicals to give unsymmetrical ketones with the photocatalyst back.

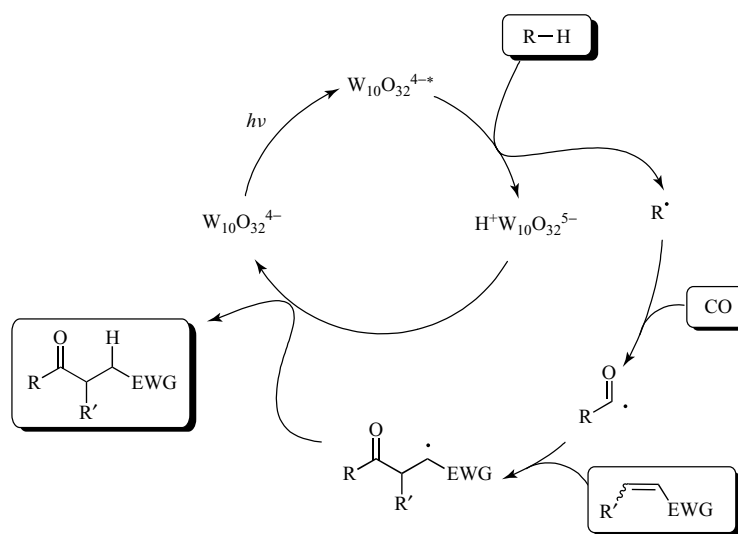
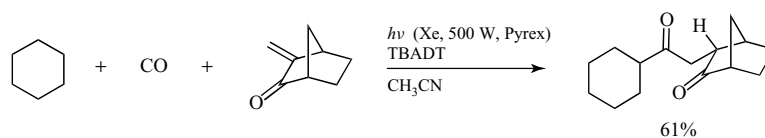
Microflow system for these photo-irradiative carbonylations is yet to be established, but the prototype of a stopped-flow reactor was examined in sample preparation for positron emission tomography (PET), for which biologically active compounds labeled with ^{11}C are widely used as tracers. Långström *et al.* applied the photo-induced atom transfer radical carbonylation to PET labeling



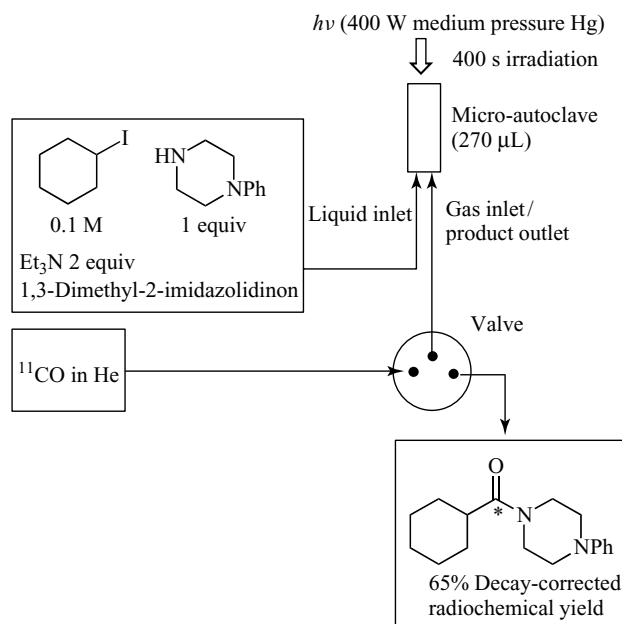
Scheme 17 Multicomponent reactions based on $h\nu/\text{metal}$ hybrid radical carbonylation.



Scheme 18 $h\nu$ /Pd-induced four-component coupling reaction and a possible mechanism.



Scheme 19 Photo-catalytic radical carbonylation of C-H bond of alkanes.



Scheme 20 Photoinduced atom transfer carbonylation using ^{11}C in a stopped flow system.

chemistry using ^{11}C carbon monoxide.⁶⁴ Since ^{11}C has a short half-life ($t_{1/2} = 20.3$ min), fast reactions are required. To realize fast reaction, they developed a special reaction system, using a micro-autoclave, and employed the stopped-flow technique. The system consists of a micro-autoclave (270 μl) equipped with a sapphire window and light source (Scheme 20). The micro-autoclave was filled with ^{11}C in helium, and then the solution of substrates was transferred to the reactor with a 35- to 40-MPa pressure (partial pressure of CO = circa 200–500 Pa). The reaction mixture was irradiated by a light source for several minutes. After the irradiation, the reaction mixture was collected in a product vial through a valve.

Using this system, ^{11}C -labeled carbonyl compounds were synthesized with high radiochemical yields. For example, the reaction of iodocyclohexane with ^{11}C and *N*-phenylpiperazine under irradiation by a 400-W medium-pressure Hg lamp for 400 seconds gave ^{11}C -labeled amide in 65% decay-corrected radiochemical yield (Scheme 20).⁶⁵ ^{11}C -labeled esters and carboxylic acids were also obtained with a similar reaction system.^{66–68} The stopped-flow reaction system is adaptable for fast tracer screening by simply changing either the iodides or the nucleophiles.

5 CONCLUSION

A wide variety of radical reactions, involving group 14 metal hydride-mediated radical reactions, radical carbonylations, radical polymerizations, and photo-induced radical reactions, can be carried out using a microreactor. Shorter reaction time, higher yield and product selectivity, and higher energy efficiency can be achieved using microreaction technology, in which contributions are made by superior thermal efficiency, efficient mixing, precise temperature and residence time control, and efficient photo-irradiation inherent to tiny reaction channels. Some examples verified that gram- to kilogram-scale production can be carried out using a microreactor. Having demonstrated the successful, selective, and efficient performance of a number of important synthetic reactions using microreactors, the new device technology will spread as a useful tool to carry out various thermally and photo-induced radical reactions.

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Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations

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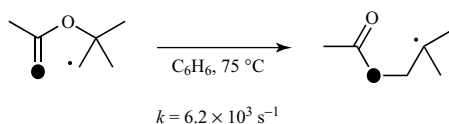
1 INTRODUCTION

In addressing the topic of radical rearrangements, one is immediately confronted by the question of definition as were previous authors faced with a similar task, most notably Beckwith and Ingold in the preparation of their outstanding 1980 opus on the subject.¹ On perusing their chapter, which was written at the dawn of the modern era of the application of radical reactions in organic synthesis and which remains pertinent and informative even today, one is struck by the breadth of the field 30 years ago when it already required 150 printed pages and 786 literature citations for adequate summary. What is equally striking is that virtually all modern classes of radical rearrangement were already known at the time, leading to the conclusion that what has transpired since has been more a revolution in the manner in which radical reactions are viewed, a major and useful part of the synthetic chemistry armory and not simply a series mechanistic curiosities, rather than any great quantum leap forward. What has become apparent since the Beckwith and Ingold chapter is that the very extensive body of thermochemical and kinetic data pertaining to radical reactions, which already stretched to two volumes at the time of Kochi's important compendium in 1973² and which has been enormously extended since, permits, perhaps more than in any other area of preparative

chemistry, the rational, informed planning of sequences of reaction steps for use in preparative chemistry. C–C bond-forming rearrangements, such as the 5-hexenyl–cyclopentylmethyl ring-closure (see **Unusual Cyclizations** and **Radical Cascade Reactions**), and its many cousins, along with C–C bond cleavage reactions such as the cyclopropylmethyl to 3-butenyl rearrangement and aryl radical migrations (neophyl type rearrangements, see **Radicals and Carbohydrates**), are covered extensively elsewhere in this encyclopedia. As such, this article focuses on rearrangements that do not involve reorganization of the basic carbon skeleton of the initial radical but are based on carbon heteroatom bond formations and cleavages and their use in setting up carbon-centered radicals for C–C bond-forming processes. In particular, the focus is on two such rearrangements: those that involve the shifting of esters and related groups and hydrogen atom migration.

2 THE 1,2-SHIFT OF ESTERS

In the early days of the application of free radicals to organic synthesis, a major selling point was the inertness of carbon-centered radicals toward many functional groups such as various carbonyl systems. This changed gradually following the independent discovery of the interaction of carbon radicals with



Scheme 1 β -Acyloxyalkyl radical rearrangement with inversion of carbonyl and carboxyl oxygens.

esters by the Surzur and Tanner groups.^{3–5} Thus, it was demonstrated, serendipitously at first, that certain β -acyloxyalkyl radicals undergo rearrangement to give the more thermodynamically stable radical (Scheme 1).

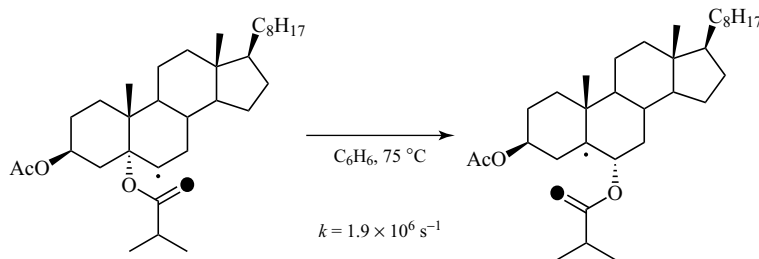
This novel rearrangement soon attracted the attention of physical organic chemists who determined rate constants and used isotopic labeling methods to demonstrate the inversion of the carbonyl and carboxyl oxygen atoms in the course of the early examples (Scheme 1).⁶ The very simple examples described at that time were found to have rate constants some 100-fold smaller than the prototypical 5-hexenyl radical cyclization, whence the early dictum regarding the inertness of radicals toward esters. Subsequent work, however, following an initial observation from the Kocovsky group,⁷ revealed that some examples of the acyloxy rearrangement are rapid and even exceed the rate of the 5-hexenyl radical cyclization (Scheme 2).^{8,9}

Moreover, the faster examples were found by labeling methods to proceed with a high degree of retention of the original carbonyl and carboxyl oxygens. Much work, experimental and computational, subsequently was conducted on the acyloxy rearrangement which culminated in the hypothesis of two parallel concerted mechanisms, the slower and more typical one involving a five-membered cyclic transition state and a faster, less common one with a three-membered cyclic transition state (Scheme 3).^{6,10}

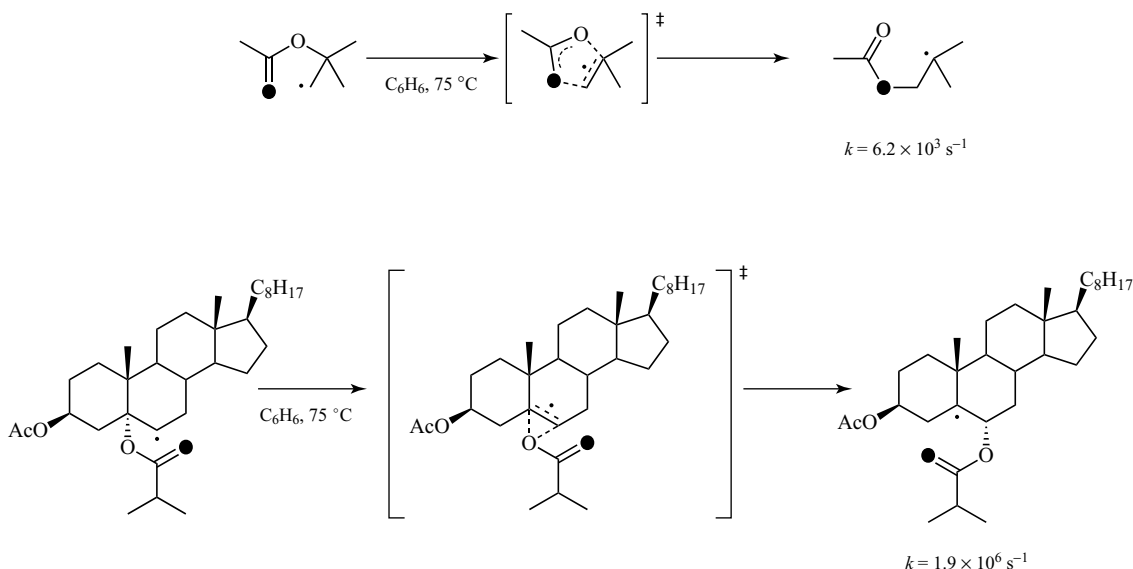
In agreement with the suggestion of Sprecher,¹¹ subsequent work by Crich, Newcomb, and their coworkers, which focused attention on the influence of polar effects on the rearrangement rate, resulted in the assignment of a mechanism involving the fragmentation of the initial radical to give an alkene radical cation/carboxyl anion pair that undergoes very rapid recombination to the product radical (Scheme 4).^{12,13}

This two-step fragmentation/recombination pathway involving the intermediacy of an alkene radical cation fits the vast majority of the experimental facts and explains, for example, why neither γ -acyloxyalkyl radicals^{3,4} nor β -acyloxy aryl radicals rearrange (Scheme 5).¹⁴ Computational work on the related acyloxyvinyl radicals concludes that such species can undergo rearrangement albeit with a significant barrier and by a fragmentation–recombination pathway.¹⁵

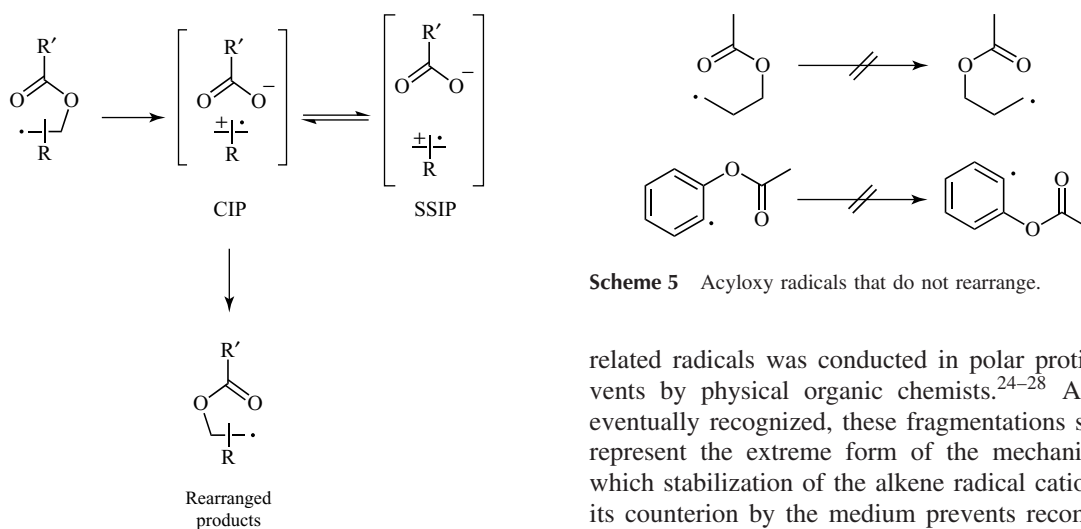
In the early 1990s, the Crich and Giese groups independently reported that phosphate esters,^{16–19} and even nitrate and sulfonate esters,²⁰ undergo a directly analogous rearrangement albeit more rapidly than the typical carboxyl shift. Isotopic and stereochemical labeling experiments revealed these more rapid rearrangements to take place predominantly with retention of the phosphoryl and phosphoryloxy oxygen atoms.^{17–19,21,22} Similar three and five-membered cyclic transition states were drawn for these rearrangements, until the later work of Crich and Newcomb revealed their polar components and even demonstrated directly for the first time the intermediacy of the alkene radical cation.¹³ At the time of writing, this fragmentation–recombination reaction involving an alkene radical cation/anion pair is considered to be general, with the tightness of the ion pair and the rate of recombination determined by the stability of both the alkene radical cation and the anion.²³ Thus, the



Scheme 2 β -Acyloxyalkyl radical rearrangement with retention of carbonyl and carboxyl oxygens.



Scheme 3 Initially proposed three- and five-membered cyclic transition states for the acyloxy migration.



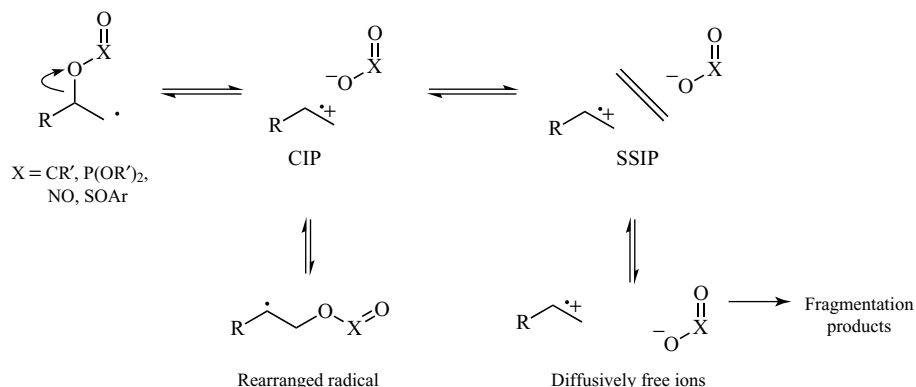
Scheme 5 Acyloxy radicals that do not rearrange.

Scheme 4 Fragmentation/recombination mechanism for the acyloxy rearrangement.

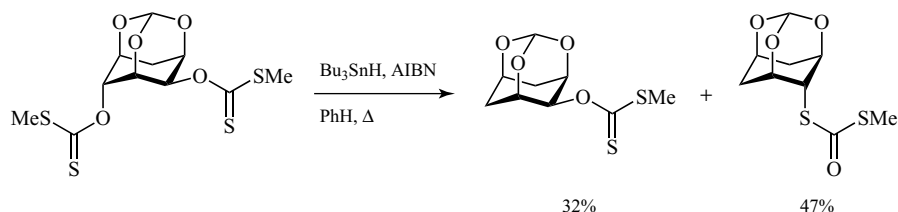
more basic carboxylates lead to a tighter ion pair than the phosphates, resulting in an instantaneous collapse to the product radical and the lack of scrambling of the label typically observed. Beginning even earlier than these studies on the rearrangement reactions, typically conducted in nonpolar solvents, an ongoing series of reactions on the fragmentation of β -acyloxyalkyl, β -(phosphatoxy)alkyl, and

related radicals was conducted in polar protic solvents by physical organic chemists.^{24–28} As was eventually recognized, these fragmentations simply represent the extreme form of the mechanism in which stabilization of the alkene radical cation and its counterion by the medium prevents recombination and leads ultimately to an alternative reaction manifold (Scheme 6). Alkene radical cations generated in this manner may be productively employed in preparative chemistry when intercepted by nucleophiles such as allyl and butenyl amines.^{29–31} Such tandem processes that couple nucleophilic attack with radical cyclization take place with a measure of memory of the absolute stereochemistry of the initial ester, indicating that trapping takes place at least partially at the level of the contact ion pair.^{32–34}

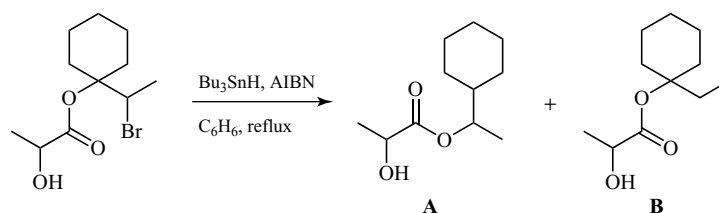
Unlike simple γ -acyloxyalkyl radicals (Scheme 5), alkyl radicals substituted at the



Scheme 6 Unified mechanism for the rearrangement and fragmentation of β -ester-substituted alkyl radicals.



Scheme 7 Rearrangement of a γ -thionocarbonyloxy alkyl radical.



No Lewis acid: 75% (**A**:**B** = 1:>99)
 with $Sc(OTf)_3$, 2,6-lutidine: 54% (**A**:**B** = 93:7)

Scheme 8 Lewis acid catalysis of the β -acyloxy alkyl rearrangement.

γ -position with thiocarbonyl esters are capable of rearrangement (Scheme 7). These reactions presumably proceed through a stepwise mechanism with ring-closure to a 1,3-oxathian-2-yl radical with subsequent ring-opening.³⁵

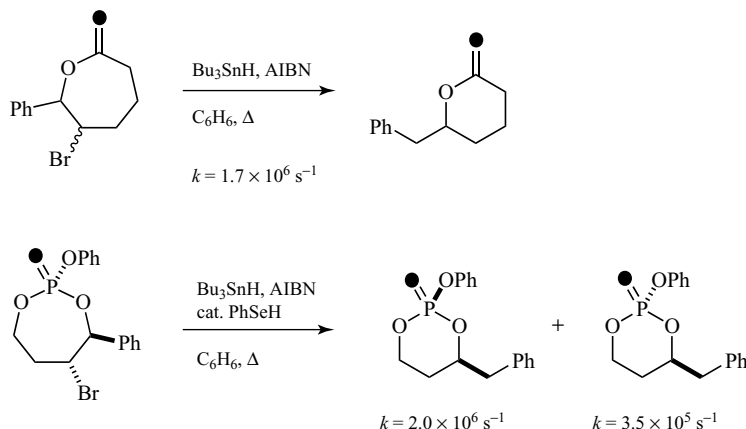
As might be expected from its mechanism, the β -acyloxy alkyl rearrangement can be catalyzed by the inclusion of certain Lewis acids (Scheme 8).³⁶

Lactones may also be caused to undergo both ring contraction (Scheme 9) or expansion by the acyloxy migration depending on the constitution of the initial radical.^{37–40} Cyclic phosphate esters can similarly

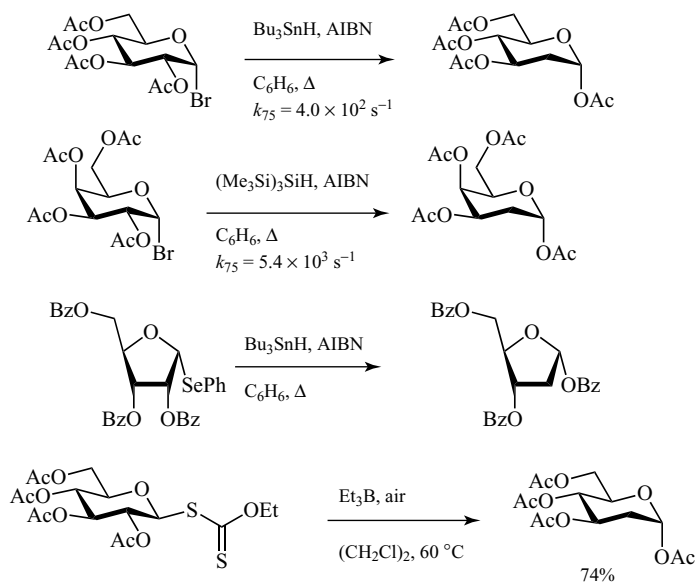
be induced to undergo related ring expansions and contractions (Scheme 9).⁴¹

From a preparative standpoint, undoubtedly the most useful examples of the acyloxy shift are those enabling the preparation of 2-deoxy sugars (see **Radicals and Carbohydrates**) (Scheme 10).^{42–48} As Giese pointed out, these rearrangements are thermodynamically favored, as the loss of radical stabilization energy is more than compensated for by the gain of the anomeric effect.^{9,43,49}

Phosphate esters also migrate to the anomeric position under radical conditions. In doing so,



Scheme 9 Radical ring contractions of lactones and cyclic phosphates showing rate constants and labeling patterns.



Scheme 10 Practical synthesis of 2-deoxy sugars by the acyloxy shift.

they generate 2-deoxy glycosyl phosphates which may be employed in glycosylation reactions (Scheme 11).^{16,17,19}

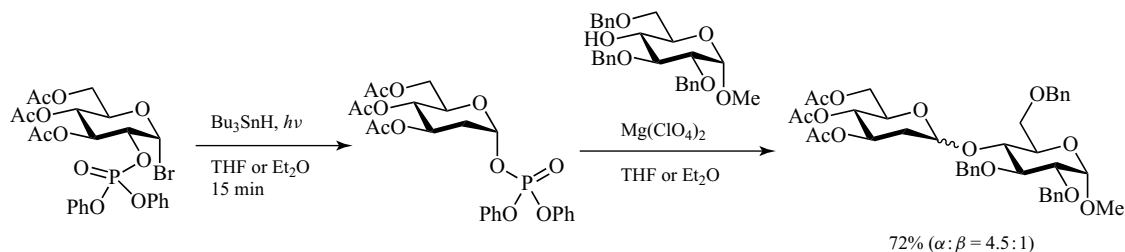
In contrast with the migration to the anomeric center in sugars, it has been demonstrated that acyloxy groups migrate away from the nucleoside 1'-position when a radical is generated at the 2'-center (Scheme 12).^{50–54} Evidently, radical stabilization by two heteroatoms is worth more energetically than the anomeric effect in this example.

The literature on the rearrangements and fragmentations of acyloxy alkyl and related radicals

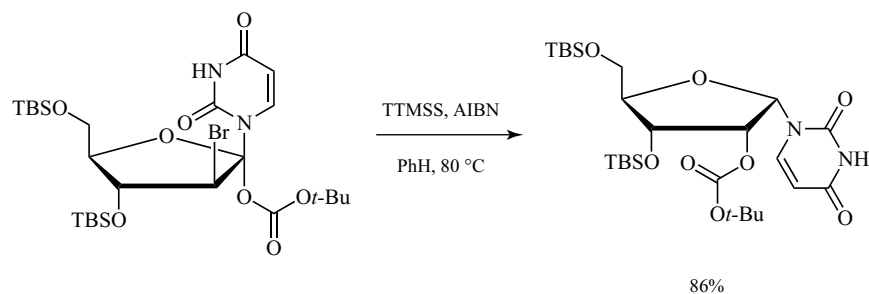
was reviewed comprehensively in 1997 and again in 2006, when a complete mechanistic picture was presented.^{6,23}

3 HYDROGEN ATOM MIGRATION

The Hofmann–Löffler–Freitag reaction of *N*-haloamines in acidic media giving pyrrolidines is historically perhaps the first example of a hydrogen atom migration.^{55,56} In this reaction,



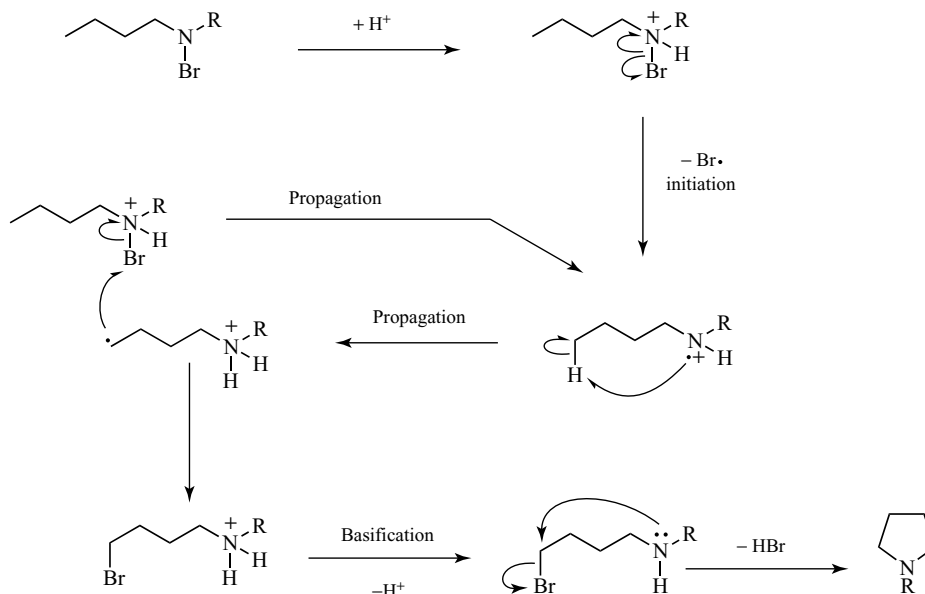
Scheme 11 Rearrangement to form a 2-deoxy glycosyl phosphate and its subsequent employment in a glycosylation reaction.



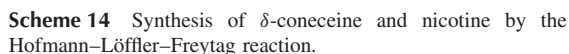
Scheme 12 Shift of an acyloxy group away from the nucleoside 1'-position.

an ammonium radical cation abstracts a hydrogen atom from an alkyl chain via a six-membered cyclic transition state to give a δ -aminobutyl radical that undergoes chain transfer by halogen

atom abstraction from a further molecule of *N*-haloamine.⁵⁷ The initial product is therefore a δ -aminobutyl halide that undergoes cyclization on subsequent basification of the reaction mixture

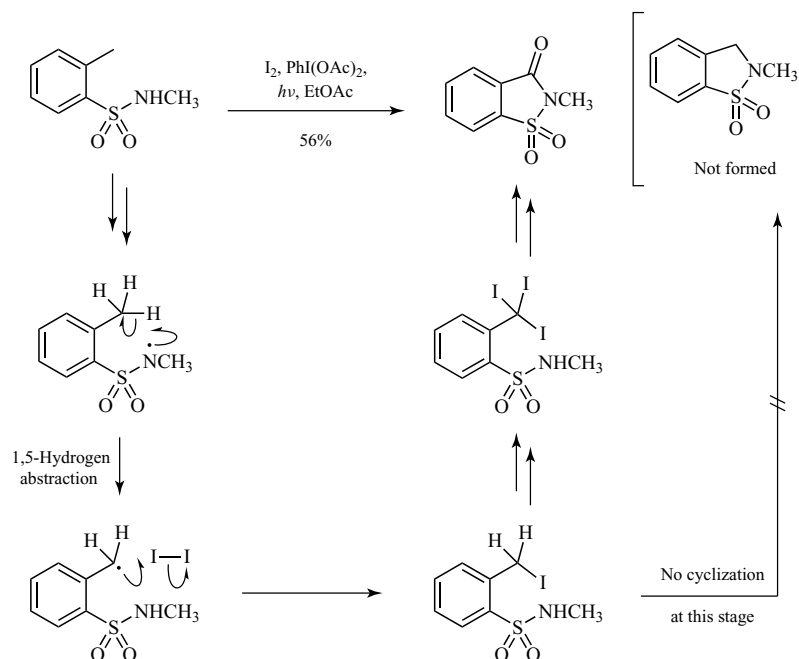


Scheme 13 Mechanism of the Hofmann–Löffler–Freytag reaction.

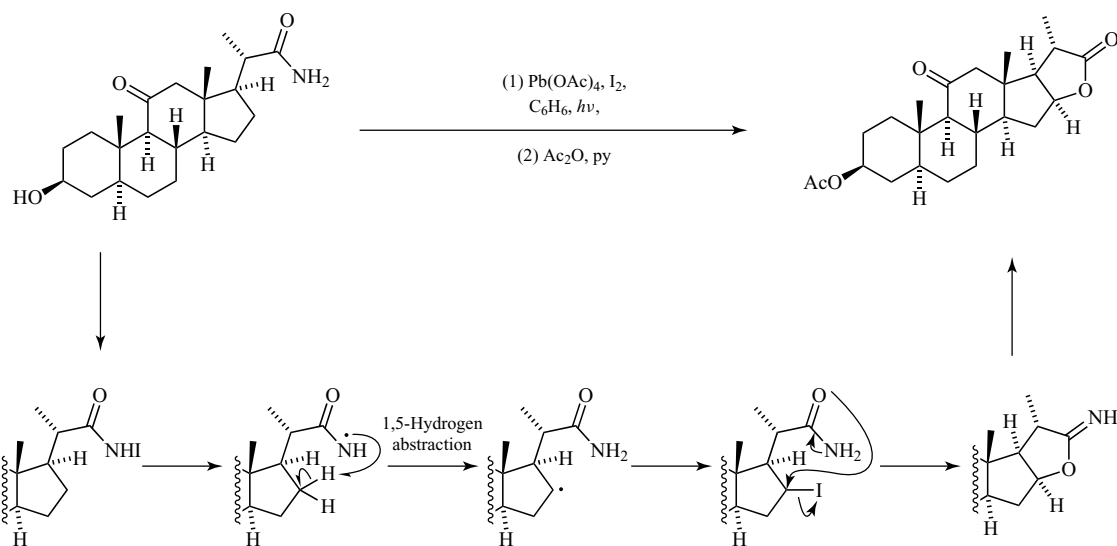


However, the need to synthesize *N*-haloamines, or their equivalents, and the strongly acidic conditions worked against the extensive use of this reaction in fine synthesis until the development of alternative, more practical entries into electron-deficient, nitrogen-centered radicals.⁶¹

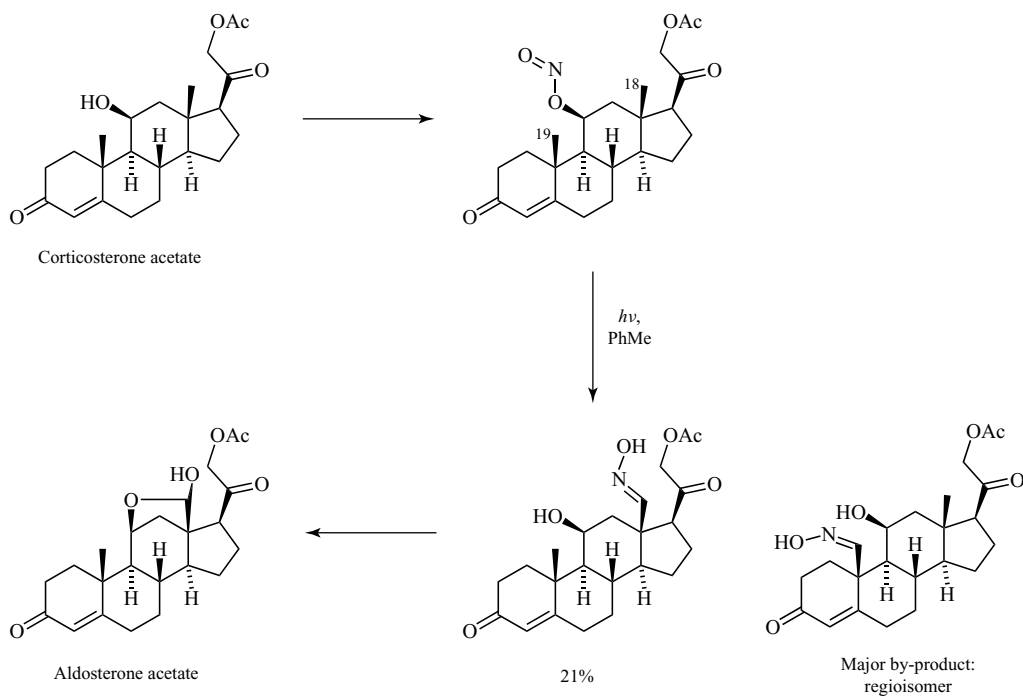
The analogous δ -, or 1,5-hydrogen abstraction reaction by alkoxy radicals took off rapidly as a major synthetic reaction after Barton's seminal synthesis of aldosterone by means of nitrite ester photolysis (Scheme 17).⁶⁹ In this chemistry, hydrogen atom abstraction is followed by selective combination of the alkyl radical with the NO $\cdot$ radical generated in the photolysis step owing to the operation of the Fischer–Ingold persistent radical effect (see **Fundamentals of Controlled/Living Radical Polymerization, Nitroxides in Synthetic Radical Chemistry, and Nitroxide-Mediated Polymerization and its Applications**).⁷⁰ The nitrosoalkane generated in this manner then undergoes tautomerization in the usual manner to give the isolated oxime.⁷¹



Scheme 15 Multiple 1,5-hydrogen abstractions by a sulfonamidyl radical.



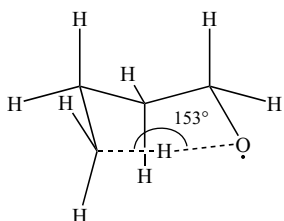
Scheme 16 1,5-Hydrogen abstraction by an amidyl radical.



Scheme 17 Key steps in Barton's first synthesis of aldosterone.

Other methods for the generation of alkoxy radicals in preparative systems either directly preceded Barton's contribution or soon followed it, including the use of lead tetraacetate,⁷² the use

of mercuric oxide and iodine,⁷³ and the photolysis of hypohalites^{74,75} and sulfonate esters.⁷⁶ More recently, the combination of iodobenzene diacetate and iodine has been extensively exploited by the



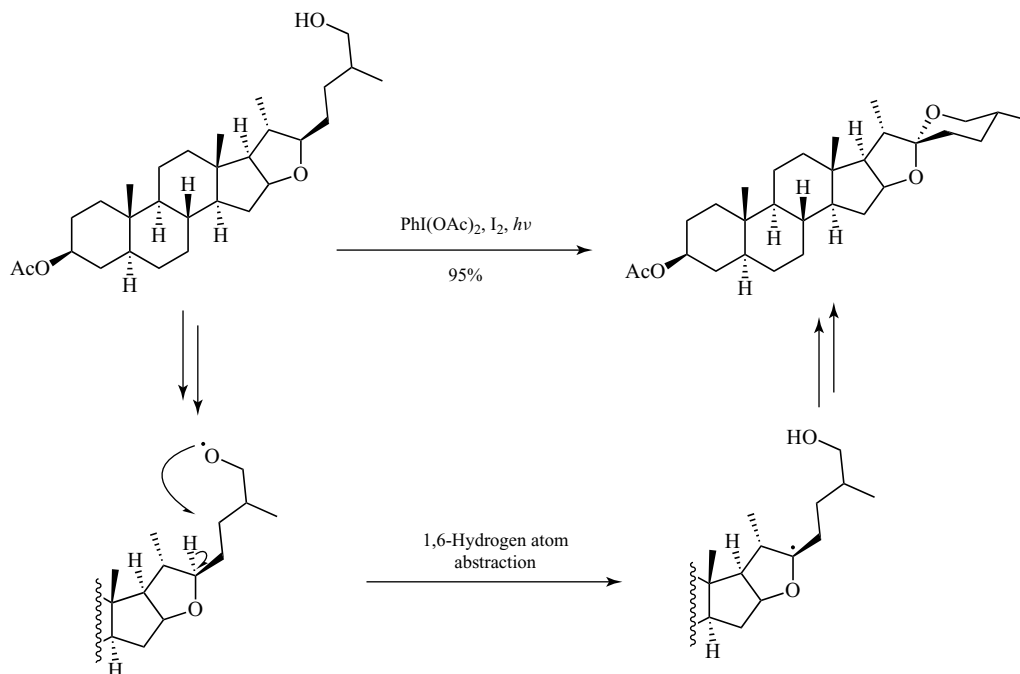
Scheme 18 Houk's computed envelope-like transition state for 1,5-hydrogen atom abstraction by alkoxy radicals.

Suarez group.⁷⁷ The early work on remote hydrogen abstraction by alkoxy radicals has been reviewed a number of times,^{59,60,78–80} and the picture emerges that, as clearly foreseen by Barton, abstraction takes place predominantly through a six-membered cyclic transition state to give a 4-hydroxybutyl radical in the vast majority of cases.⁵⁹ Computational work by Houk revealed the transition state for these hydrogen atom abstractions to resemble more a five-membered ring in an envelope conformation rather than the chair-like six-membered ring envisioned by Barton.⁸¹ In this transition state, the breaking and forming bonds to the migrating hydrogen subtend an angle of $\sim 153^\circ$ (Scheme 18). Recent

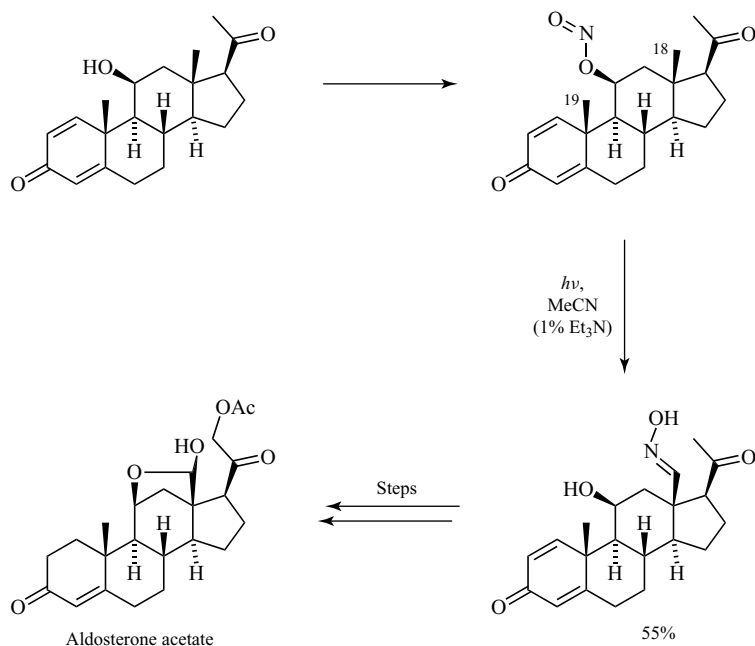
kinetic work by the Newcomb group has defined the Arrhenius parameters for the 1,5-hydrogen atom abstraction by simple primary alkoxy radicals in the moderate polarity solvent trifluoromethylbenzene, affording a rate constant of $2.7 \times 10^7 \text{ s}^{-1}$ at 20°C .⁸²

The relatively strict requirements for a quasi-linear transition state at the migrating hydrogen atom strongly disfavor hydrogen atom abstraction through smaller than six-membered cyclic transition states. Indeed, competing alkoxy radical fragmentation is typically the observed reaction pathway when hydrogen atom abstraction is not possible from the δ - or more remote positions. Hydrogen atom abstractions involving seven-membered ring cyclic transition states are well known when the bond energies render them favorable,^{83,84} as in the example of Scheme 19.⁷⁷

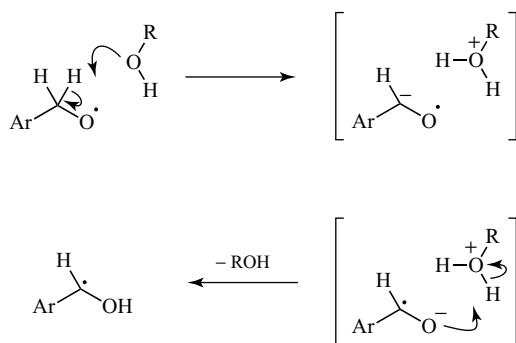
Even within the most common series of 1,5-hydrogen atom abstractions, changes in regioselectivity can be affected by subtle changes in molecular conformation that impinge on the ability to achieve the optimal transition state geometry. A case in point is taken from Barton's original work on aldosterone synthesis in which use of the A-ring



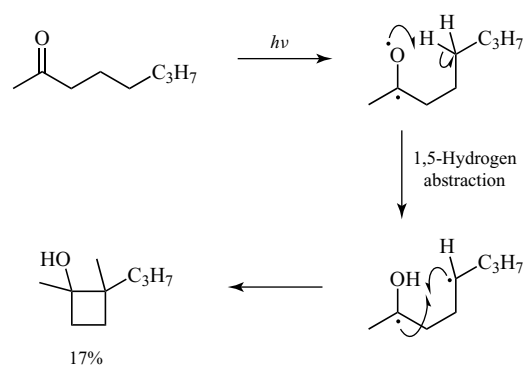
Scheme 19 Example of 1,6-hydrogen atom abstraction by an alkoxy radical.



Scheme 20 Barton's second aldosterone synthesis illustrating the dependence of hydrogen-atom abstraction on conformation.



Scheme 21 Abbreviated mechanism for OH-assisted 1,2-hydrogen atom migration.

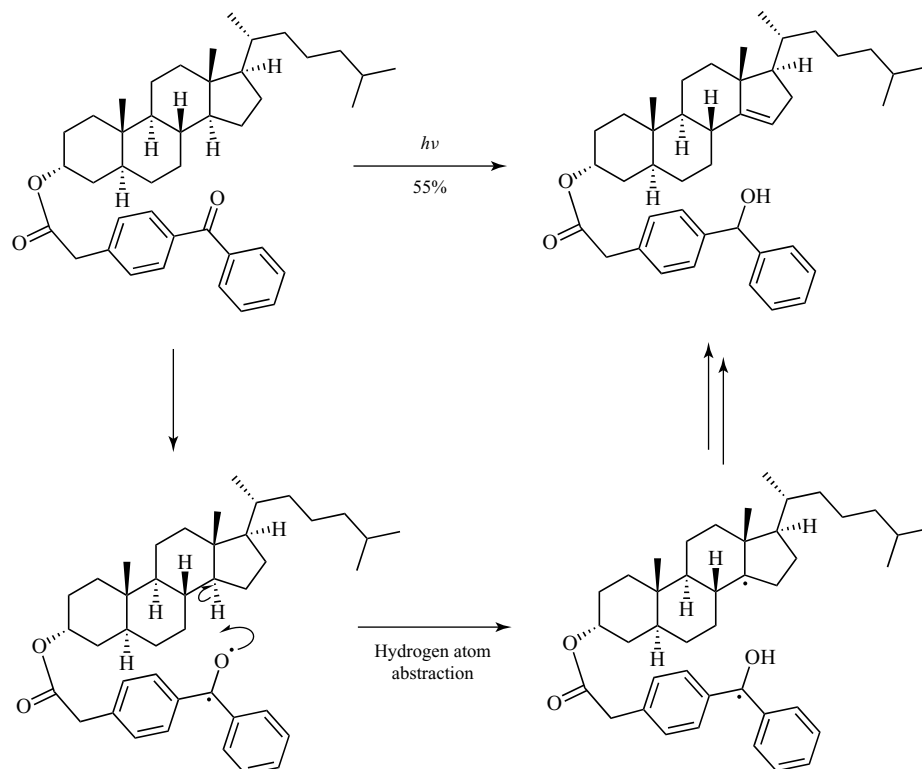


Scheme 22 Norrish–Yang cyclobutanol synthesis with 1,5-hydrogen atom abstraction by a photoexcited ketone.

enone (Scheme 17) gave only 21% of the oxime resulting from abstraction from the C18 methyl group due in part to competing abstraction from the alternative angular methyl C19.⁶⁹ Conversion of the A-ring enone to the corresponding cross-conjugated dienone, thereby changing the conformation of the steroidal nucleus, more than doubled the yield of the product arising from hydrogen atom abstraction at the desired C18 position (Scheme 20).⁸⁵

The 1,2-hydrogen atom shift in alkoxyalkyl radicals to give ketyl radicals is a known and rapid

process in water or alcohols. Extensive mechanistic work including the determination of deuterium kinetic isotope effects has resulted in the proposition of a number of mechanisms for this reaction of which that of Ingold and coworkers best takes account of all experimental parameters (Scheme 21). In view of the mechanism, this reaction is not a true rearrangement of an alkoxy radical but is included here insofar as it is a serious competing reaction of 1,5-hydrogen atom abstractions of alkoxy radicals



Scheme 23 Remote C–H bond functionalization by an excited state ketone.

when they are carried out in alcoholic or aqueous solutions.^{86–88}

Evidently, the 1,5-hydrogen atom abstraction of alkoxy radicals is closely related to the Norrish type II photoprocess and the Norrish–Yang cyclobutanol synthesis (see **Synthetic Radical Photochemistry**), in which an excited state ketone abstracts hydrogen from the γ -position (Scheme 22).^{89,90}

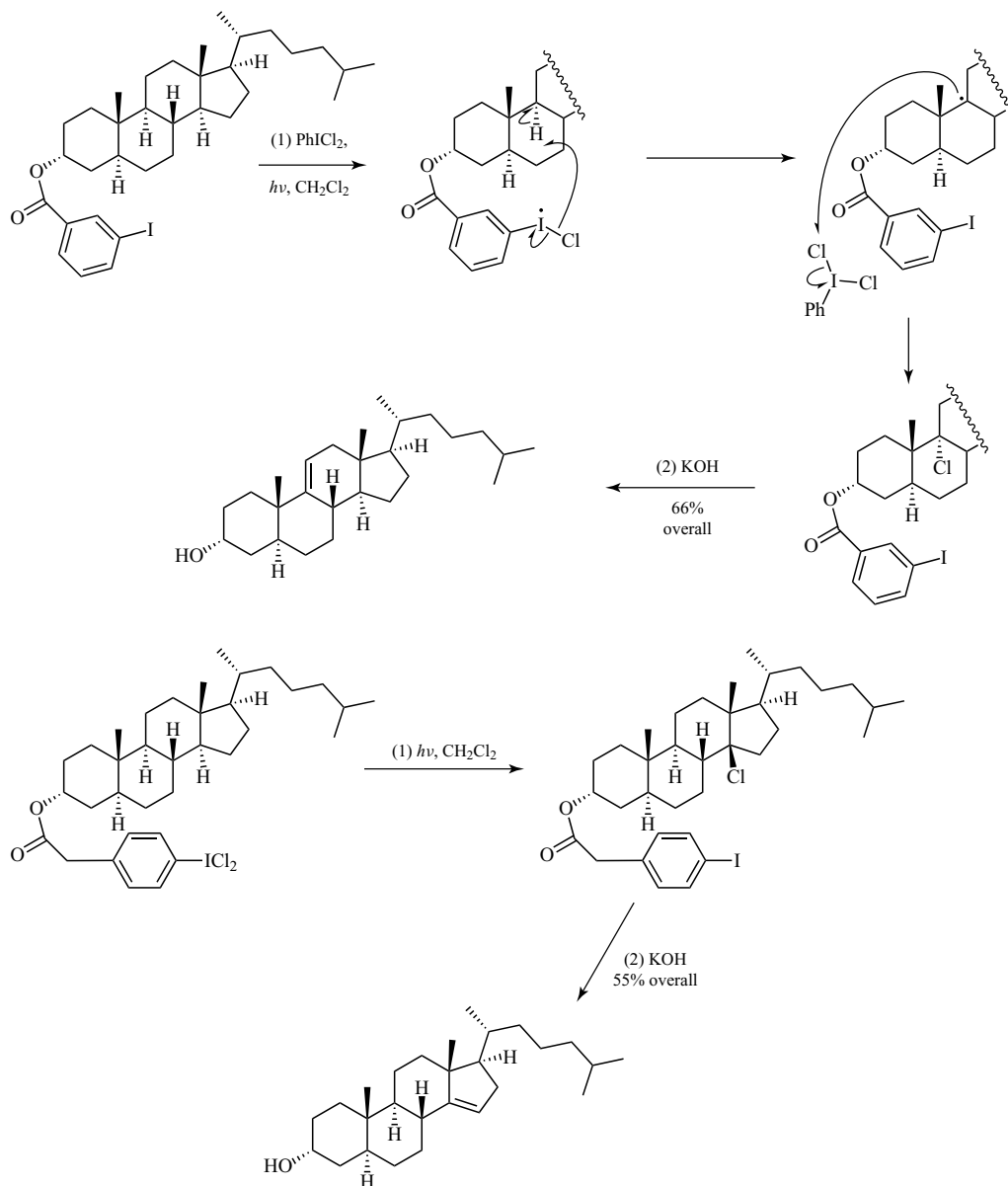
Photoexcited ketones have been employed to achieve hydrogen atom abstraction from more remote positions when substitution or conformational constraints prevent abstraction from the δ -position (Scheme 23).^{90,91} However, the relatively poor selectivity of such processes for remote functionalization arising from the highly reactive nature of the triplet ketone prompted the development of more selective processes based on weaker hydrogen atom abstracting systems.

The work of Breslow using iodobenzoate esters in the presence of iodobenzene dichloride has set the standard for such remote functionalization processes and enabled the selective functionalization of the

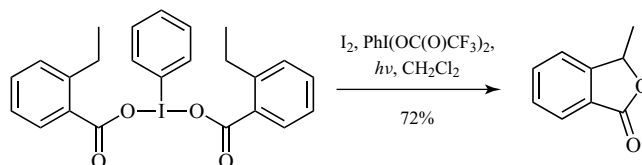
steroid nucleus at a variety of tertiary positions depending on the position of the iodine atom on the benzoate group (Scheme 24).^{91,92}

Although the vast majority of work on hydrogen atom abstraction by heteroatom-based radicals has focused on aminium radical cations and on alkoxy radicals, other oxygen and nitrogen-centered radicals have also been investigated. Thus, while aliphatic carboxyl radicals undergo decarboxylation too rapidly to take part in hydrogen atom abstractions, such processes are known for the much longer lived arylcarboxyl radicals, as illustrated in Scheme 25.⁹³

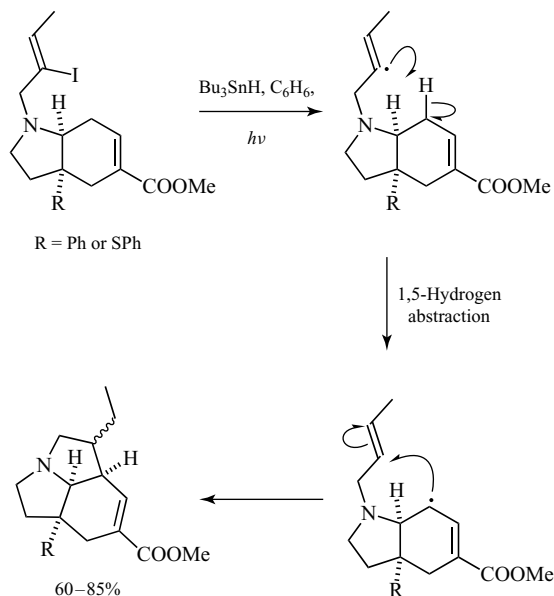
In recent years, attention has turned from heteroatom-centered radicals to carbon-centered radicals and in particular the use of vinyl and aryl radicals for the abstraction of hydrogen from sp^3 C–H bonds wherein the driving force is evidently provided by the formation of an sp^2 C–H bond at the expense of its weaker sp^3 equivalent. Such processes evidently have very similar requirements for



Scheme 24 Selective remote functionalization of tertiary C–H bonds by iodoarene-derived radicals.



Scheme 25 1,5-Hydrogen atom abstraction by a carboxyl radical.



Scheme 26 1,5-Hydrogen abstraction by a vinyl radical.

a quasi-linear transition state geometry at the migrating hydrogen atom, as their alkoxy and aminium radical counterparts and six-membered cyclic transition states are by far the most common processes.

Although such processes have long been known,¹ one of the earliest examples of their employment in a synthetic context was recorded by Parsons (Scheme 26).⁹⁴

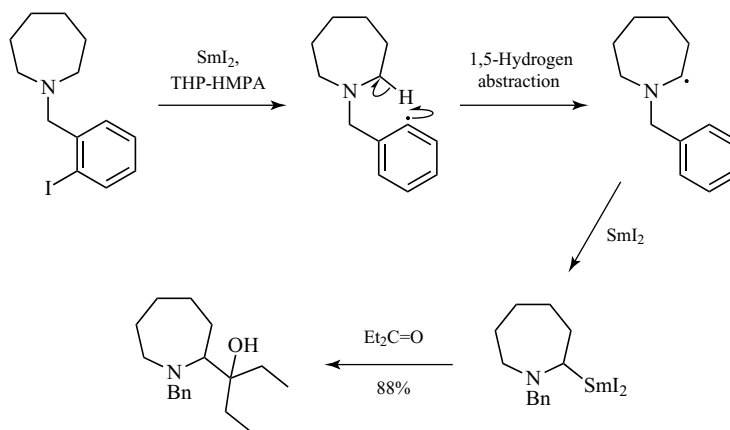
Much subsequent work was conducted by the Curran group, extending this concept of intramolecular hydrogen atom abstraction by vinyl radicals

followed by radical cyclization. The term radical translocation was coined for this process which, because of the need to overcome competing processes, especially vinyl radical reduction by the chain transfer reagent, functions best for hydrogen atom abstraction from the weaker polarized C–H bonds of ethers and acetals.^{95–100}

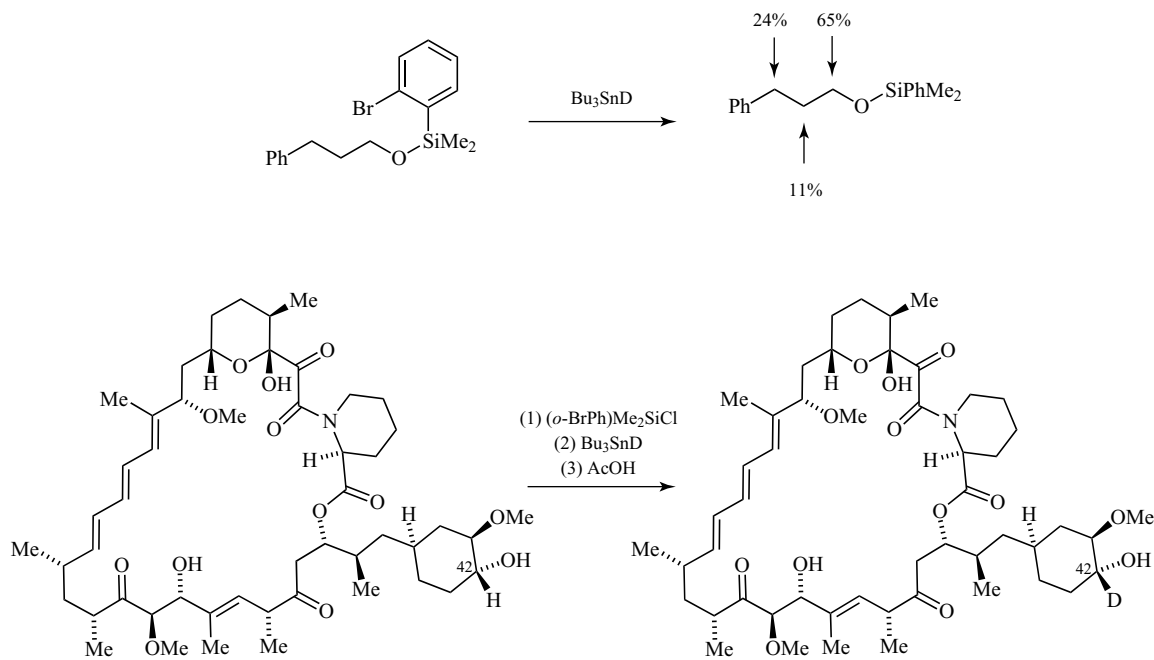
1,5-Hydrogen abstraction by an aryl radical resulting from an *ortho*-halobenzyl-protecting group on oxygen or nitrogen results in a radical adjacent to the heteroatom. Scheme 27 shows a nitrogen-protecting radical-translocating group, *o*-iodobenzyl. The initial radical is generated using samarium iodide, and a second equivalent of that reagent gives a metallated intermediate which is trapped by electrophiles.¹⁰¹

A variant on the theme employs *o*-haloarylsilyl ethers to generate a siloxyalkyl radical for application in subsequent processes. 1,6- and 1,7-Hydrogen atom abstractions were found to compete significantly with the major 1,5-hydrogen abstraction pathway when the oxygen-protecting group dimethyl(*o*-bromophenyl)silyl was used as a radical precursor, as measured by deuterium incorporation in a tin deuteride reduction (Scheme 28). Nevertheless, this method could be used to introduce a deuterium label regioselectively at C42 into a complex natural product, namely, rapamycin (Scheme 28).¹⁰²

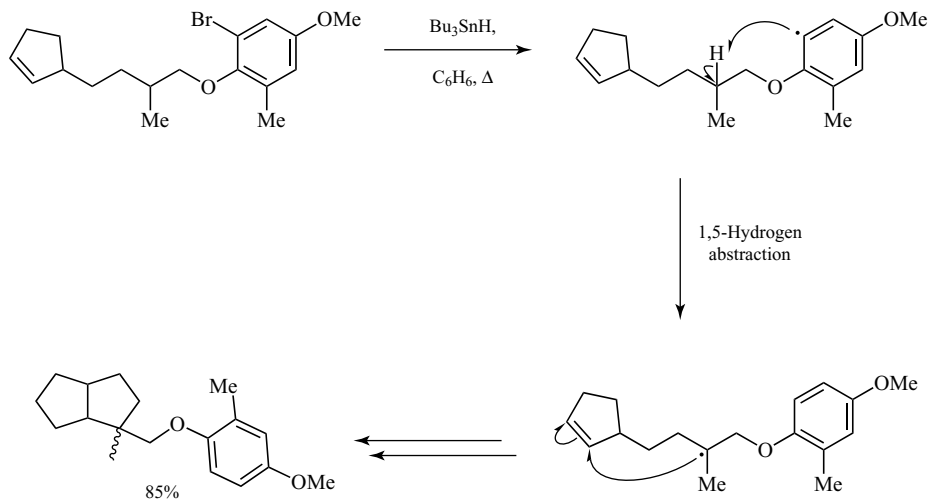
With *O*- and *N*-benzyl (or benzoyl) or *O*-phenylsilyl based protecting translocating groups, 1,5-hydrogen abstraction should result in a radical at the carbon bearing the (protected) heteroatom. Protecting-translocating groups based



Scheme 27 Radical translocation from a protecting group.



Scheme 28 Simple and complex examples of hydrogen atom abstraction from a silylether-based protecting group.

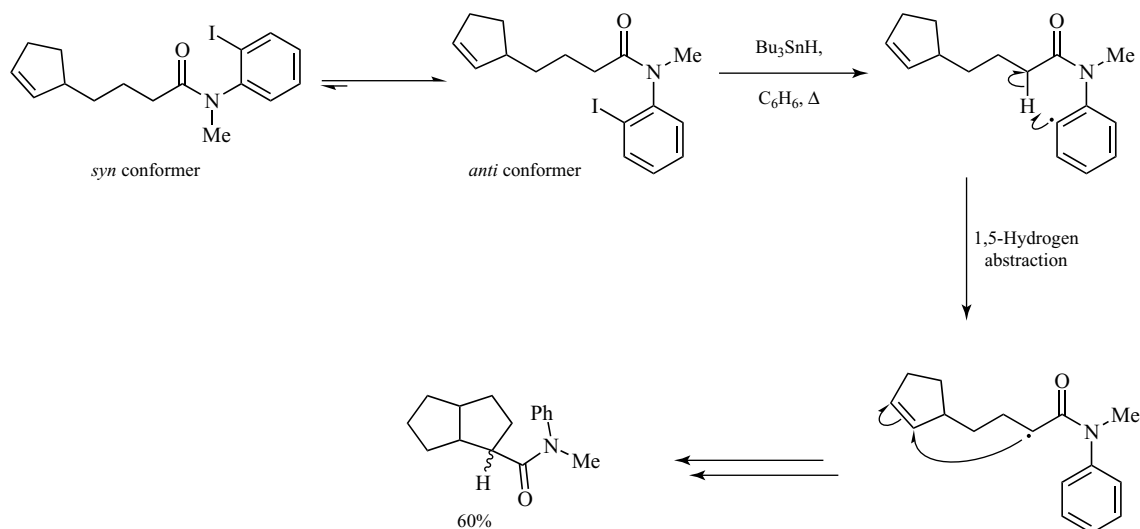


Scheme 29 1,5-Hydrogen atom abstraction in an aryl ether.

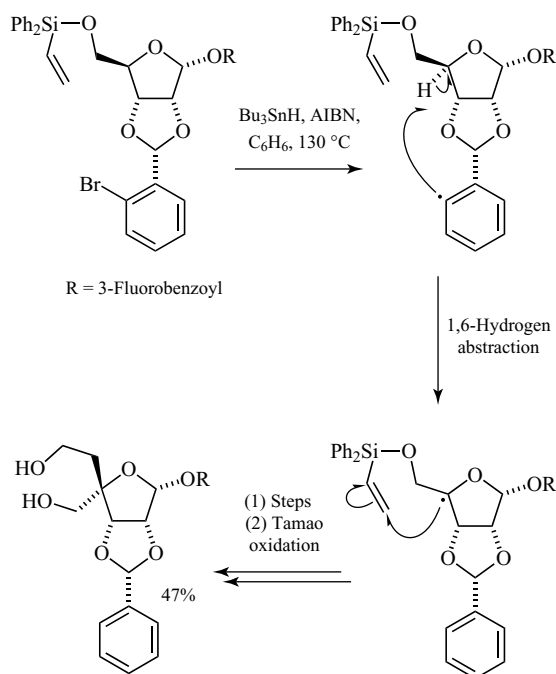
on *p*-methoxyphenyl ethers are designed to functionalize more remote unactivated C–H bonds. 1,5-Hydrogen abstraction should result in a radical on the carbon vicinal to the carbon bearing the heteroatom. Curran found that 1,6-hydrogen abstraction was sometimes seen to a significant extent, depending on the substituents on the

radical formed after abstraction. In the example shown in Scheme 29, 1,5-hydrogen atom abstraction is favored by the formation of a tertiary radical.⁹⁷

Along similar lines, carboxylic acids may be protected and activated as amides of *N*-methyl-*o*-iodoaniline. A favorable conformation



Scheme 30 1,5-Hydrogen abstraction from in an anilide.



Scheme 31 1,6-Hydrogen atom abstraction in a benzylideneacetal.

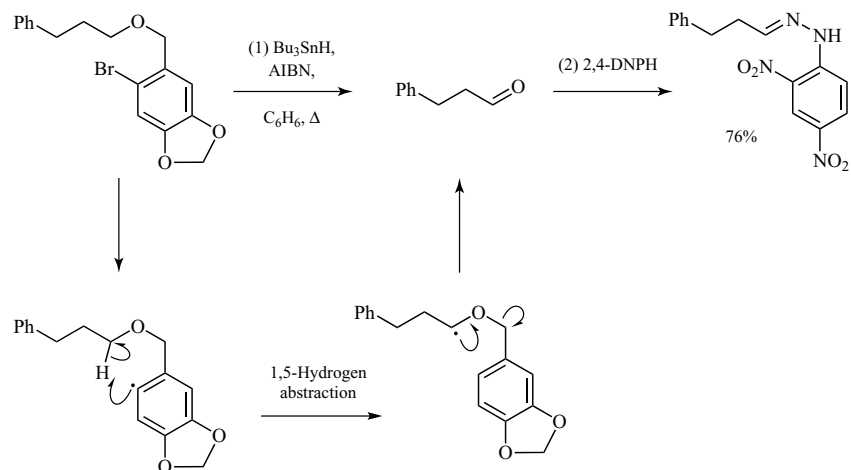
is crucial to successful 1,5-hydrogen abstraction, and this could be potentially problematic in amides with restricted rotation about the amide

bond. Fortunately, the *o*-iodoanilides show a significant preference (>95 : 5) for the required *anti* conformation, and radical translocation to a position α to the carbonyl group is seen (Scheme 30).¹⁰³

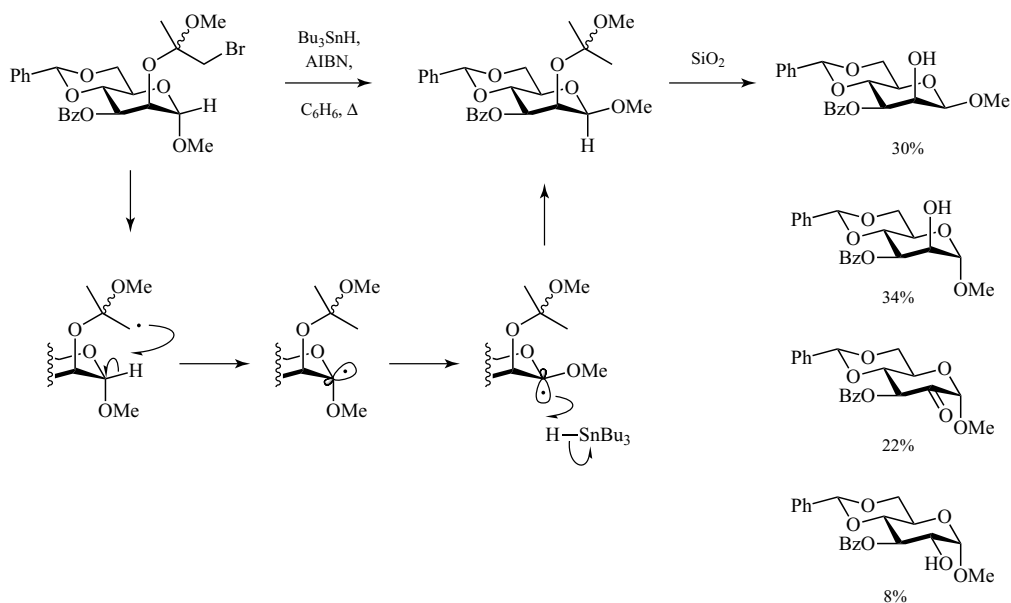
A 2-bromobenzylidene group has been used as a protecting-radical-translocating group for 1,2-*cis*diols and was employed in the synthesis of a branched-chain sugar. The rigid *cis*-fused bicycle and *endo* stereochemistry of the benzylidene stereocenter make 1,5-hydrogen abstraction by the radical generated at the *ortho* position of the benzylidene impossible. Therefore, only 1,6-hydrogen abstraction is seen (Scheme 31).¹⁰⁴

A slight redesign of the basic radical translocation concept led to that of self-immolative protecting groups, whereby the *o*-halobenzyl ethers lead to benzyloxyalkyl radicals following 1,5-hydrogen atom abstraction and then, by expulsion of a benzyl radical, to a ketone. In this manner, the oxidation of an alcohol protected in the form of a functionalized benzyl ether to a carbonyl group may be achieved under what are effectively reducing conditions (Scheme 32).¹⁰⁵

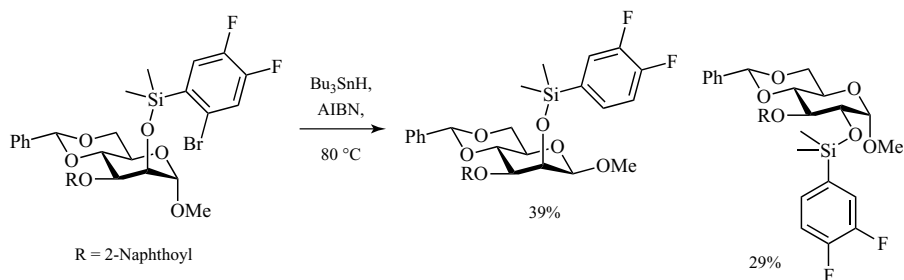
As noted above, 1,5-hydrogen atom abstraction typically dominates radical translocation processes,¹⁰⁶ but even the best laid plans go awry. Thus, in a planned inversion of an α -mannopyranoside to its β -isomer by a 1,5-hydrogen atom abstraction from a alkyl radical



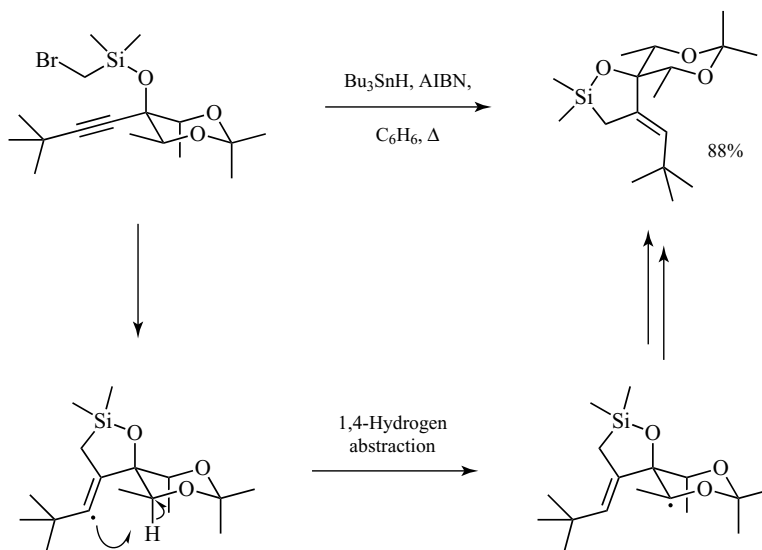
Scheme 32 The self-immolative protecting group strategy.



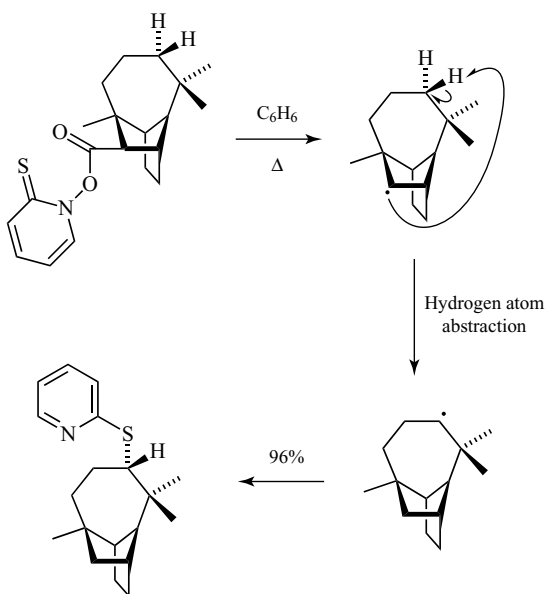
Scheme 33 Unanticipated 1,4-hydrogen atom abstraction encountered by Crich and coworkers.



Scheme 34 Curran's reliance on 1,6-hydrogen atom abstraction in approaching the radical inversion of an anomeric center.



Scheme 35 1,4-Hydrogen atom abstraction in a severely crowded environment.



Scheme 36 Transannular hydrogen atom abstraction by an alkyl radical.

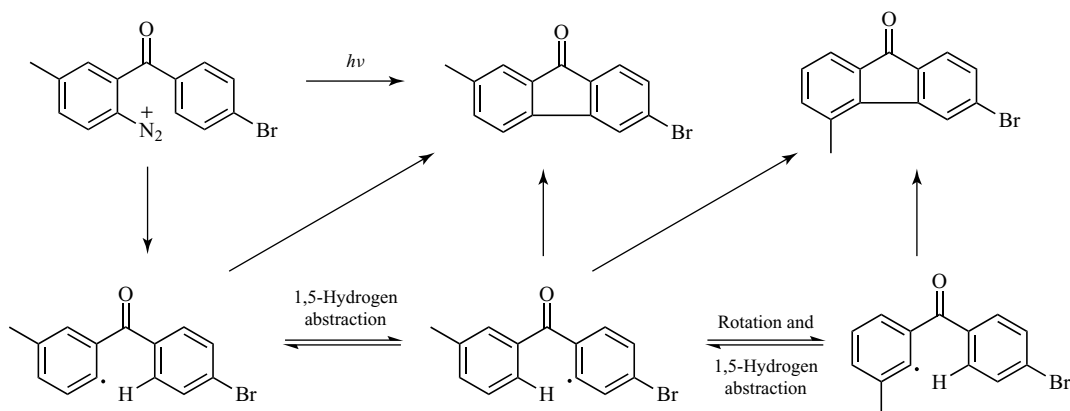
precursor appended to O_2 , a series of products arising from 1,4-hydrogen abstraction from C2 were seen (Scheme 33).¹⁰⁷ Tackling the same problem, Curran and coworkers relied with moderate success on the weaker nature of the anomeric C–H bond

to achieve the desired process with an aryl radical through a seven-membered cyclic transition state (Scheme 34).¹⁰⁸

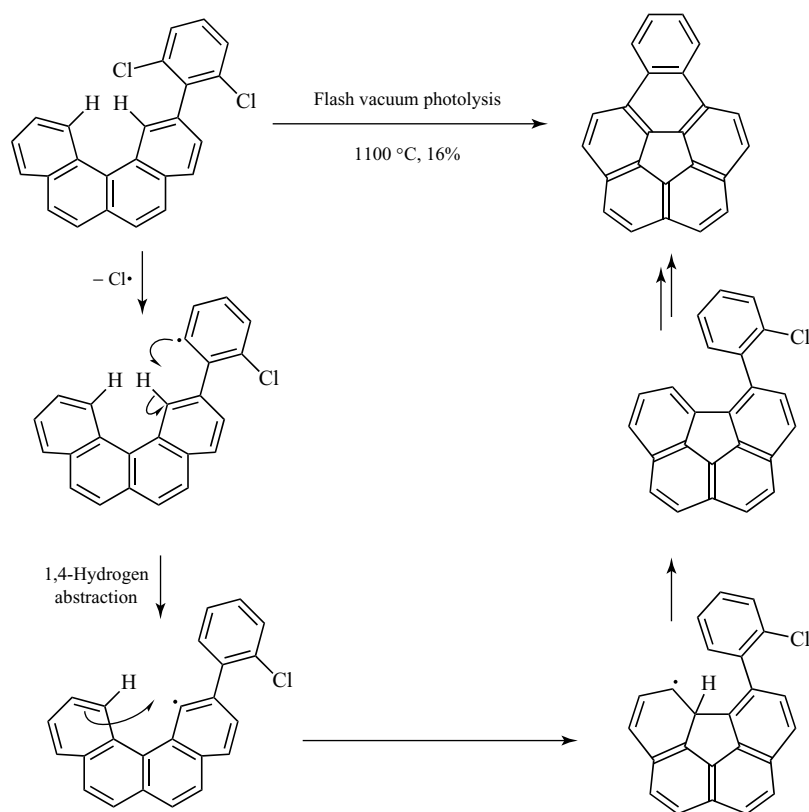
Other examples of 1,4-hydrogen atom abstraction by aryl and vinyl-centered radicals are found in the work of the Ingold and Gilbert groups.^{109,110} As in other instances of this kind, the high degree of substitution in the example given (Scheme 35) limits the conformation and results in a relatively facile 1,4-hydrogen atom abstraction.¹¹¹

Intramolecular hydrogen atom abstraction by alkyl radicals is far less common than that by aryl and vinyl radicals, as it obviously does not possess the same thermodynamic driving force. Nevertheless, in favorable circumstances such processes can function, as is clear from Scheme 33. In a further such example, Ourisson, Zard, and their coworkers noted transannular hydrogen atom migration through a six-membered transition state imposed by the rigidity of the bicyclic skeleton (Scheme 36).¹¹²

Intramolecular C–H abstraction reactions may be caused to occur at sp^2 C–H bonds if the abstracting radical is itself an aryl (or presumably vinyl) radical and if competing abstraction from sp^3 C–H bonds is not available. As has been amply demonstrated, such situations occur with *o*-aryloxy aryl radicals and related species including *o*-aryloxyaryl radicals (Scheme 37).^{113,114} In a related work by Scott, a



Scheme 37 1,5-Hydrogen atom migration between two aryl radicals.

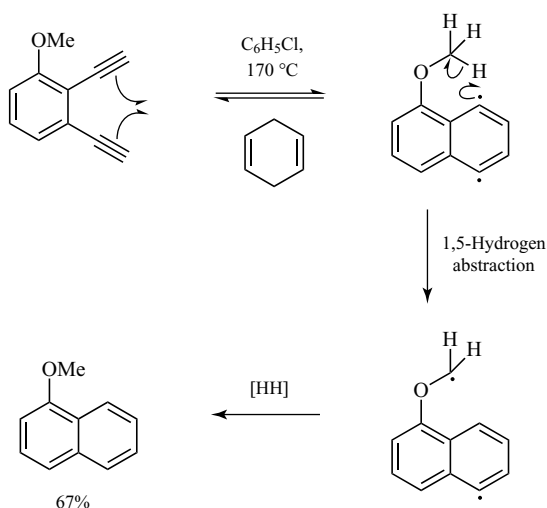


Scheme 38 1,4-Hydrogen atom abstraction between aryl radicals in a corannulene synthesis.

1,4-hydrogen atom shift between two sp^2 -hybridized carbons was a crucial step in a synthesis of benzo[*a*]corannulene (Scheme 38).¹¹⁵

1,4-Arenediyls generated by the Bergman cyclization are also susceptible to intramolecular

hydrogen atom abstractions when a C–H bond of suitable bond dissociation energy is correctly disposed. For example, it was demonstrated that a naphthalene-1,4-diyl generated in this manner could be trapped by 1,5-hydrogen atom abstraction,



Scheme 39 1,5-Hydrogen abstraction by a naphthalene-1,3-diyl generated by Bergman rearrangement.

thereby displacing the enediyne-diyl equilibrium (Scheme 39).^{116,117}

4 CONCLUSION

There is a rich and varied chemistry of radical rearrangements beyond the simple formation and cleavage of C–C bonds. This chemistry may be employed to set up C–C bond-forming rearrangements or it may compete with them. Certainly, synthetic chemists need to be aware of such processes, as some are rapid. Alternatively, such rearrangements may be productively employed in systems that do not involve C–C bond-forming reactions at any stage, as in Barton's classical aldosterone synthesis.

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Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry

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1 INTRODUCTION

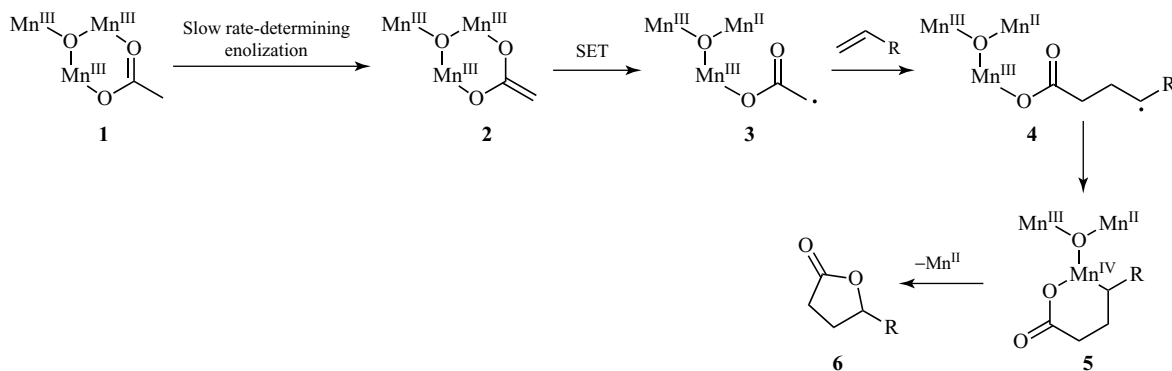
This article covers oxidative radical reactions mediated by manganese(III) acetate (MAN), cerium(IV) ammonium nitrate (CAN), and various iron(III) salts. The formation of C–C bonds will form the focus of this overview. Much of the chemistry of Mn(III), Ce(IV), and Fe(III) involves the formation of electrophilic radicals (or related species) from CH-acidic compounds. These radicals can undergo C–C bond formation with the production of new “adduct” radicals. The adduct radicals can undergo oxidative elimination to form alkenes, or oxidative substitution or ligand transfer to form C–X bonds. Additionally, these adduct radicals can undergo reduction by H-atom transfer from solvent or substrate; overall the substrate has undergone no net redox change in such a reaction. Owing to space limitations, the reduction of adduct radicals will only be mentioned in passing.¹ Additionally, this overview covers only C–X bond-forming reactions^{2,3} in which they are part of a reaction sequence that has involved formation of a C–C bond; aryl–aryl coupling reactions (see **Radical Arylations**)^{4–6} and reactions that are catalytic in metal⁷ are not covered. Applications of the reported methodologies are illustrated in the context of complex molecules synthesis. A number of excellent reviews covering various aspects of the oxidative radical chemistry of manganese, cerium, and iron

are available and should be consulted for comprehensive coverage: Mn(III)^{1,2,8–12}, Ce(IV),^{3,7,13–17} and Fe(III).^{4,6}

2 GENERAL MECHANISMS

In order to be able to rationalize reactivity and plan synthetic routes that involve oxidative radical reactions, it is necessary to have some working knowledge of the mechanisms of such reactions.¹² In its most generic form, exposure of an electron-rich species (most frequently an enol/enolate, an aromatic ring, or a heteroatom) to Mn(III), Ce(IV), or Fe(III) salts results in single-electron oxidation of the organic substrate to generate a free or metal-bound radical or radical cation. The radical/radical cation can then undergo a number of reactions which generally result in the formation of adduct radicals. Oxidative radical reactions differ from more standard radical reactions in the numerous possible pathways available for conversion of these adduct radicals into products. The fate of adduct radicals are discussed below.

MAN (represented in the schematics as Mn(OAc)₃) is an oxo-centered triangle of Mn(III) atoms with bridging acetates,¹⁸ typical of many transition-metal acetates. (In this review, it is assumed that all reactions are conducted with MAN dihydrate rather than anhydrous MAN unless



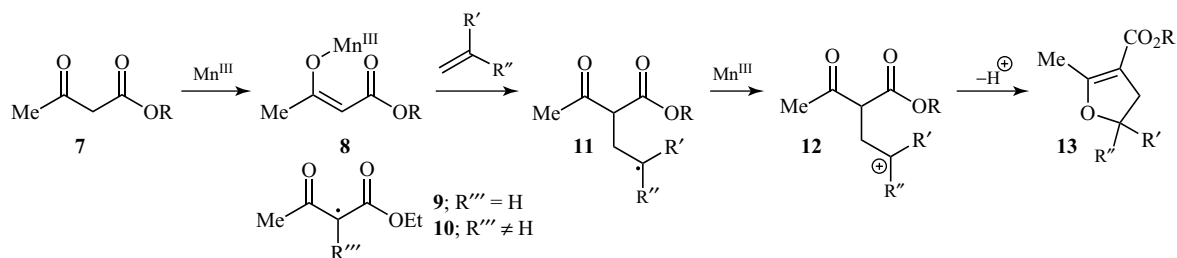
Scheme 1 Mechanism of γ -lactone formation.

explicitly stated.) The reagent was first used in organic chemistry for the synthesis of γ -lactones from alkenes and acetic acid. The mechanism of the reaction is believed to involve rate-determining deprotonation of a bridging acetate to give the manganese enolate **2** (Scheme 1).^{19–21} Single electron transfer (SET) then occurs to give the electrophilic free radical **3** which adds in a regioselective manner to an alkene to give the more stable secondary adduct radical **4**. Formation of the γ -lactone product **6** from the adduct radical **4** requires a further single-electron oxidation. MAN will not oxidize isolated primary and secondary radicals to the corresponding carbenium ions; however, it will oxidize γ -carboxy radicals to give γ -lactones, and a number of mechanisms have been proposed for this conversion.¹² One possibility is illustrated.

In the reaction between alkenes and CH-acidic β -keto esters, two distinct mechanisms are believed to operate. With α -substituted β -keto esters, formation of the corresponding Mn(III) enolate is believed to be rate-determining followed by rapid

SET to give the corresponding electrophilic radical **10** which undergoes rapid addition to an alkene (Scheme 2).^{22,23} By contrast, with unsubstituted β -keto esters (**7**) and alkenes, formation of the corresponding Mn(III) enolate **8** is fast and the experimental evidence indicates that direct addition of the Mn(III) enolate onto the alkene occurs to give radical **11** and that radical **9** is not formed. Here the tertiary adduct radical **11** would be oxidized by MAN to give a cation **12** which is trapped to give product **13**.

Hence, the more acidic unsubstituted β -keto acids/esters add to alkenes directly from the Mn(III) enolate, whereas with substituted β -keto acids/esters an electrophilic radical is formed which subsequently adds to an alkene. In a similar manner, alkenyl malonates undergo addition/cyclization reactions via the corresponding malonyl free radicals,²³ whereas with alkenyl Meldrum's acid derivatives the Mn(III) enolate undergoes direct addition/cyclization onto an alkene to give the corresponding adduct radical.²⁴



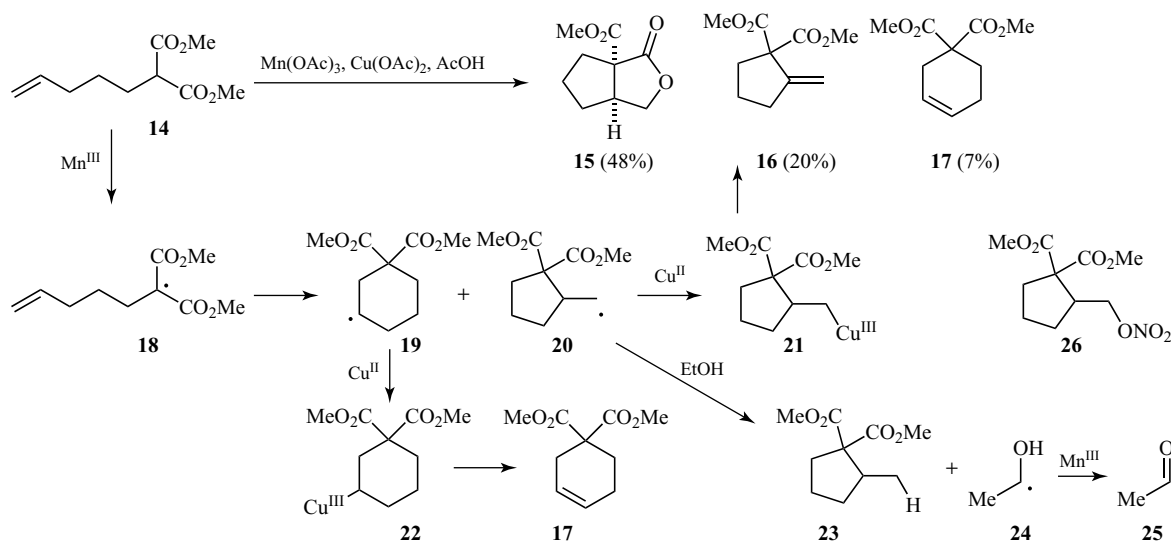
Scheme 2 Mechanisms of addition of β -keto esters to alkenes.

In all these systems, the adduct radical can undergo a number of reactions. As noted previously, Mn(III) readily oxidizes γ -carboxy radicals to the corresponding γ -lactones and will oxidize tertiary radicals to the corresponding carbenium ions which undergo S_N1 and E_1 processes. Mn(III) oxidizes isolated primary and secondary radicals only very slowly, and here hydrogen abstraction from the solvent or substrate is the major pathway. Overall, there is no net change in oxidation level of the substrates (i.e., no net oxidation) and these reactions will be mentioned only briefly. On the basis of the pioneering work of Kochi,²⁵ Heiba and Dessau demonstrated that copper(II) acetate oxidizes secondary radicals to alkenes 350 times faster than MAN.^{26,27} Copper(II) acetate is now widely used in conjunction with MAN to allow efficient oxidation of primary and secondary alkyl radicals generally to give alkenes. A number of these processes are illustrated by the cyclization of 4-pentenyl malonate **14** (Scheme 3).²³ On exposure to MAN, the free radical **18** is formed which cyclizes to an approximate 1:9 mixture of adduct radicals **19**:**20**. In the presence of copper(II) acetate, the corresponding copper(III) intermediates **22** and **21** are formed which undergo β -hydride elimination to give the corresponding alkenes **17** and **16**; in general, oxidative elimination mediated by copper(II) acetate occurs to give the less substituted *E*-olefin (see below). The

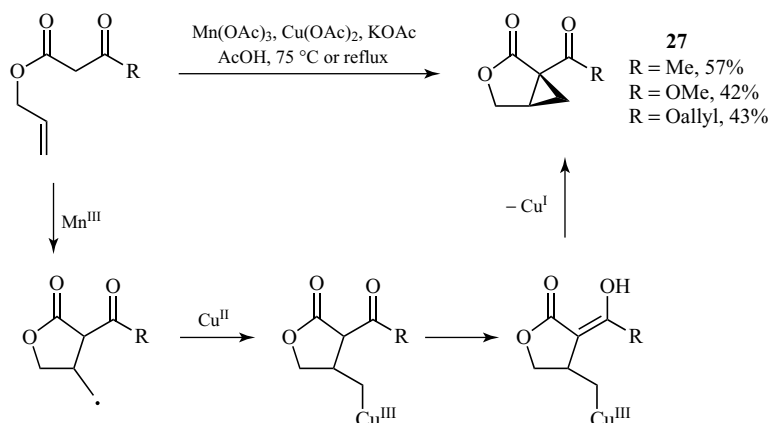
γ -lactone **15** is also formed from the copper(III) intermediate **21**, presumably by substitution with one of the carbonyl groups of the malonate followed by hydrolysis. If the reaction is conducted using ethanol as solvent in the absence of a copper(II) salt, then the methylcyclopentane **23** is formed. Here, oxidation of the primary radical **20** by MAN is very slow and hydrogen atom transfer from the solvent occurs to give **23** and the α -hydroxy radical **24** which is oxidized to acetaldehyde **25** by Mn(III); the reduction of vinylic adduct radicals by hydrogen-atom transfer from solvent is synthetically useful.^{1,28,29} Similar mechanisms will be operating with CAN and iron(III) salts.³⁰ With CAN, products of ligand transfer are frequently formed. The use of CAN in acetic acid with $Cu(BF_4)_2$ and malonate **14** gives the γ -lactone **15** in 83% yield, whereas in the presence of acetic anhydride the nitrate **26** is formed in 81% yield by an oxidative ligand transfer mechanism.³¹

The copper(III) intermediates formed in these reactions can also form cyclopropanes (e.g., **27**) presumably by displacement of copper(III) by an enol/enolate (Scheme 4).^{32,33} Adduct radicals formed in the presence of MAN can be directly converted into azides,³⁴ chlorides,^{35,36} carboxylic acids^{37,38} (addition to carbon monoxide), and ketones³⁹ (addition to nitriles).

Baciocchi⁴⁰ and Flowers^{41–44} have studied the mechanism of the addition of β -dicarbonyl



Scheme 3 Mechanisms of product formation from adduct radicals.



Scheme 4 Mechanism of cyclopropane formation.

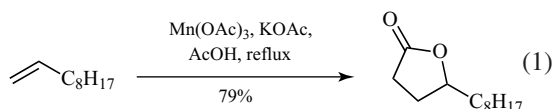
compounds to alkenes mediated by CAN and by ceric tetrabutylammonium nitrate (CTAN)—an organic soluble version of CAN. Flowers has shown that, unlike related reactions mediated by MAN, CAN and CTAN can directly oxidize enols to form radical cations which can add to alkenes or lose a proton prior to alkene addition (see below).

3 INTERMOLECULAR REACTIONS

3.1 γ -Lactones from Alkenes and Carboxylic Acids

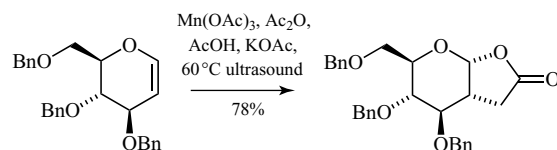
3.1.1 Use of Acetic Acid

The formation of γ -lactones by the reaction of alkenes with acetic acid in the presence of MAN was reported in 1968 by Heiba and Dessau⁴⁵ and Bush and Finkbeiner.⁴⁶ A wide variety of alkenes have been used for this purpose.¹⁹ For example, addition of acetic acid to 1-decene gives the corresponding γ -lactone in 79% yield (1).¹⁹



This procedure has recently been used for the synthesis of a number of carbohydrate-based γ -lactones from 1,2 and 2,3-glycals and acetic acid in the presence of acetic anhydride using ultrasound to

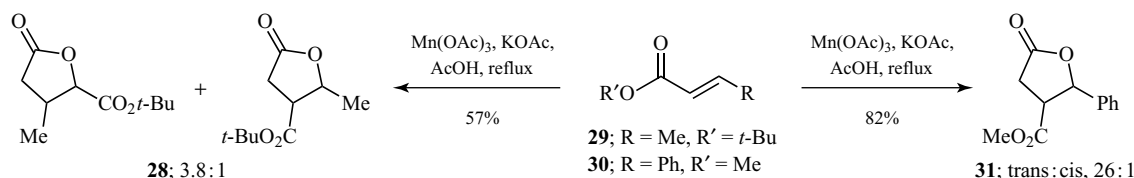
facilitate the reaction. An example is shown in (2).⁴⁷ Here, the regioselectivity of the addition is governed by the interaction of the low-energy singly occupied molecular orbital (SOMO) of the electron-deficient radical **3** interacting with the highest occupied molecular orbital (HOMO) of the glycal—a polarity-matched reaction. The use of MAN and CAN with sugar-based substrates has been widely studied by Linker (see below).^{48,49}



(2)

With other unsymmetrical di- and tri-substituted alkenes, the regioselectivity of γ -lactone formation is a balance of steric factors coupled with the relative stabilities of the adduct radicals. *tert*-Butyl crotonate **29** yields a 3.8 : 1 regioisomeric mixture of γ -lactones **28**, whereas methyl cinnamate **30** gives the corresponding γ -lactones **31** with almost complete regiocontrol, illustrating the enhanced stability of the intermediate benzylic radical (Scheme 5).¹⁹

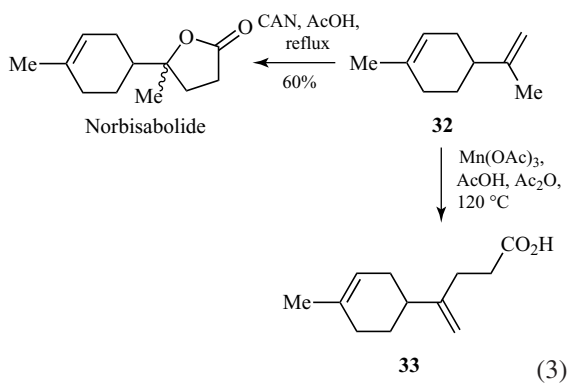
The functionalization of [60]fullerene (C₆₀) using MAN with acetic acid, propionic acid, or malonic acid to yield the corresponding γ -lactones has been reported.⁵⁰ The oxidation of γ -carboxy radicals by Mn(III) to form γ -lactones also occurs with certain vinyl radicals.⁵¹ The formation of γ -lactones from acetic acid and alkenes mediated by Ce(IV) has been far less investigated than the corresponding Mn(III)-mediated reactions. Heiba and



Scheme 5 Regioselective formation of γ -lactones.

Dessau reported the formation of the corresponding γ -lactone from the reaction between 1-octene or styrene and acetic acid in the presence of CAN or other Ce(IV) salts.^{52,53}

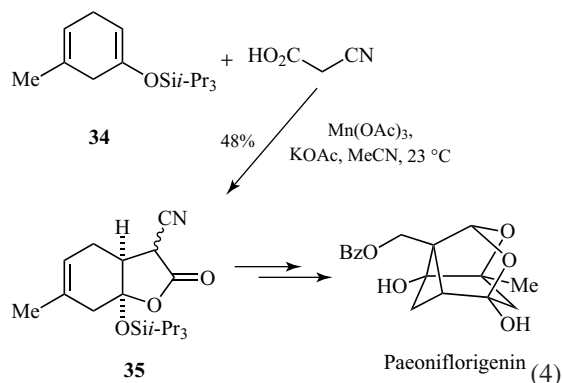
More recently, the direct synthesis of the natural product norbisabolide as a 1 : 1 mixture of diastereomers from limonene and acetic acid mediated by CAN has been achieved (3).⁵⁴ A previous synthesis of norbisabolide involved the reaction of limonene **32** with acetic acid in the presence of MAN and acetic anhydride which gave the diene **33**. The diene **33** was converted to norbisabolide in 43% overall yield on exposure to formic acid.⁵⁵ The formation of **33** from limonene in the presence of MAN is in keeping with the known propensity of acetic anhydride to give reduced yields of γ -lactones in Mn(III)-mediated reactions.^{19,56}



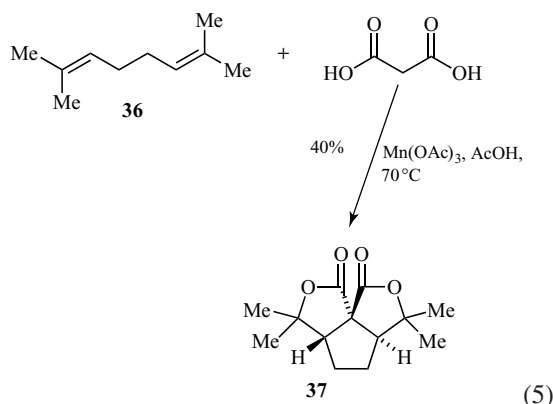
3.1.2 Use of Acetic Acid Derivatives

A wide variety of other carboxylic acids have been used in conjunction with MAN and alkenes to give the corresponding γ -lactones, and the area has been thoroughly reviewed.⁹ Of particular interest is the use of carboxylic acids such as cyanoacetic acid,^{20,53,57,58} malonic acid,^{59–61} and monoalkyl-malonic acids^{20,58,62–66} which have particularly acidic CH protons and therefore will add to alkenes to give γ -lactones using acetic acid as the solvent.

The γ -lactonization methodology using α -substituted malonic acids has been developed and used by Corey in the total synthesis of the biologically active natural products paeoniflorin and paeoniflorigenin.⁶⁷ Exposure of the silyl enol ether **34** to excess cyanoacetic acid in the presence of MAN gave the γ -lactone **35** in 48% yield (4); the major side product was silylated cresol arising from oxidation of the electron-rich substrate **34** under the reaction conditions. In this chemo- and regioselective transformation, the cyanoacetic acid radical adds to the most electron-rich position of the most electron-rich double bond in **34**. The use of CAN for γ -lactone annulation of alkenes with substituted acetic acids has been only sparsely studied.^{54,68} Reasonable yields of the γ -lactone annulation of limonene with cyanoacetic acid, chloroacetic acid, and propionic acid have been reported.⁵⁴

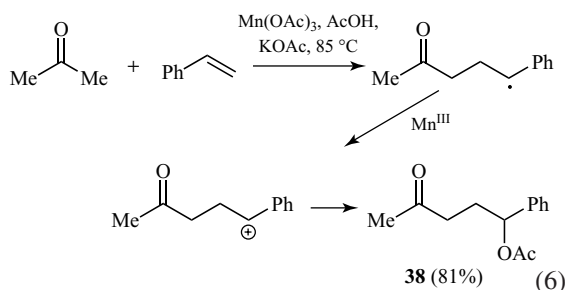


The addition of malonic acids to alkenes and dienes is of interest, as it results in a great increase in molecular complexity in a one-pot reaction (5).^{60,61} The reaction of the diene **36** with malonic acid gives the tricyclic bis-lactone **37**.⁶¹ In this reaction, two C–C bonds, two C–O bonds, three rings, and three stereocentres are formed in a single step from simple linear starting materials.



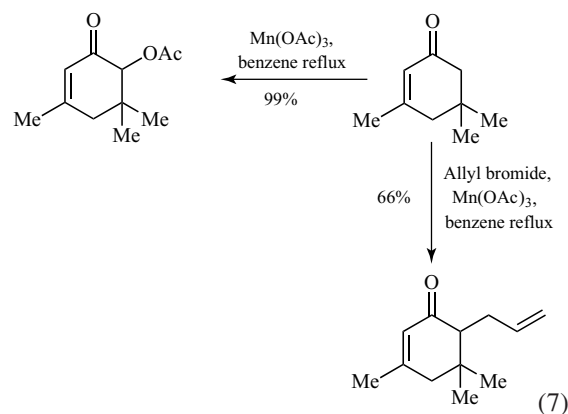
3.2 Aldehydes and Ketones

Mn(III)-mediated addition of aldehydes to alkenes gives rise to numerous products generally in low yield, and as such are not particularly synthetically useful and will not be discussed further.^{9,10} On exposure to MAN^{26,27} or CAN,⁶⁹ ketones generate α -oxoalkyl radicals. Multiple products are frequently formed in the reaction of ketones with alkenes and yields are frequently modest. The reaction of styrene with acetone in the presence of MAN gives the corresponding acetate **38** in good yield owing to the ready oxidation of the benzylic adduct radical to the corresponding cation which is then trapped by acetate (6).⁷⁰ The reaction of acetone with aromatic compounds mediated by MAN and CAN has been studied.^{71,72}

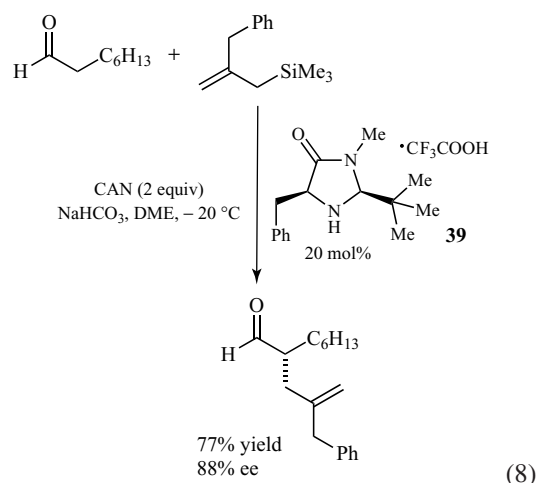


The allylation of a range of (mainly) cyclic α,β -unsaturated ketones and α -alkoxy and β -alkoxy α,β -unsaturated ketones using anhydrous MAN and allyl bromide in benzene provides an alternative to enolate allylation (7).^{73,74} In the absence of allyl bromide, the α' -acetoxy ketone is formed in excellent yield; this is a general procedure for the α' -acetoxylation of unsaturated ketones.^{75–77}

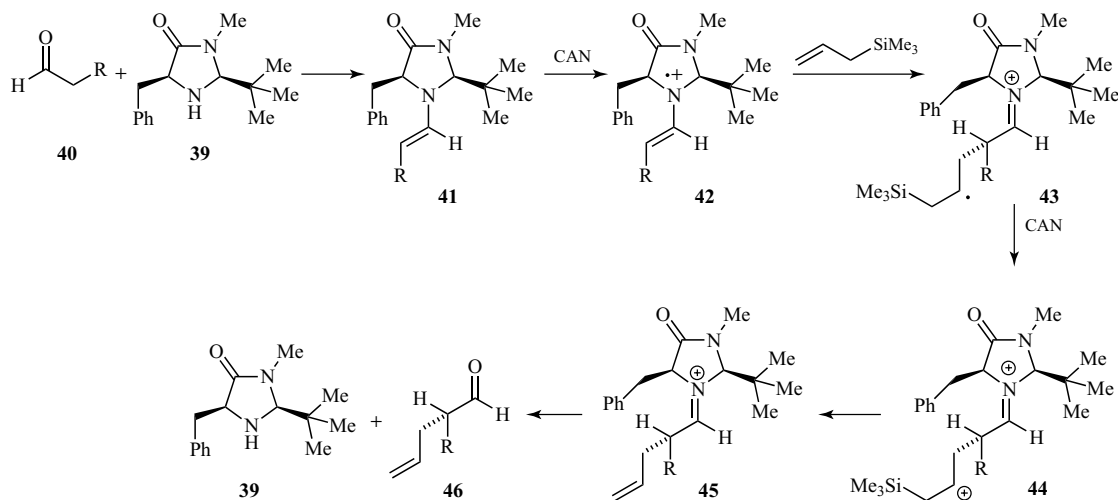
The addition of ketones to enol acetates gives 1,4-diketones or dimethyl acetals in the presence of either Mn(III)⁷⁸ or Ce(IV).⁷⁹ The use of Ce(IV) gives higher yields of product, although with both metals the yields quoted are with respect to the oxidant in the presence of excess ketone and alkenyl acetate.



Recently, MacMillan has reported a wide variety of catalytic enantioselective oxidative radical reactions which he has termed *SOMO catalysis* (see **Stereoselective Radical Reactions**). The first of a series of publications was concerned with the α -allylation of aldehydes in the presence of CAN (8),⁸⁰ which has since been extended to the catalytic enantioselective allylation of cyclic ketones.⁸¹



The mechanism of this reaction most likely involves initial stereoselective enamine formation between the aldehyde **40** and the amine catalyst



Scheme 6 Mechanism of enantioselective allylation.

39 (Scheme 6).⁸² Oxidation of the electron-rich enamine **41** then occurs to give the radical cation **42** which adds to the allylsilane giving the adduct radical **43**. Oxidation of the adduct radical **43** to the β -silyl cation **44** using a second equivalent of CAN followed by electrofugal loss of silicon and iminium ion hydrolysis delivers the allylated aldehyde **46** and regenerates the amine catalyst **39**.

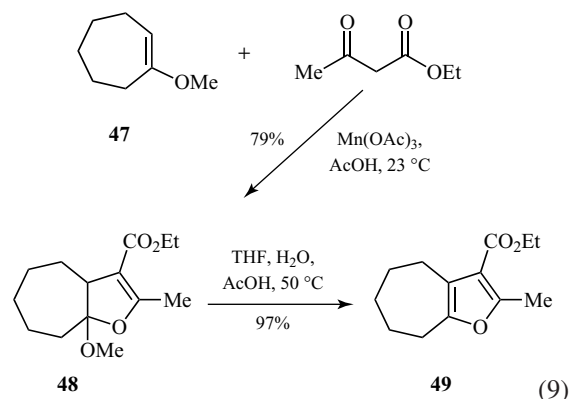
This is a very powerful synthetic methodology that has been used for the catalytic enantioselective formation of 1,4-dicarbonyl compounds using enol silanes in place of allylsilanes,⁸³ as well as the catalytic enantioselective formation of β -nitroaldehydes, useful precursors to β -aminoaldehydes, using silylnitronates in place of allylsilanes.⁸⁴ The use of styrenes as the radical acceptors in these reactions gives rise to the corresponding γ -nitroaldehydes with control of up to three contiguous stereocenters.⁸⁵ A further asymmetric process involves the use of vinyl trifluoroborate salts for the asymmetric vinylation of aldehydes.⁸⁶

3.3 Addition of β -Dicarbonyl and Related Compounds to Alkenes

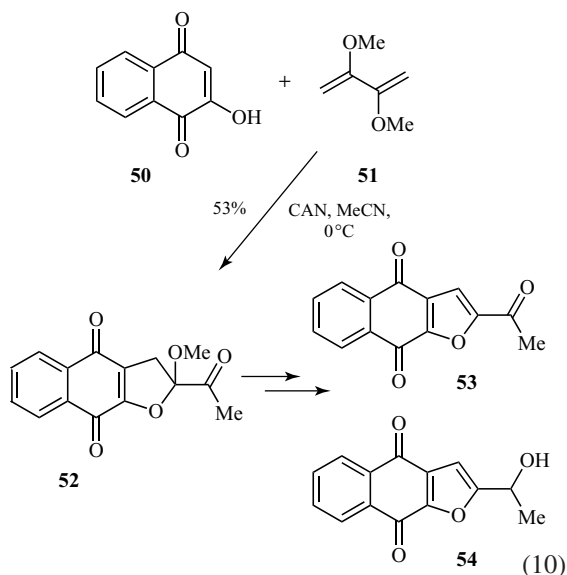
3.3.1 Synthesis of Dihydrofurans

The synthesis of dihydrofurans (DHF) from the reaction of β -keto esters and β -diketones with

alkenes mediated by MAN and CAN has been very widely studied since the initial report of Heiba and Dessau.⁸⁷ A wide range of alkenes engage in this reaction.^{88,89} Corey and Mellor demonstrated the use of *endo*-cyclic enol ethers as substrates^{89–91} to form DHFs in the presence of β -keto esters, β -diketones, and esters of acetone dicarboxylic acid. For example, exposure of the enol ether **47** and ethyl acetoacetate to MAN in acetic acid gave the bicyclic enol ether **48** in good yield, which on treatment with acid gave the corresponding furan **49** (9).⁸⁹ Thio ethers and *exo*-cyclic enol ethers can also be used for DHF and sulfur heterocycle synthesis.^{92–95} Other groups have reported the formation of spirocyclic DHFs from 1,1-disubstituted alkenes using MAN⁹⁶ and CAN.^{97,98}

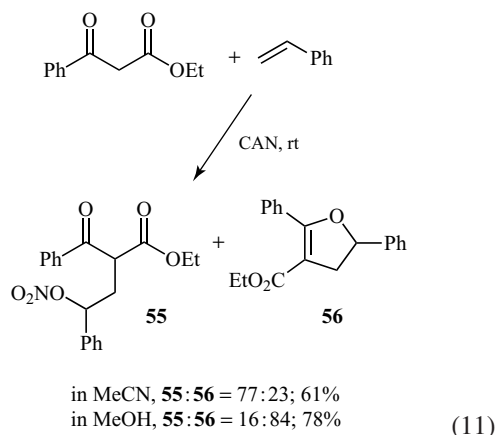


Lee⁹⁹ and others^{100,101} have investigated the addition of β -dicarbonyl compounds to conjugate dienes, including enol ethers, using MAN and CAN. The reaction of **50** with **51** gave the acetal **52**, which was used to prepare the anticancer natural products **53** and **54** (10).⁹⁹ Further examples of the use of **50** as the β -dicarbonyl component in Mn(III)-mediated synthesis of DHFs have been reported.¹⁰²

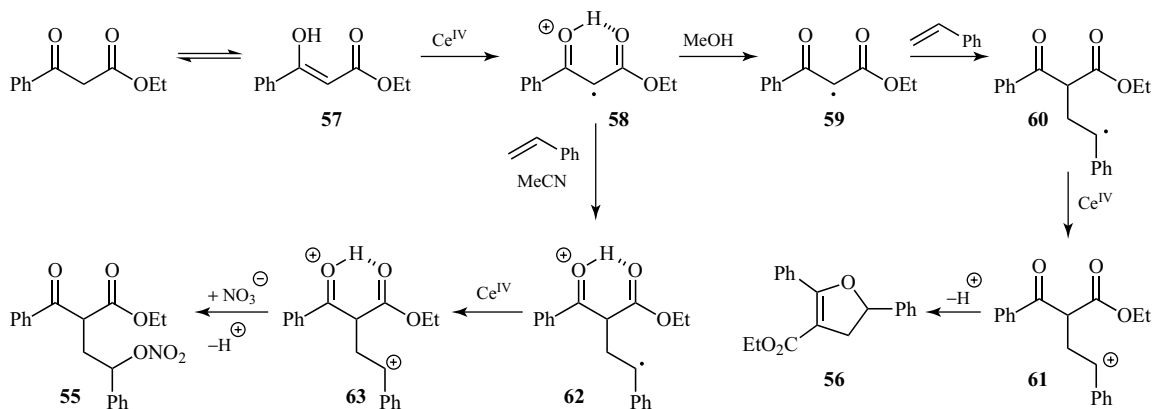


The addition of β -keto esters and β -diketones to variously substituted alkenes mediated by CAN or CTAN has also been widely studied.^{40,103} Flowers⁴¹ has demonstrated a solvent-dependent synthesis of DHFs (11). Treatment of a range of β -diketones and β -keto esters with styrenes and CAN in methanol or

acetonitrile gave predominantly the DHF (e.g., **56**) or the organic nitrate (e.g., **55**); the nature of the aryl group on the ketonic substrate also affected the product distribution.



In-depth mechanistic analysis led to the following proposed reaction pathway to account for the solvent dependent product distribution (Scheme 7): Direct oxidation of the enol **57** gives the radical cation **58**. In MeOH, the radical cation readily loses a proton to give the radical **59**, which reacts with styrene to give adduct radical **60**. Further single-electron oxidation yields the benzylic cation **61**, which forms the DHF **56** on deprotonation. In the aprotic solvent acetonitrile, the radical cation **58** reacts directly with styrene to give the adduct radical **62**. Further oxidation by Ce(IV) gives the benzylic cation **63**, which suffers from restricted rotation due to intramolecular hydrogen bonding and therefore traps nitrate anion to give product **55**.



Scheme 7 Solvent-dependent DHF/nitrate formation.

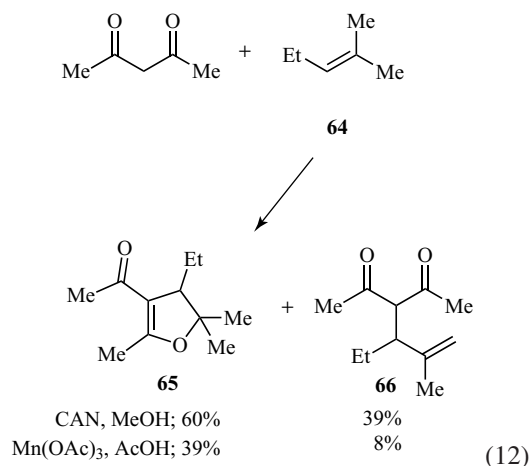
Flowers⁴⁴ and Hwu¹⁰⁴ have independently studied the reaction between β -dicarbonyl compounds and allylsilanes to give silyl-containing DHFs or allylated products, depending on the reaction conditions. Flowers has also investigated the use of silyl enol ethers in place of β -dicarbonyl compounds in these reactions. The addition of a 1,3-ketoaldehyde to a silyl enol ether mediated by CAN has been used by Baran in model studies toward the synthesis of maoecrystal V.¹⁰⁵

Vinyl sulfides are excellent substrates for the CAN-mediated formation of DHFs on reaction with β -dicarbonyl compounds with yields generally being higher using CAN rather than MAN.^{106–109} The addition of β -keto esters and β -diketones to indoles to yield DHFs mediated by MAN has also been reported.¹¹⁰

DHFs fused to C₆₀ have been synthesized using both β -keto esters and β -diketones in reasonable yields (based on consumed [60]fullerene).^{111,112} The functionalization of fullerenes with a range of pro-radical species including malonates,^{111,113,114} diallylamines,¹¹⁵ phosphonates,¹¹⁶ β -amino ketones, and esters¹¹⁷ under the influence of MAN has been reported.

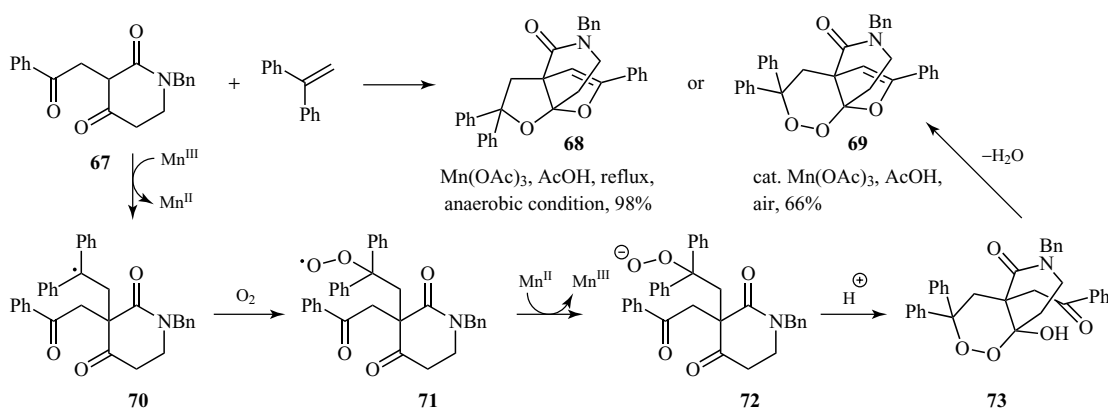
Nair and coworkers have widely studied the formation of DHFs by the addition of β -diketones and β -keto esters to a range of alkenes mediated by CAN including a comparative study with MAN.^{101,118–120} In their study, CAN-mediated reactions were generally slightly higher yielding and faster than Mn(III)-mediated reactions. As an example, the addition of acetylacetone to the hindered alkene **64** occurred regioselectively at the less hindered end of the alkene to give the DHF **65** and

the alkene **66** (12).¹²⁰



Various substituted alkenes undergo reaction with CAN or MAN in the presence of β -dicarbonyl compounds with yields generally being higher with substituents on the alkene substrate which are readily able to stabilize the intermediate carbenium ions.^{96,121} The regiochemistry of DHF formation has been investigated using trifluoromethyl acetyl acetone as the β -dicarbonyl component.¹²²

Nishino has developed an efficient route to a wide range of tricyclic and endoperoxide propellanes using tricarbonyl substrates. For example, under anaerobic conditions, exposure of a range of tricarbonyl substrates such as **67** to an electron-rich alkene and MAN gave the propellane **68** (Scheme 8).^{123,124} If rigorous exclusion of oxygen was not achieved, then mixtures of the propellanes **68** and **69** were obtained and conducting



Scheme 8 Formation of propellanes.

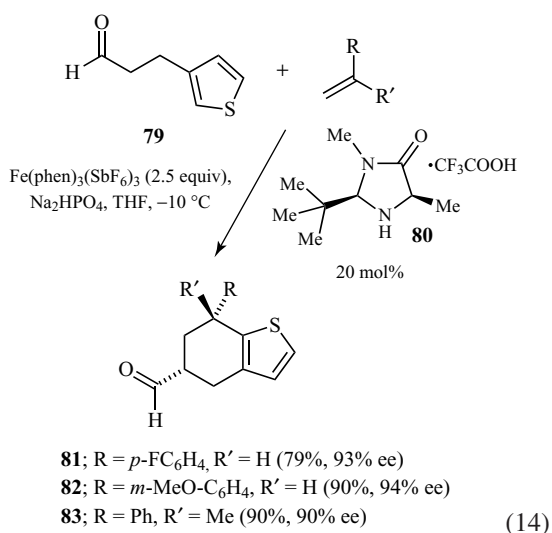
A wide variety of β -dicarbonyl equivalents have been used for DHF formation. The natural product 4-hydroxycoumarin has been used as a β -dicarbonyl component in DHF synthesis^{102,129} and for the key step in the synthesis of the natural product fercoprolone.¹³⁰ The nitrogen analog of 4-hydroxycoumarin has been used for the synthesis of araliopsine and related quinoline alkaloids.^{131,132} Other β -dicarbonyl equivalents used in the synthesis of DHFs include β -keto amides¹³³ and β -cyano ketones^{134–136} and 4-hydroxy-2-quinolones.¹³⁷ β -Keto sulfones are also viable substrates for DHF formation under oxidative radical conditions.^{138–141}

The addition of β -dicarbonyl and related compounds to heteroaromatics mediated by MAN or

3.3.3 Addition and Subsequent Cyclization onto an Aryl Ring

Iron(III) catalysts have been used by MacMillan as single-electron oxidants in catalytic

enantioselective addition–cyclization reactions which allow the rapid increase of molecular complexity.¹⁵⁹ A number of aldehydes bearing a diverse range of electron-rich aromatic groups (e.g., thiophenes, indoles, catechols, benzofurans) undergo oxidative coupling–cyclization with a range of styrenes to give cyclohexanes bearing two stereocentres in good yield and with high enantio- and diastereoselectivity. For example, the thiophene-substituted aldehyde **79** undergoes coupling with a range of styrenes in the presence of the organocatalyst **80** and iron(III) hexafluoroantimonate to give the cyclohexanes **81–83** (14); extension of the method to the use of aldehydes bearing allylsilanes was also reported.

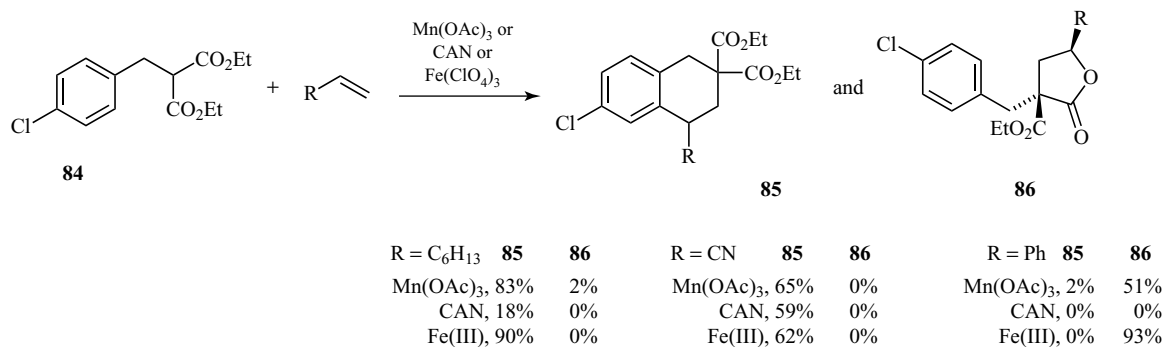


In an early example of addition–cyclization using β -dicarbonyl compounds, Citterio reported

the addition of malonyl radicals onto alkenes with subsequent cyclization onto an aromatic ring in the presence of Mn(III), Ce(IV), and Fe(III) salts.¹⁶⁰ This is an efficient process that works with a very wide variety of aromatic and olefinic substrates. As part of this study, diethyl 4-chlorobenzylmalonate **84** and a range of alkenes were treated with MAN in acetic acid at 60°C , CAN in methanol at 20°C , and iron(III) perchlorate in acetonitrile at 20°C (Scheme 9). Both with 1-octene and acrylonitrile, good yields of the corresponding benzannulated products **85** were isolated with Mn(III) and Fe(III) mediators, whereas the use of CAN resulted in the predominant formation of products of oxidative elimination and ligand transfer (not shown). Using styrene as the alkene gave rise to the corresponding γ -lactones **86** in good yield.

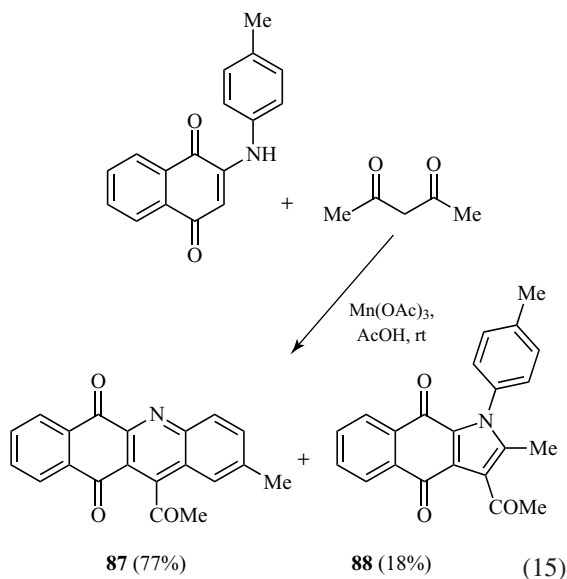
The use of alkynes as substrates in similar reactions resulted in the formation of the analogous dihydronaphthalenes, rearranged dihydronaphthalenes, and spirocyclic products.¹⁶¹ In a related study, Citterio reported the reaction of dialkylpyridylmethyl malonates with alkenes and alkynes in the presence of Mn(III), Ce(IV), and Fe(III) salts to give dihydroquinolines or isoquinolines in high yields¹⁶²; the use of 3-picolylmalonates gave regioisomeric mixtures of products with both alkenes and alkynes.

Chuang has widely developed addition–cyclization methodologies using MAN or CAN over a number of years.^{110, 163–165} For example, addition of acetylacetone to 2-amino-1,4-naphthoquinones followed by cyclization onto a pendent aromatic group gives the tetracyclic product **87** along with the tricyclic heterocycle **88** (15)¹⁶⁶; the use of bulkier β -dicarbonyl compounds generally gave the



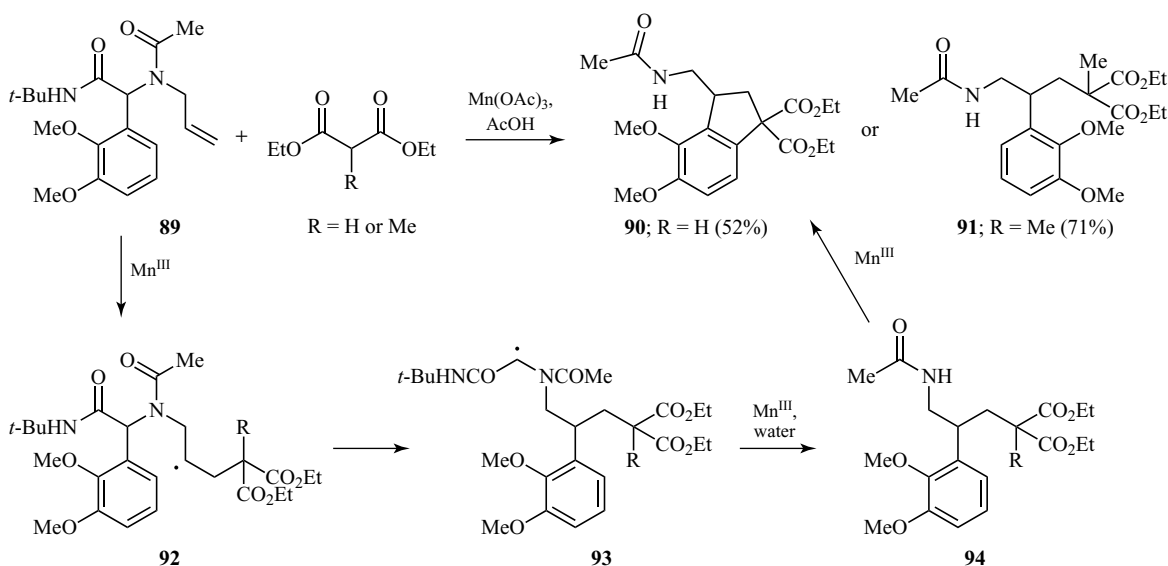
Scheme 9 Metal-dependent formation of tetrahydronaphthalenes or γ -lactones.

tetracyclic products with higher selectivity. Chuang has reported a similar method for the formation of phenols and furans from 2-benzoyl-1,4-benzo- and naphthoquinones.^{167,168} Addition–cyclization reactions involving heteroaromatics have also been reported.^{169,170}

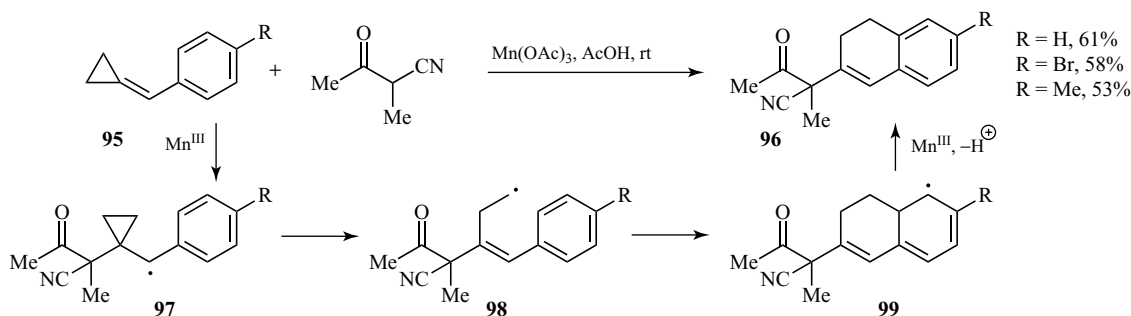


A powerful synthesis of indanes and δ -aminomalonates by a one-pot Ugi reaction, radical addition–cyclization cascade has recently been reported.¹⁷¹ Thus treatment of a variety of aromatic aldehydes, isocyanides, and carboxylic acids gave the Ugi products (e.g., **89**), which upon treatment with malonates or β -keto esters in the presence of MAN gave indanes or δ -aminomalonates (Scheme 10). The reaction most likely proceeds by formation of the adduct radical **92**, which undergoes neophyl rearrangement to give **93**. Further oxidation of **93** followed by hydrolysis gives **91**. If the malonate still carries an acidic CH proton, further oxidation and cyclization occurs to yield the indane **90**.

Huang has reported an addition–rearrangement–cyclization reaction of a range of β -dicarbonyl compounds with methylene cyclopropanes in the presence of MAN.^{172,173} As an example, exposure of a range of methylene cyclopropanes **95** to an α -cyanoketone and MAN gave the corresponding dihydronaphthalenes **96** (Scheme 11).¹⁷² A likely mechanism for this reaction involves a methylcyclopropyl–homoallyl rearrangement of adduct radical **97** to give **98**, which undergoes cyclization onto the aromatic ring followed by further Mn(III)-mediated oxidation to give the product.



Scheme 10 Cyclization–rearrangement of Ugi products.



Scheme 11 Addition–rearrangement–cyclization to give dihydronaphthalenes.

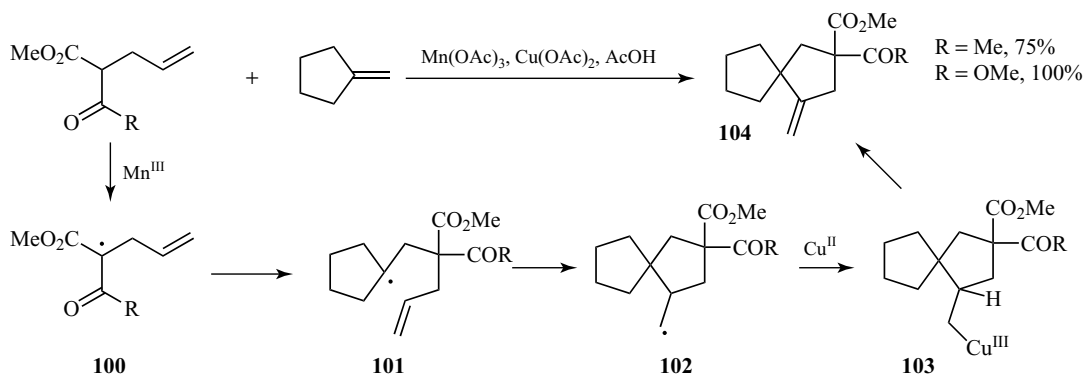
3.3.4 Addition and Subsequent Cyclization onto an Alkene

The addition of malonates and related β -dicarbonyl compounds carrying pendent unsaturation to olefins followed by subsequent cyclization is a very powerful method for multiple C–C bond formation.^{39,174,175} An example is shown in which spirocyclic products are formed in good yield (Scheme 12).¹⁷⁴ The mechanism of the reaction most likely involves the regioselective addition of the malonyl/acetoacetyl radical **100** to methylene cyclopentane to give the tertiary adduct radical **101**. The adduct radical undergoes rapid 5-*exo*-trig radical cyclization to give the primary radical **102**, which gives the products **104** on oxidative elimination in the presence of copper(II) acetate. This is a powerful synthetic transformation resulting in the formation of two C–C bonds, two

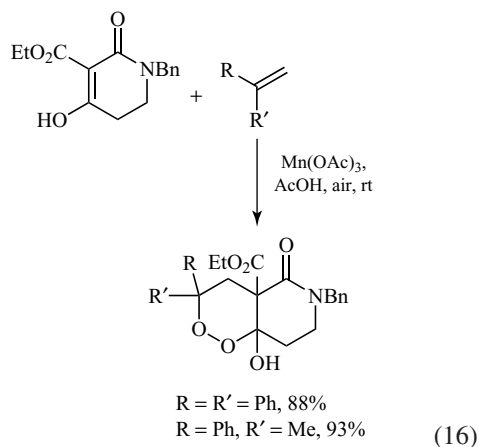
rings, and an alkene in one step from simple substrates.

3.3.5 Other Addition Reactions

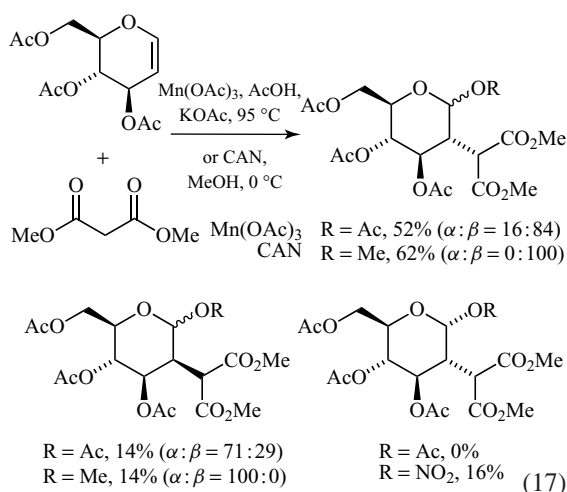
Nishino has been very active in the area of Mn(III)-mediated intermolecular radical additions and has reported a number of methods for the synthesis of endoperoxides from alkenes using MAN and a wide range of β -dicarbonyl equivalents including β -diketones,¹⁷⁶ β -keto esters,^{176–178} amides,^{126,176,179,180} sulfoxides,¹⁴¹ sulfones,¹⁴¹ and phosphinates.¹⁴¹ An example of this work involves the formation of endoperoxides from β -keto amides and alkenes with sub-stoichiometric MAN in air at ambient temperature (16).¹⁸⁰ The mechanism for product formation is analogous to that shown in Scheme 8. Diperoxides can also be formed in certain instances.¹⁸¹



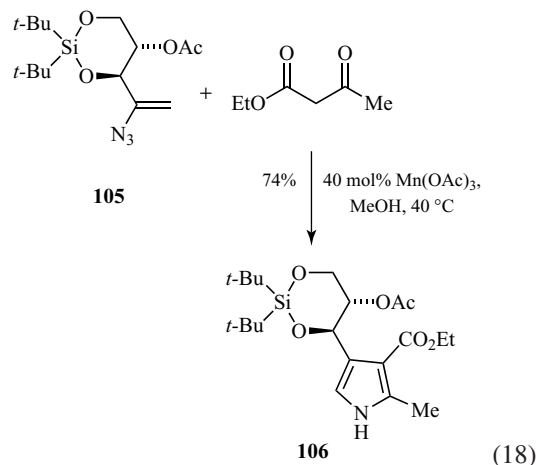
Scheme 12 Spirocycle formation by addition and subsequent cyclization.



The intermolecular addition of malonates, nitroalkanes, and related compounds to glycals in the presence of MAN or CAN has been widely studied by Linker for the synthesis of 2-*C*-glycosides. In an early publication,¹⁸² Linker exposed tri-*O*-acetyl-*D*-glucal to dimethyl malonate and MAN or CAN, which delivered the corresponding 2-*C*-glucosides in good overall yield (17); the Ferrier rearrangement product (not shown) was also isolated in 10% yield in the Mn(III)-mediated reactions. A number of other glycals and dialkyl malonates and nitroalkanes^{183,184} have been used in these reactions.^{185,186} Additionally, the complete suppression of anomeric nitrate formation could be achieved by using anhydrous CAN.^{187,188} Disaccharides can also be functionalized using this methodology.¹⁸⁴ The addition of nitroalkenes to non-sugar enol ethers and silyl enol ethers mediated by CAN has also been studied.¹⁸⁹

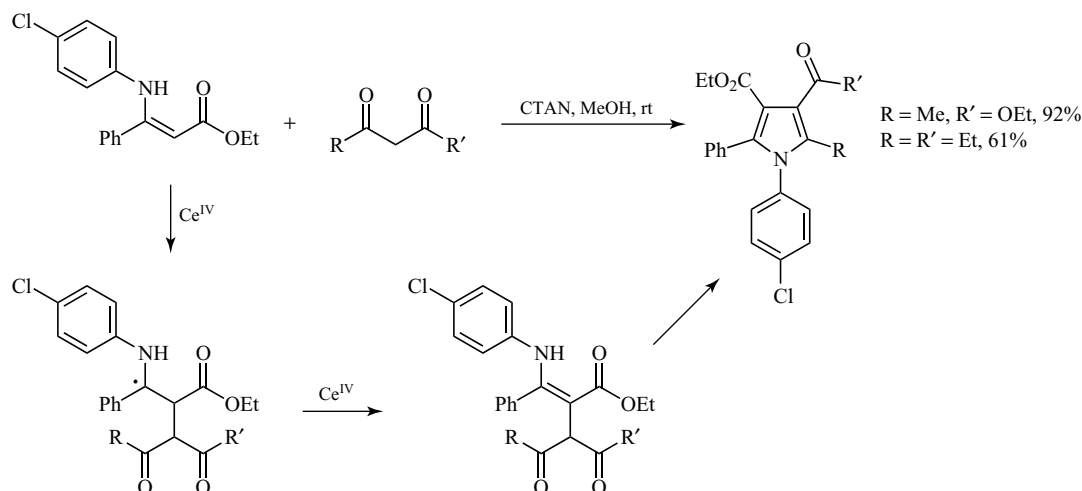


An interesting synthesis of pyrroles from vinyl azides was recently reported using sub-stoichiometric quantities of MAN (5–40 mol%).¹⁹⁰ One of the many reported examples involves the synthesis of the pyrrole **106** from the triol derivative **105** and ethyl acetoacetate in 74% yield (18). Overall, this is not an oxidation but nevertheless is of mechanistic and synthetic interest.



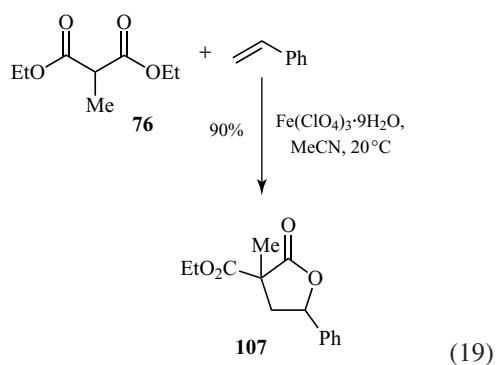
Chuang has published widely on the synthesis of five-membered aromatic nitrogen heterocycles formed between a range of β -dicarbonyl and related compounds with quinones^{191–197} and vinylogous carbamates^{198,199} in the presence of MAN or Ce(IV) salts. Two of the many examples are shown in Scheme 13, along with a proposed mechanism for pyrrole formation. Thus, pyrroles are readily formed by oxidative radical reaction of β -dicarbonyl compounds with enamines in the presence CTAN or MAN; yields were generally highest when CTAN was used.¹⁹⁸

The addition of malonates to alkenes under the influence of transition-metal salts has been widely studied. In some early studies, Citterio demonstrated that iron(III) perchlorate was an effective mediator of oxidative radical reactions giving γ -lactones (**107**) in good yields (19)²⁰⁰; yields were significantly lower with alkyl-substituted alkenes. The use of butadiene in this reaction resulted in the formation of the corresponding spirocyclic product. The addition of malonates to styrene and related alkenes, under the influence of CAN, gave lower yields of the γ -lactones corresponding to **107**, and mixtures



Scheme 13 Formation of pyrroles from enamines and β -dicarbonyl compounds.

of products were frequently formed.^{120,201,202}

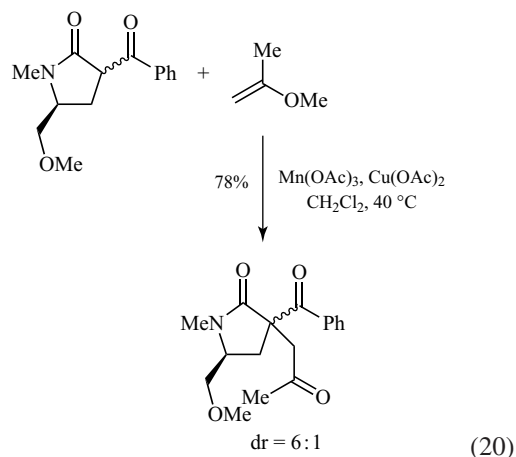


With MAN, dimethyl malonate, and styrene, a low yield of the γ -lactone corresponding to **107** was reported; however, when stilbene was used as the substrate, the corresponding γ -lactone product was formed in 86% yield as a single diastereomer.²⁰³

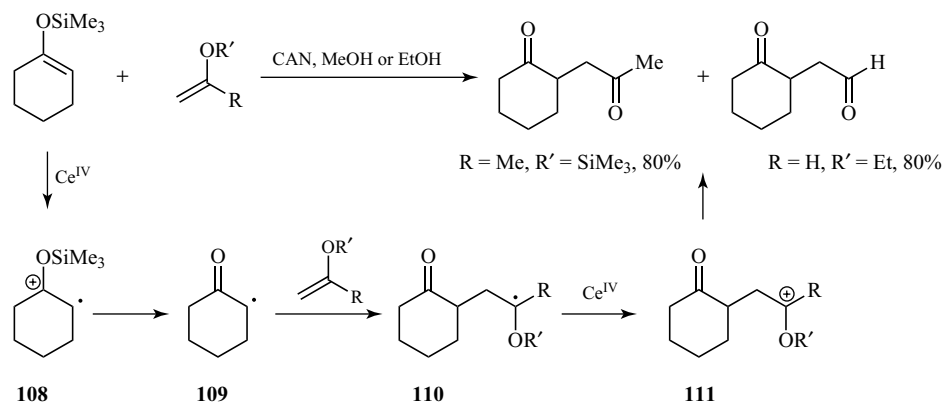
The addition of dialkyl malonates carrying additional carbonyl functionality to alkenes leads to dihydropyrans in good yield.²⁰⁴ Allenes have also been used as substrates for reaction with dimethyl malonate and ethyl cyanoacetate mediated by MAN.^{205,206}

Enol ethers have been widely used as substrates in oxidative radical chemistry. Corey and Ghosh reported MAN-mediated addition of acetoacetyl radicals to isopropenyl acetate to directly give 1,4-diketones in good yield.⁹¹

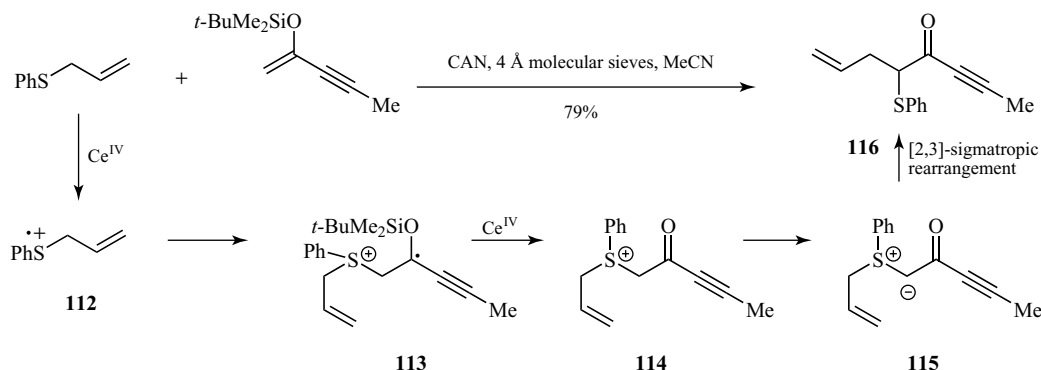
Parsons has extended this methodology to the synthesis of a wide range of 1,4-keto aldehydes²⁰⁷ and to an auxiliary controlled diastereoselective synthesis of 1,4-diketones (**20**).²⁰⁸



The use of silyl enol ethers as substrates in CAN-mediated reactions has been widely studied. In early and synthetically interesting examples,^{209,210} Baciocchi reported the synthesis of 1,4-diketones and keto aldehydes by the treatment of silyl enol ethers or ethyl vinyl ether, respectively (Scheme 14). The mechanism of these reactions involves direct oxidation of the electron-rich silyl enol ether with CAN to give a radical cation **108**,



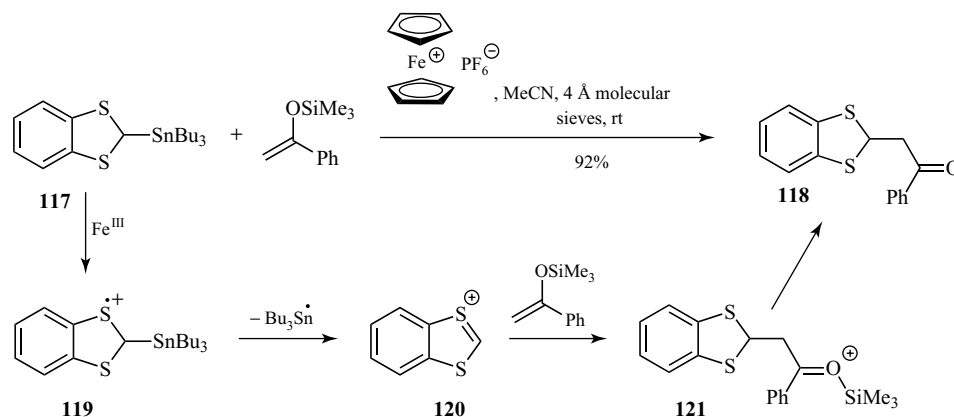
Scheme 14 Dimerization of enol ethers.

Scheme 15 Mechanism of α -thioketone formation.

which either undergoes addition to the second enol ether or gives the corresponding radical **109** followed by subsequent enol ether addition. Oxidation of the adduct radical **110** by CAN gives the corresponding oxocarbenium ion **111**, which readily yields the product. In these reactions, the more electron rich of the two substrates is preferentially oxidized. The addition of silyl enol ethers to ethyl vinyl ether mediated by CAN has been reported by other research groups.²¹¹ The use of silyl dienol ethers and dienes in these reactions has been studied,^{212,213} as well as the reaction between enamines and silyl enol ethers.²¹⁴ It should be noted that silyl enol ethers do not form the corresponding radical cations with MAN, although they can be used as electron-rich acceptors of electrophilic radicals formed in Mn(III)-mediated reactions⁶⁷; more commonly, Mn(III) picolinate is used for such reactions.^{215,216}

The reaction of allyl sulfides and conjugated silyl enol ethers with CAN yields allylated products (Scheme 15).²¹⁷ Here, the electron-rich sulfur atom is readily oxidized by CAN to give the radical cation **112**, which undergoes addition to the silyl enol ether giving **113**. A further single-electron oxidation followed by loss of the silyl group yields the sulfonium salt **114**. Ylide formation with subsequent [2,3]-sigmatropic rearrangement gives product **116**.

The generation of thiocarbenium ions by the oxidation of 2-tributylstannyl-1,3-dithianes and related compounds by Ce(IV) and Fe(III) salts has been studied by Narasaka.^{218,219} These cations react with silyl enol ethers and related electron-rich alkenes to give sulfur-containing products. Of the many examples reported, the reaction of the stannane **117** with a silyl enol ether mediated by ferrocenium hexafluorophosphate is illustrative (Scheme 16).²¹⁹ Thus, single-electron oxidation at sulfur yields the



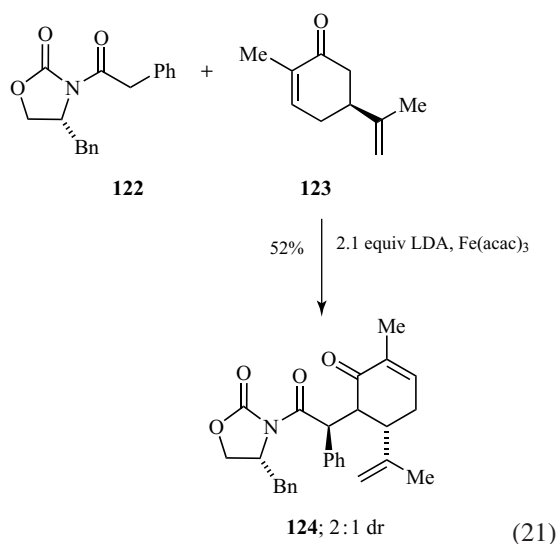
Scheme 16 Formation and reaction of a thiacarbenium ion.

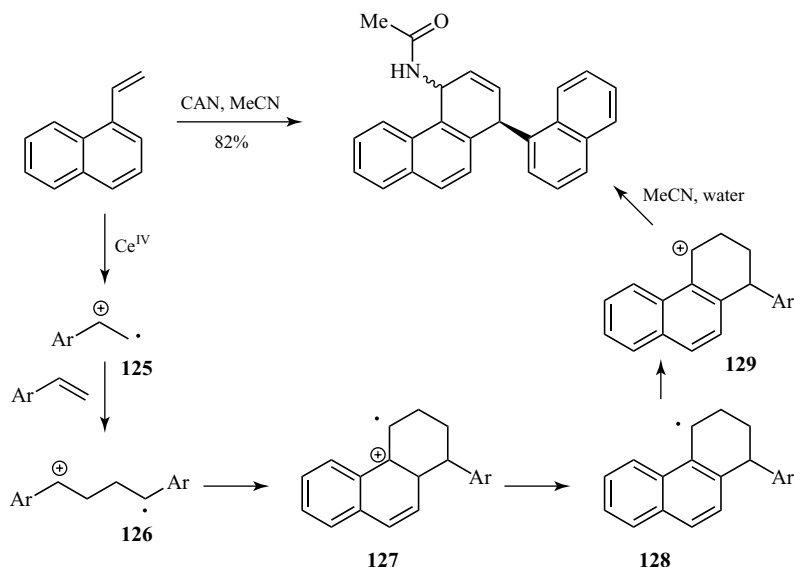
radical cation **119**, which loses tributyltin radical to give **120**. Reaction of the cation **120** with the silyl enol ether gives the oxocarbenium ion **121**, which on loss of the trimethylsilyl cation gives the product **118**. In a similar manner, *N*-acyl iminium ions are readily formed by oxidation of α -tributylstannyl amides with ferrocenium hexafluorophosphate or CAN and undergo reaction with silyl enol ethers.²²⁰ α -Tributylstannyl esters undergo CTAN-mediated oxidation to give electrophilic radicals, which add to silyl enol ethers and other electron-rich olefins to give 1,4-dicarbonyl compounds.²²¹

3.3.6 Homo and Heterocoupling

The electrophilic radicals that are generally formed at the start of the reaction sequence in many the reactions considered thus far are prone to dimerization, which can occur in synthetically useful yields.^{222–230} Nicolaou has used such a dimerization in the synthesis of the natural product hybocarpone.²³¹ The head-to-head dimerization of 1,3-bis(trimethylsilyloxy)buta-1,3-dienes mediated by CAN has been reported for the synthesis of 1,4-dihydroquinones.²³² Although the homocoupling of enolates mediated by iron(III) salts has been known for a long time,^{228–230} the heterocoupling of enolates has only recently been studied because of the inherent difficulties of realizing an oxidative coupling between two chemically similar entities in high yield without recourse to using one coupling partner in excess. Such a transformation is inherently attractive, as it would give rise to

a 1,4-dicarbonyl compound, which is traditionally more difficult to prepare than the corresponding 1,3 or 1,5 -dicarbonyl compounds. Baran has demonstrated that iron(III) salts are capable of coupling imide enolates with ketone enolates, as well as oxindole enolates with ketone enolates, in synthetically useful yields via an SET mechanism^{233,234}; copper(II) salts were also efficient oxidants for a range of heterocouplings. One of the many examples is shown in (21). Thus, treatment of a mixture of the two substrates **122** and **123** with 2 equiv of lithium di-*iso*-propylamide (LDA) followed by addition of 2 equiv of iron(III) acetylacetonate gave the heterodimer **124** in 52% yield as a 2:1 mixture of diastereomers at the stereocenter adjacent to the ketone.





Scheme 17 Formation of α -acetamido tetralins.

Treatment of electron-rich aromatics with single-electron oxidizing agents such as Ce(IV), Mn(III), and Fe(III) salts results in the formation of radical cations from which a range of products may be formed via C–C and/or C–X bond formation.¹⁶ One of the most impressive examples of such reactions involves the reaction of a range of styrenes with CAN in acetonitrile which gives the α -acetamido tetralins in good yield (Scheme 17).²³⁵ The likely mechanism of this process involves the formation of the radical cation **125**, which reacts with a second molecule of substrate to give the radical cation **126**. Cyclization occurs to give a third radical cation **127**, which loses a proton to give the radical **128**. Further single-electron oxidation occurs to give the cation **129**, which is trapped by acetonitrile to give the product on hydrolysis.

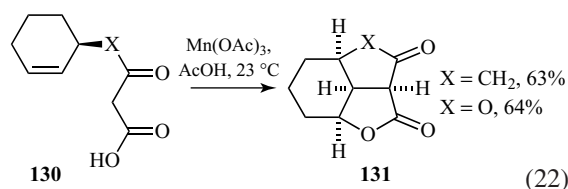
4 INTRAMOLECULAR REACTIONS

4.1 Monocyclization

4.1.1 Cyclizations Involving Carboxylic Acids

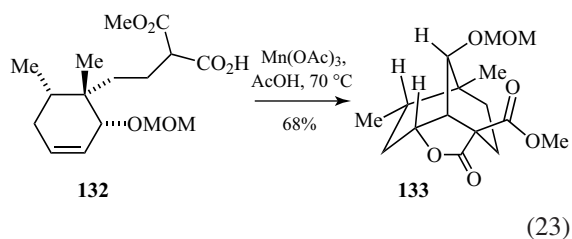
The cyclization of radicals derived from β -keto acids and related compounds onto alkenes results

in the formation of bi- and tricyclic γ -lactones in good yield.²³⁶ As an example, treatment of the β -keto acid **130** (X = CH₂) with MAN delivers the tricyclic γ -lactone **131** (X = CH₂) in 63% yield, whereas cyclization from the corresponding malonic half ester **130** (X = O) gave the tricyclic γ -lactone **131** (X = O) in 64% yield (22).

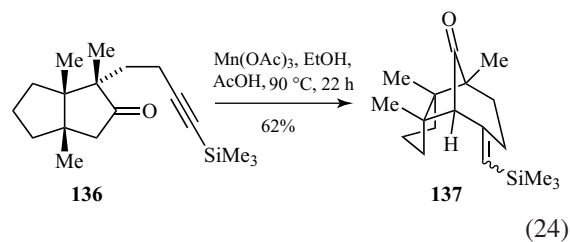


In a related manner, Snider demonstrated the formation of bridged bicyclic γ -lactones on exposure of unsaturated malonic acids to MAN,²³⁷ and Fristad has demonstrated the formation of fused bicyclic γ -lactones by the cyclization of unsaturated malonic acids and derivatives thereof.²³⁸ Paquette has used the MAN-mediated cyclization of malonic acid derivatives in a synthesis of 14-epiupial—the epimer of the natural product upial. Thus, treatment of the malonic acid monomethyl ester **132** with MAN in acetic acid delivered the tricyclic γ -lactone **133** in 68% yield, which was advanced

to 14-epiupial in nine further steps (23).²³⁹



in the formation of mainly oligomeric material.



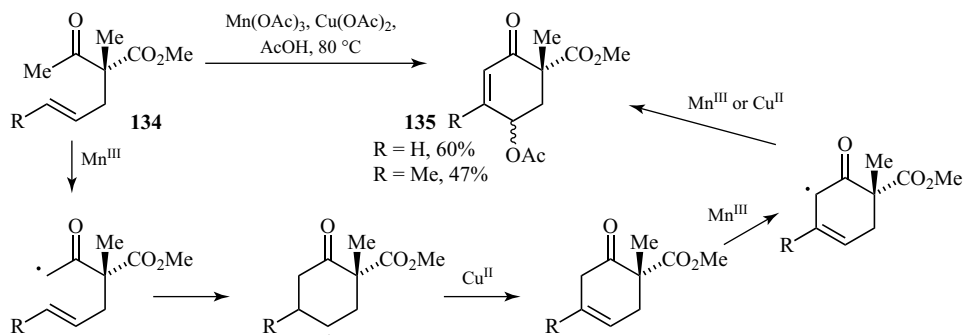
4.1.2 Cyclizations with Aldehydes and Ketones

The intramolecular oxidative cyclization of ketones mediated by MAN is generally much more efficient than the corresponding intermolecular process. Snider has studied this process widely.^{240–242} As an example, exposure of the methyl ketones **134** to MAN and copper(II) acetate results in the formation of the cyclohexenyl acetates **135** as a mixture of diastereomers (Scheme 18). A plausible mechanism for this reaction is shown. Similar methodology has been developed for the synthesis of a wide range of bridged bicyclic ketones.^{240–243}

Intramolecular ketone cyclizations onto alkynes have been used in the total synthesis of racemic gymnomitrol.²⁴⁴ Thus, treatment of the ketone **136** with excess MAN in a mixed solvent system delivered the tricyclic ketone **137** in 47% yield (62% based on recovered starting material) as a mixture of alkene stereoisomers, which was converted into gymnomitrol in two further steps (24); use of a terminal acetylene substrate resulted

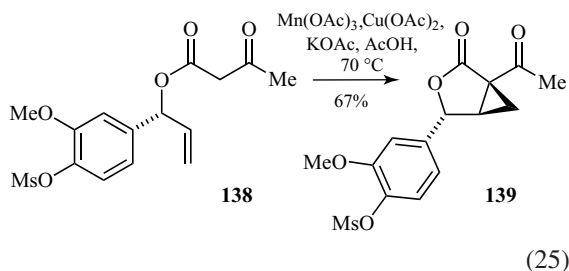
4.1.3 Cyclizations with β -Keto Esters

Cyclization of electrophilic radicals derived from β -keto esters are by far the most extensively explored cyclization reactions and have been used in the synthesis of numerous natural products. As a general guide, oxidative radical cyclizations of substituted β -keto esters are higher yielding than cyclizations of unsubstituted β -keto esters because further oxidation of the product is possible in the latter case. However, unsubstituted β -keto esters can cyclize onto terminal alkenes in the presence of copper(II) acetate to give good yields of cyclopropanes (Scheme 4).^{32,33} A diastereoselective cyclopropanation reaction has been developed²⁴⁵ and used by Brown for the synthesis of furofuran lignan natural products xanthoxylol, epipinoresinol, methylxanthoxylol, and epieudesmin.^{246,247} The key step in these syntheses was the preparation of the cyclopropyl γ -lactone **139** in good yield and 25:1 dr (diastereoisomeric ratio) from the acetoacetate **138** (25).²⁴⁷ Orena²⁴⁸ has reported an analogous chiral auxiliary controlled synthesis of cyclopropanes from methoxycarbonyl acetamides. The synthesis

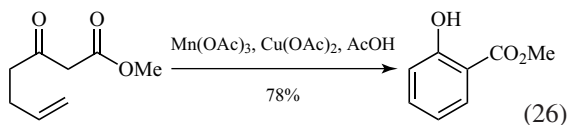


Scheme 18 Cyclization of methyl ketones.

of substituted cyclopropanes has been reported by Nishino.²⁴⁹

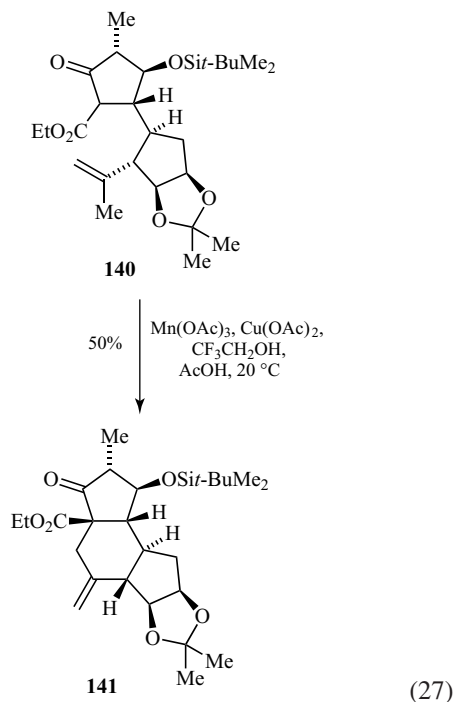


Early work on the cyclization of β -keto esters demonstrated that competition between 6-*endo* and 5-*exo*-trig cyclization is determined both by the alkene substitution pattern and whether the β -keto ester carries a substituent.^{22,36,250–254} As an example, Snider^{36,250} and Peterson²⁵³ developed an efficient synthesis of salicylate esters which relied on over-oxidation of the initially formed cyclohexane to ultimately yield the aromatic product; prevention of product over-oxidation can be achieved by using α -chloro- β -keto esters as substrates.²² The use of MAN and copper(II) acetate resulted in an efficient procedure for the synthesis of 3-alkyl salicylates (26).^{36,250} Here, the general trend for 6-*endo*-trig cyclization with terminal alkenes is illustrated. 4-Alkyl salicylates could be prepared by using MAN in the presence of lithium chloride.³⁶

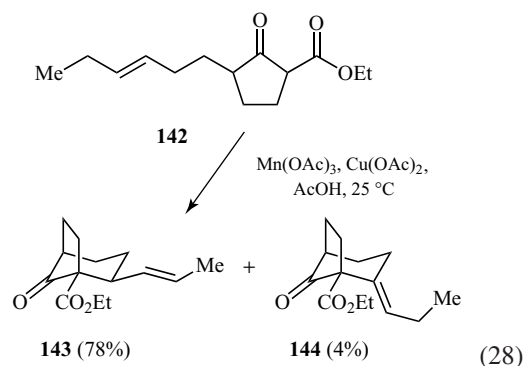


The 6-*endo* mode of cyclization of β -keto esters has been exploited by Prunet in the synthesis of the ABC ring system of hexacyclinic acid.²⁵⁵ Here, treatment of the complex acetoacetate **140** with MAN and copper(II) acetate gave the tetracyclic

product **141** in 50% yield (27).

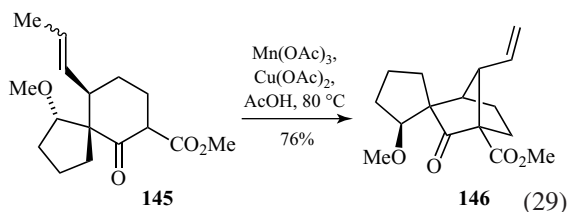


6-*Exo*-trig cyclizations of radicals derived from acetoacetates are frequently highly stereoselective, proceeding through chair-like transition states.^{252,256} The synthesis of bridged bicyclic alkenes by 6-*exo*-trig cyclization is feasible (28).²⁵² Here, the acetoacetate **142** gives the alkenes **143** and **144** in good yield. Formation of **143** is a good illustration of the predominant formation of the less substituted *E*-alkene from alkyl copper(III) intermediates.

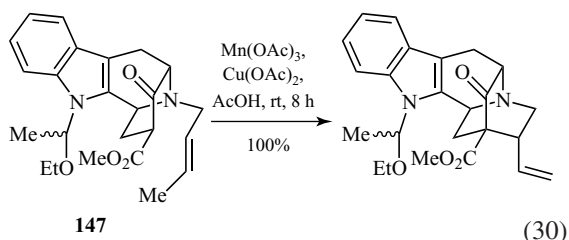


This methodology has been used by Nicolaou in a total synthesis of the polycyclic skeleton

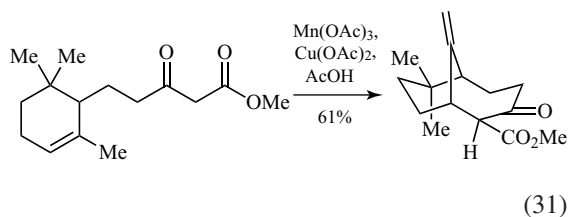
of vannausol A.²⁵⁷ Formation of the tricyclic acetoacetate **146** occurs in good yield on exposure of **145** to MAN and copper(II) acetate (29).



An early example of a 6-*exo*-trig radical cyclization of a β -keto ester in complex molecule synthesis is shown in (30). The highly functionalized β -keto ester **147** underwent cyclization in the presence of MAN and copper(II) acetate to give the corresponding terminal alkene in quantitative yield²⁵⁸; the tertiary amine may well be protonated under the acidic reaction conditions thereby preventing N-oxidation.

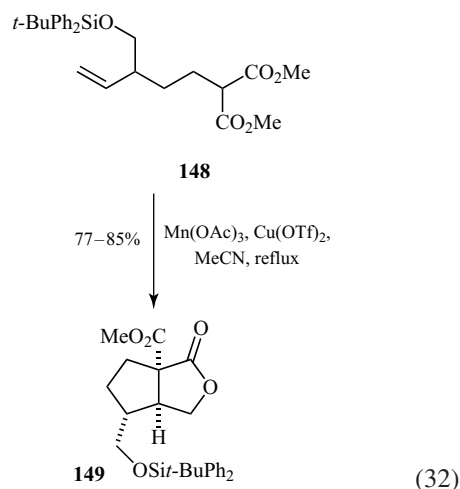


When competition between 6-*exo* and 7-*endo*-trig cyclization arises, mixtures of products favoring the 7-*endo* mode are frequently observed.^{259,260} A 7-*endo*-trig cyclization of an acetoacetate has been used by White in a synthesis of the dihydro derivative of pallescensin D (31).²⁶¹ In this reaction, the 7-*endo*-trig reaction is the exclusive mode of cyclization as the 6-*exo*-trig mode is disfavored by double-bond substitution. The identical transformation in the absence of copper(II) acetate was reported by Ruveda at a similar time.²⁶²

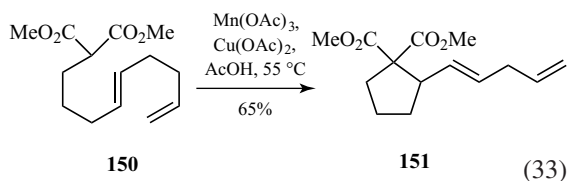


4.1.4 Monocyclizations with Malonates and Related Compounds

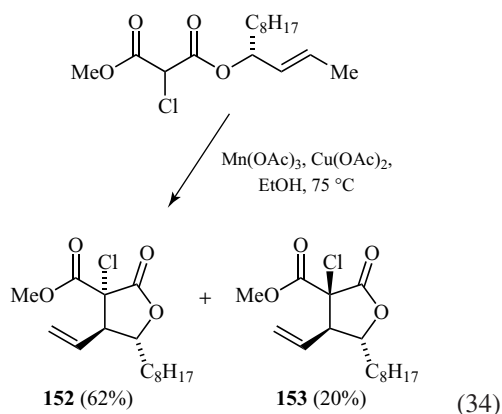
The cyclization of malonates to form fused cyclopentane γ -lactones was originally reported by Snider and further studied by others (Scheme 3).²³ Burton has shown that high yields of γ -lactones may be formed by the cyclization of 4-pentenyl malonates in the presence of MAN and copper(II) triflate in acetonitrile and has used this methodology in the synthesis of the cyclopentane-containing natural product 7,11-cyclobotryococca-5,12,26-triene (32).^{263,264} Here, the malonate **148** gave the [3.3.0]-bicyclic γ -lactone **149** in good yield and with >13:1 dr; formation of the major diastereomer was in accord with the Houk–Beckwith model for 5-*exo*-trig radical cyclizations.^{265,266}



The 5-*exo*-trig cyclization of alkenyl malonates in the presence of copper(II) acetate gives rise to alkenes. Reaction of the diene malonate **150** with MAN and copper(II) acetate in acetic acid gave the alkene **151**, demonstrating the rapid trapping of the adduct radical by copper(II) (33).²⁶⁷ Other examples of 5-*exo*-trig cyclization of 4-alkenyl malonates have been reported.^{268,269}



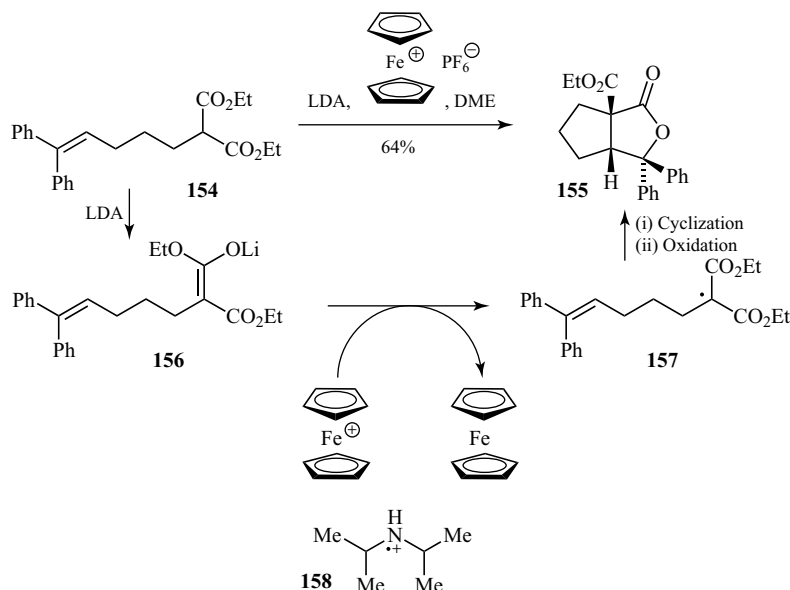
A 5-*exo*-trig cyclization was used as a key step in the synthesis of avenaciolide (34).²⁴⁵ The γ -lactones **152** and **153** were formed as a mixture of diastereomers at the malonate stereocenter, but with complete trans selectivity between the vinyl and octyl side chains. The major diastereomer was advanced to the natural product.



Jahn has championed the use of ferrocenium hexafluorophosphate as a single-electron oxidant for the conversion of lithium enolates into radicals.^{230, 270–275} These radicals undergo cyclization onto appropriately positioned alkenes and the resulting adduct radicals may be trapped with

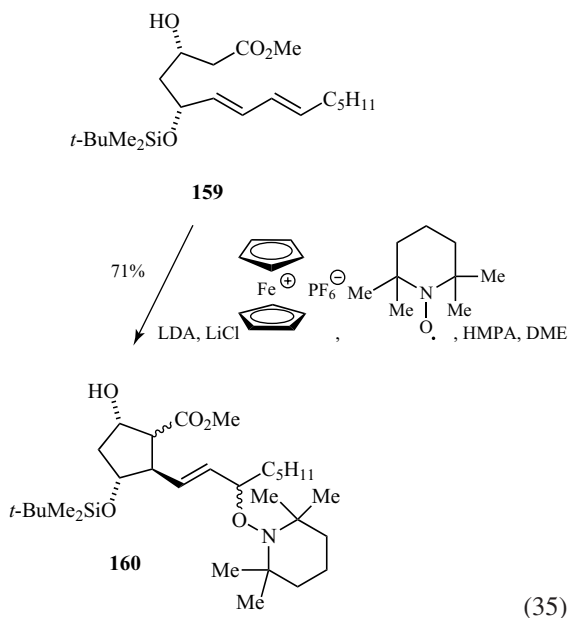
2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or undergo dimerization or further oxidation giving γ -lactones and alkenes. An example of γ -lactone formation is shown in Scheme 19.²⁷³ Thus, treatment of the malonate **154** with LDA, or BuLi, gives the lithium enolate **156** which is oxidised by the ferrocenium hexafluorophosphate to give the malonyl radical **157**; the radical cation **158**, derived by oxidation of di-*iso*-propylamine with the iron(III) salt, is the likely oxidant with other metal enolates. The malonyl radical **157** undergoes cyclization to give a doubly benzylic adduct radical, which undergoes further oxidation to give product **155**.^{270,273,274} For certain substrates, the adduct radicals formed in these reactions can be trapped by TEMPO to form C–O bonds.

An advantage of this method compared with the use of MAN and CAN is that it is not a requirement to have a particularly CH-acidic compound such as a malonate or a β -keto ester; esters themselves are good substrates. Cyclization of an ester substrate has been demonstrated in the total synthesis of 15-F_{2t}-isoprostane (35).^{275,276} Thus, cyclization of the lithium enolate derived from the diene **159** occurred in good yield to give the cyclopentane **160** as a mixture of diastereomers, which were readily processed into 15-F_{2t}-isoprostane. Pyrrolidines have



Scheme 19 Oxidative radical cyclization using ferrocenium hexafluorophosphate.

also been synthesized by this method.²⁷⁷

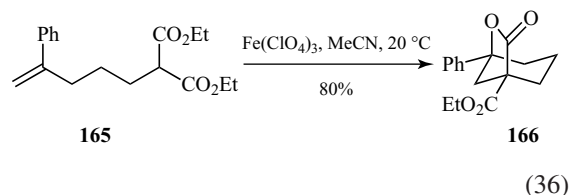


Tandem conjugate addition of lithium amides,²⁷¹ lithium enolates,²⁷² or lithium alkoxides²⁷⁸ to α,β -unsaturated esters or equivalents followed by oxidative radical cyclization–TEMPO trapping has been used to synthesize pyrrolidines, cyclopentanes, and tetrahydrofurans. In related work, treatment of unsaturated nitro compounds with sodium hydride followed by oxidation with CAN yields cyclized products.^{279,280}

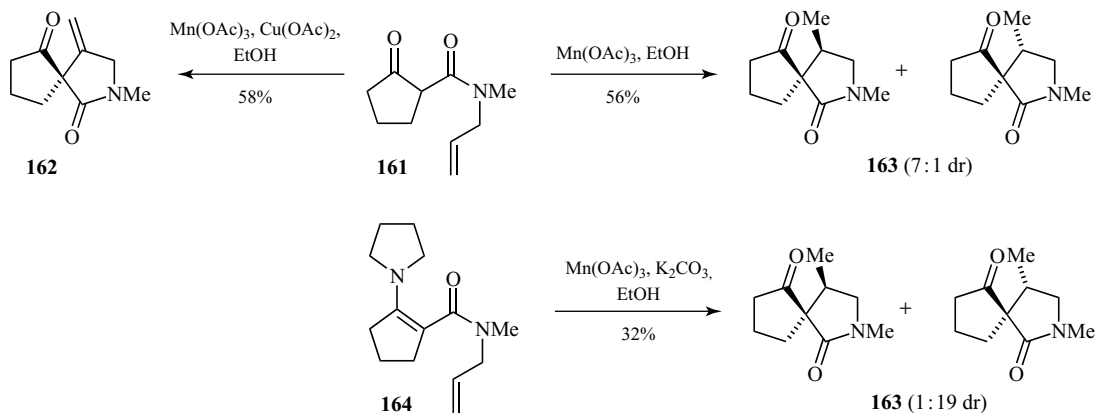
Cossy has investigated the reactions of β -keto carboxamides and their corresponding enamines in

the presence of MAN.^{281–283} Some of the many examples are shown in Scheme 20. Using anhydrous MAN in ethanol, **161** gave the methyl-substituted pyrrolidinones **163** in 56% yield as a 7 : 1 mixture of diastereomers. Here, the diastereomeric mixture of adduct radicals undergo H-atom transfer from ethanol to give products. Alternatively, in the presence of copper(II) acetate, oxidative elimination occurs to give the alkene **162**. Interestingly, the use of the enamine substrate **164** resulted in complete reversal of stereoselectivity for the formation of the methyl-substituted pyrrolidinones **163**.

There have been far fewer studies concerning the cyclization of unsaturated malonates using Ce(IV) and Fe(III) salts. Efficient 6-*endo*-trig cyclization of malonates has been reported with an appropriately sterically and electronically biased system. Thus, exposure of the malonate **165** to iron(III) perchlorate in acetonitrile gave the bicyclic γ -lactone **166** in good yield (36).²⁰⁰ 5-*Endo*-trig cyclization reactions of acetoacetamides^{284–286} and α -(methylthio)acetamides have also been reported mediated by both MAN and CAN.^{287–289}

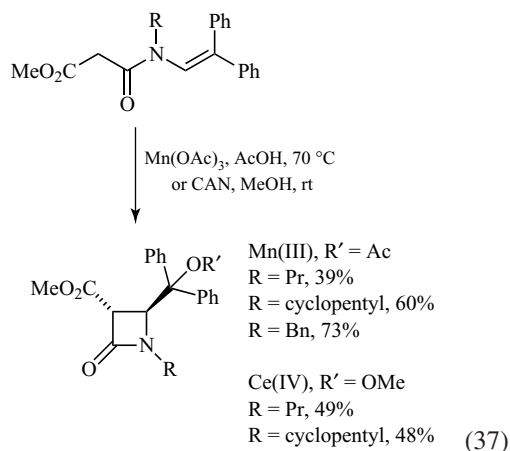


4-*exo*-trig Cyclizations of acetoacetamides under the influence of MAN or CAN are also possible with appropriately sterically and electronically



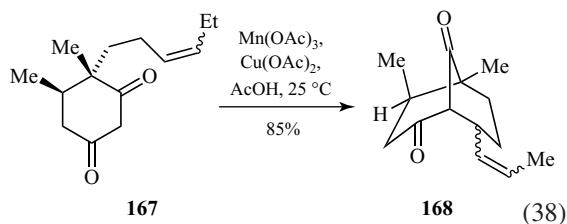
Scheme 20 Formation of spirocyclic amides.

biased systems, offering a novel route to β -lactams (37).^{290,291}



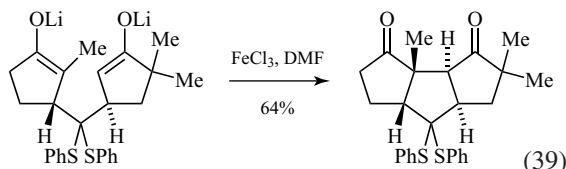
4.1.5 Monocyclizations of β -Diketones and Enolate Coupling

β -Di- and tri-ketones are some of the most reactive substrates for Mn(III)-mediated cyclizations with reactions generally being conducted at room temperature.²⁵² Mono-cyclization of such substrates has been used as a key step in the synthesis of a number of natural products. Snider developed a formal synthesis of upial by 6-*exo*-trig cyclization of the β -diketone **167**, which yielded the [3.3.1]-bicyclic diketone **168** as a mixture of stereoisomers in 85% yield (38).²⁹² A highly unusual 5-*endo*-trig cyclization has been used to synthesize model compounds related to the natural product fredericamycin A.^{293,294}

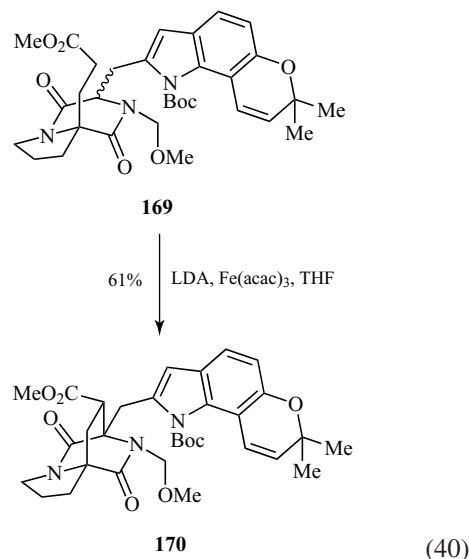


The intramolecular oxidative coupling of enolates has not been widely used in natural product synthesis, although intramolecular oxidative aryl-aryl couplings mediated by numerous transition metals have been extensively studied.⁴ The intramolecular coupling of two ketone enolates mediated by

iron(III) chloride²⁹⁵ was used in the synthesis of hirsutene (39).



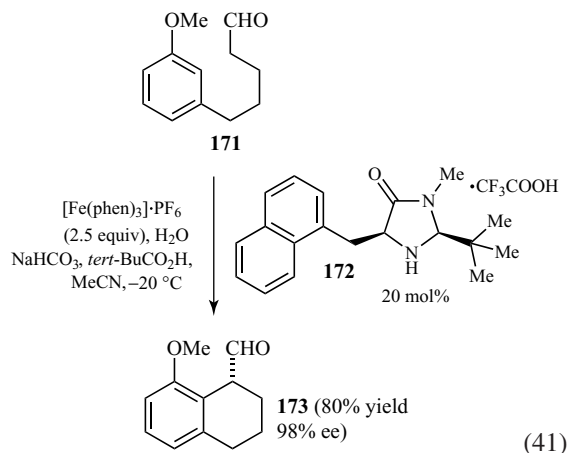
A more complex example was recently reported by Baran in the synthesis of stephacidin A.²⁹⁶ Here, exposure of the diketopiperazine **169** to 2 equiv of LDA and 2 equiv of iron(III) acetylacetonate gave the product **170** in 61% yield as a single diastereomer (40). This is an impressive transformation given the array of potentially oxidizable groups within the substrate.



4.1.6 Direct Cyclization onto an Aromatic Ring

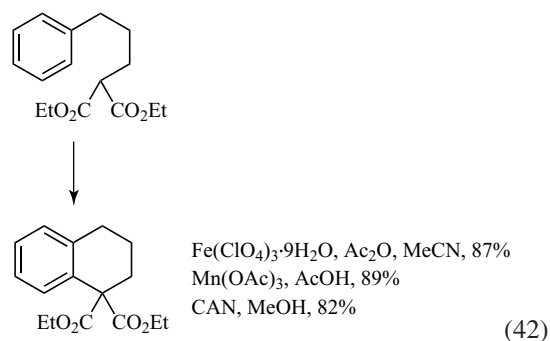
Intramolecular α -arylation reactions under oxidative radical conditions are generally higher yielding processes than the corresponding intermolecular reactions. The enantioselective α -arylation of aldehydes mediated by iron(III)²⁹⁷ or CAN^{298,299} has recently been developed. An example is shown in (41).²⁹⁷ Thus, treatment of the aldehyde **171** with the imidazolidinone catalyst **172** in the presence of iron(III) phenanthroline hexafluorophosphate and

various additives gave the α -aryl aldehyde **173** in 80% yield and 98% ee. The mechanism of the reaction is closely related to that depicted in Scheme 6.³⁰⁰ The cyclization of α -keto radicals onto aromatic rings has been used in a formal synthesis of parvifoline.³⁰¹



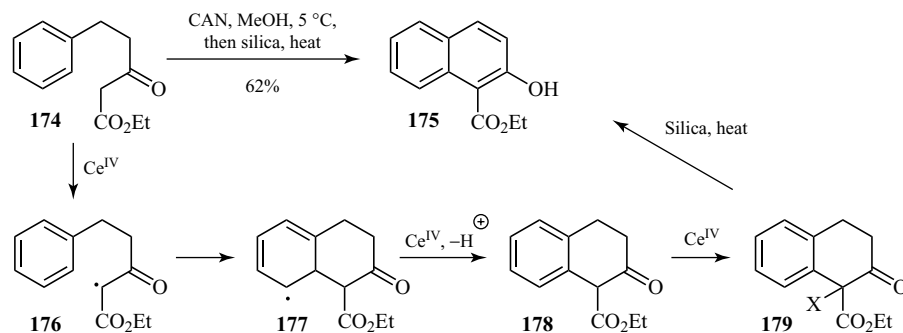
Most oxidative radical cyclizations onto aromatic rings involve the now ubiquitous β -dicarbonyl and related compounds. A great deal of work in this area has been conducted by Citterio using Fe(III),^{30,302,303} Mn(III),^{302–304} and Ce(IV) salts.^{302,305,306} The cyclization of malonates to form tetrahydronaphthalenes works equally well with any of the three metal oxidants (42).³⁰² Cyclization of the homologous malonate to give the corresponding seven-membered compound has been unsuccessful because of competing 1,5-hydrogen atom transfer and benzylic radical formation.³⁰⁴ The use of β -diketones with MAN or CAN allows the synthesis of the seven-membered rings fused to aromatic

rings without interference from 1,5-hydrogen atom transfer.^{307,308}



One of the first examples of the arylation of a β -keto ester mediated by cerium(IV) salts used cerium(IV) sulfate, although the product was formed in low yield.³⁰⁹ Cyclization of β -keto esters onto electron-rich aromatics in the presence of CAN gives the corresponding naphthalenes in modest yields³⁰⁵; MAN generally gives the products in reduced yields. One of the many examples is the formation of the naphthol **175** in 62% yield on treatment of the β -keto ester **174** with CAN followed by heating with silica gel (Scheme 21). The mechanism of this reaction involves formation of the adduct radical **177**, which undergoes oxidative rearomatization followed by further oxidative ligand transfer to give **179** (X = OAc, OMe, NO₃, or OH). Heating **179** with silica gel gives the naphthol **175**.

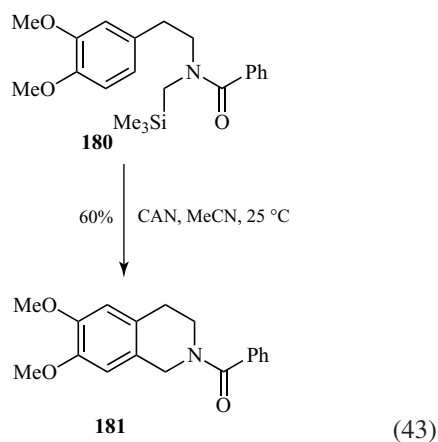
Cyclization of related compounds using MAN allows the synthesis of dihydronaphthalenes,³¹⁰ quinolines and dihydroquinolinones,^{311–313} indolines and indolinones,^{313,314} naphthoquinones,³¹⁵ and the spirocyclic core of fredericamycin.³¹⁶ The



Scheme 21 Naphthol formation mediated by CAN.

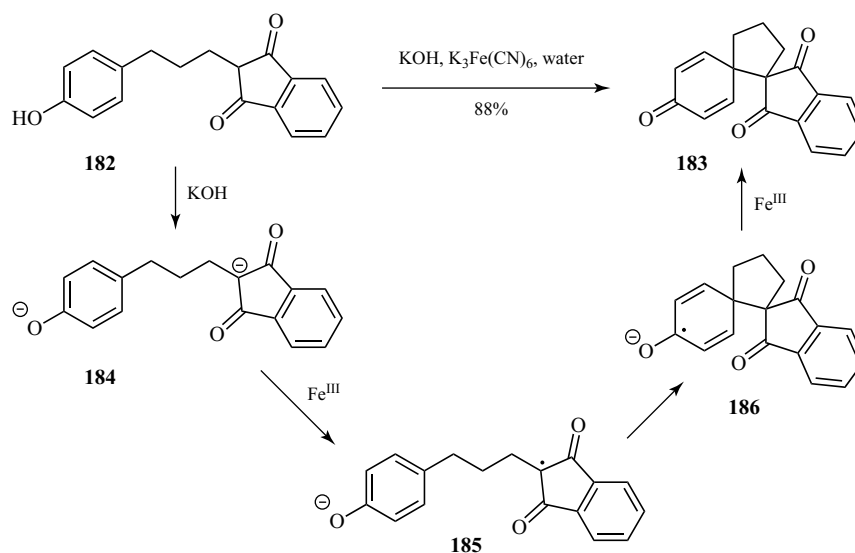
naphthoic acid component of neocarzinostatin chromophore has been synthesized by the cyclization of the reactive β -ketotrifluoroethyl esters in the presence of MAN.³¹⁷

An oxidative Pictet–Spengler reaction related to the work of Naraska has been developed by Mariano (43).³¹⁸ Here, treatment of trimethylsilylmethyl amides (e.g., **180**) with CAN yields the corresponding tetrahydroisoquinolines (e.g., **181**). The reactions proceed by the generation of an *N*-acyl iminium ion by single-electron oxidation at nitrogen followed by electrofugal loss of silicon followed by further single-electron oxidation. Cyclization onto the *N*-acyl iminium ion followed by rearomatization delivers product **181**.



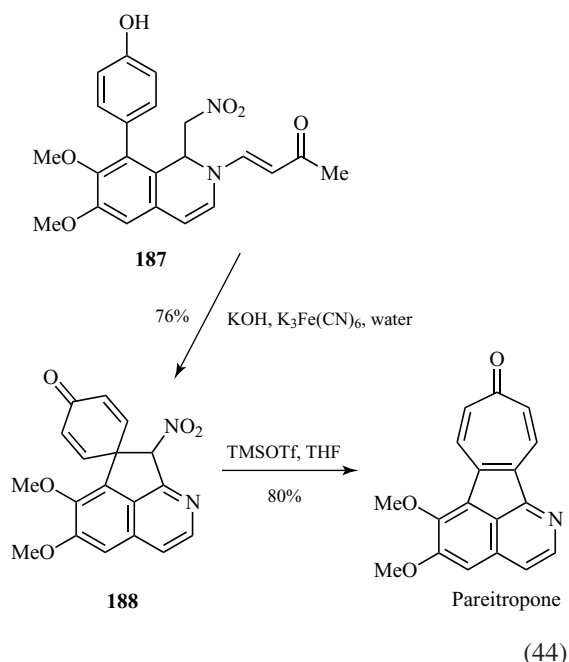
In some early work, Kende developed an efficient intramolecular oxidative coupling of phenoxides with enolates and nitronates.^{319–322} A range of cyclic CH-acidic compounds, on treatment with base and potassium ferricyanide, delivered the corresponding spirocyclic compounds in good yields; the cyclization of acyclic enolates was generally unsuccessful, and cyclizations that formed five-membered rings were generally more efficient than those to form six-membered rings.^{319,321,322} An example is shown in Scheme 22, along with a plausible mechanism for product formation.³²¹ Thus, the substrate **182** undergoes double deprotonation to give the dianion **184**. Oxidation of the enolate by iron(III) gives the β -dicarbonyl radical **185**, which undergoes 5-*exo*-trig radical cyclization to give the radical anion **186**. Further single-electron oxidation gives the product **183**.

In a similar manner, the corresponding nitro compounds undergo spirocyclization and further cyclization–rearrangement, ultimately yielding tropolone derivatives.³²⁰ This methodology has been recently exploited by Kim in the total synthesis of the cytotoxic natural product pareitropone.³²³ Here, treatment of the nitro compound **187** with excess base and potassium ferricyanide delivered the spirocyclic dienone **188**, with concomitant removal of the butenone group and oxidation to the isoquinoline (44); exposure of the isoquinoline to a Lewis acid

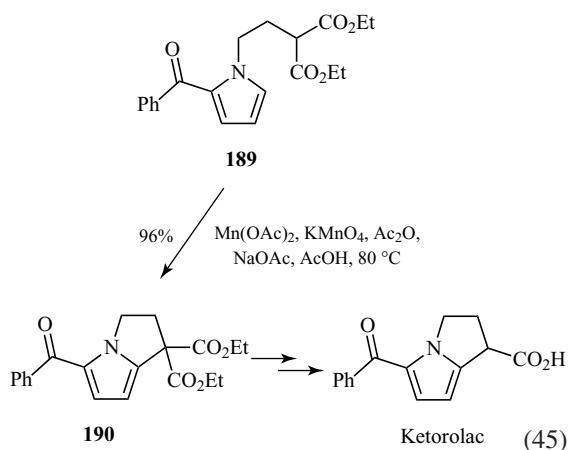


Scheme 22 Oxidative coupling of phenoxides and enolates.

gave the natural product pareitropone by a cyclopropanation–electrocyclization sequence.

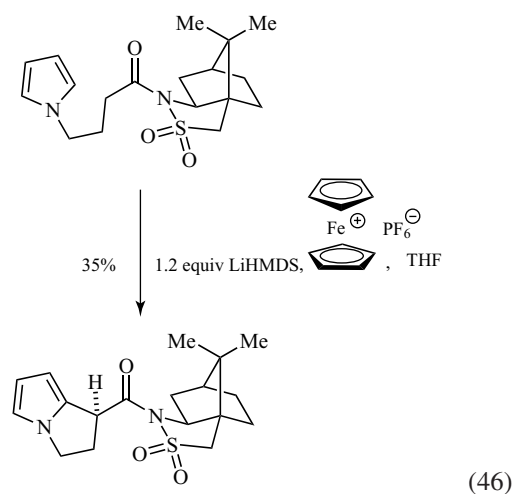


Cyclization reactions onto heteroaromatic rings have also been studied and used in the synthesis of a number of natural products. Ketorolac, a powerful non-narcotic analgesic, was synthesized by cyclization of the malonate **189** with *in situ* generated MAN (45).¹⁵⁶ The product **145** was converted into ketorolac in two further steps.

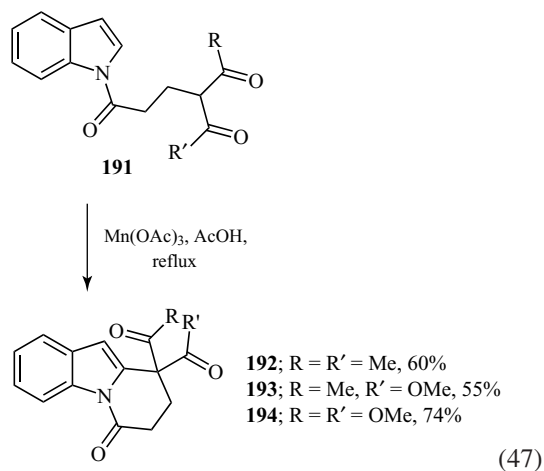


A second synthesis of ketorolac involving a diastereoselective oxidative radical cyclization was

recently disclosed by Baran, which utilized an iron(III)-based oxidant to mediate C–C bond formation (46).^{324,325}

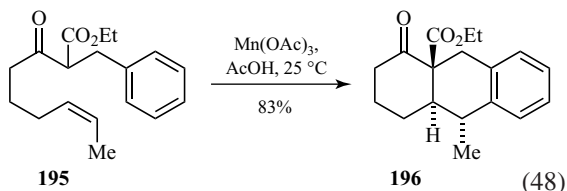


Kerr has more fully investigated the cyclization of malonyl radicals onto pyrroles under the influence of MAN and demonstrated that it is a general process for pyrroles, indoles, and indolines; indolines undergo *in situ* oxidation to indoles prior to cyclization. Malonates, acetoacetates, and β -diketones all cyclized to give the corresponding indoles in similar yields (47).^{326,327} The β -diketone **192** was advanced to the natural product meriscarpine.³²⁷ In related work, a range of indolequinones were readily prepared by cyclization of β -dicarbonyl compounds onto indoles.³²⁸

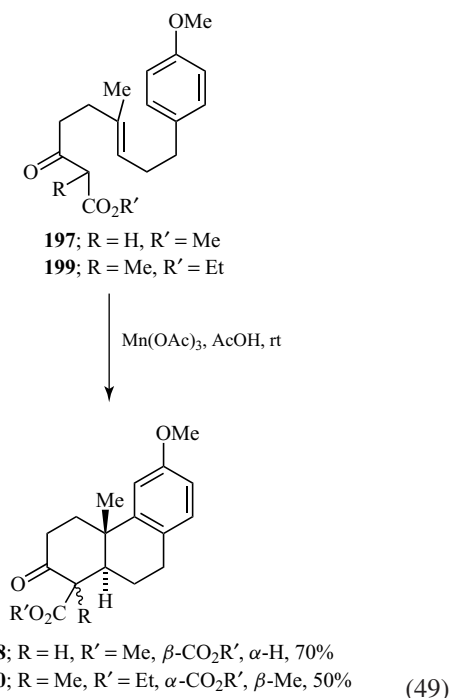


4.2 Tandem and Higher Cyclizations

Oxidative radical cyclizations are an exceedingly powerful method for the synthesis of polycyclic products by the formation of multiple C–C bonds in a single reaction with stereocontrol (see **Radical Cascade Reactions**). In particular, cyclizations to give six-membered rings are frequently highly stereoselective, as they proceed via well-organized chair transition states.²² A few early examples serve to illustrate the power of these oxidative radical cyclizations. Thus, the β -keto ester **195** forms the tricyclic product **196** in 83% yield as a single diastereomer (48).²⁵⁰ If this reaction is conducted in the presence of copper(II) acetate, the product **196** is formed in 66% yield, indicating that cyclization onto an aromatic ring is faster than oxidation of the adduct radical by copper(II); with other substrates these processes can be competitive.²² Bertrand has investigated similar reactions with allyl malonates which lead to a diverse array of products.³²⁹

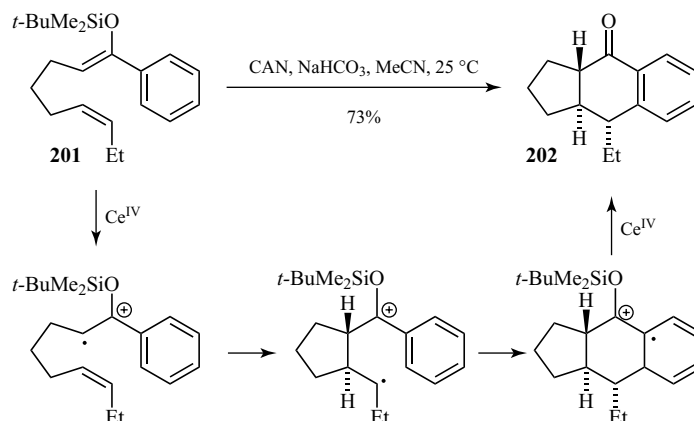


Formation of tricyclic products is shown in (49).²⁵¹ Here, cyclization of the methyl-substituted β -keto ester **199** delivers the tricyclic product **200** in 50% yield as a single diastereomer and demonstrates that cyclization occurs from the β -keto ester radical with the ester group in a pseudo-axial orientation anti to the ketone carbonyl group; this is a general feature of these cyclization reactions.^{237,251,256} With the unsubstituted β -keto ester **197**, the stereochemistry of the ester-bearing stereocenter is set by equilibration of the product **198**. The tricyclic ketone **200** has been used to synthesize the ethyl ester of *O*-methylpodocarpic acid.³³⁰ The synthesis of closely related β -keto esters bearing different aromatic substituents has been used to prepare triptotoquinones B and C³³¹; cyclizations involving the addition of an adduct radical onto a furan have also been demonstrated.³³²



A related reaction that involves cyclization from silyl enol ethers has been reported by Snider.³³³ Exposure of the silyl enol ether **201** to CAN gave the tricyclic product **202** in 73% yield (Scheme 23). A plausible mechanism for the transformation is shown; in general, copper(II) triflate gave improved yields of the cyclized products. In a related work, unsaturated ketene thioacetals give fused bicyclic γ -lactones in moderate yields on treatment with excess CAN in acetonitrile–water mixtures.³³⁴ Related to this and to the allylation of β -dicarbonyl compounds with allylsilanes reported by Flowers (Section 3.3.1), the intramolecular allylation of allyldimethylsilyl enol ethers mediated by CAN yields α -allyl ketones, offering a nontraditional route to these compounds.³³⁵

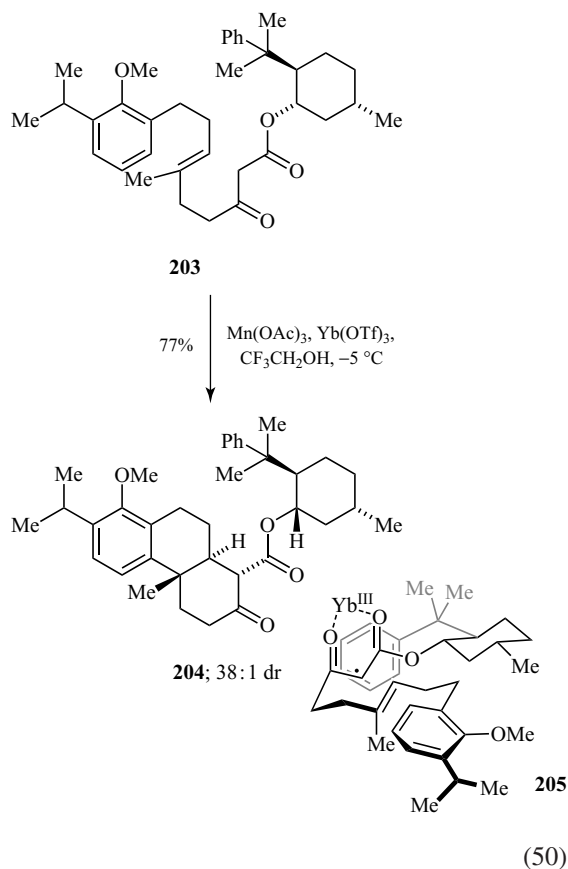
Absolute stereocontrol in the cyclization of β -keto esters and related compounds was originally studied by Snider. Initially, β -keto sulfoxides were found to be good cyclization substrates, which gave excellent asymmetric induction but modest yields of cyclized products.³³⁶ Later, the use of various chiral auxiliaries was investigated. Snider demonstrated that 8-phenyl menthol efficiently controlled the sense of asymmetric induction in the cyclization of β -keto esters; however, the sense



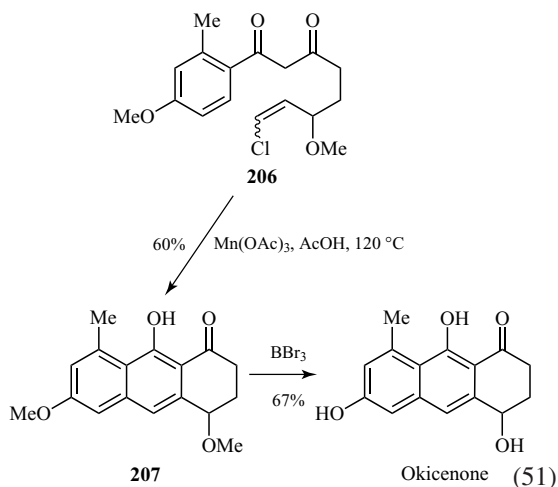
Scheme 23 Cyclization involving silyl enol ethers.

of induction was markedly dependent on substrate structure.³³⁰ Yang investigated related cyclizations and demonstrated that lanthanide triflates can markedly increase the rate and stereoselectivity of Mn(III)-mediated cyclizations of β -keto esters.^{337–339} Moreover, the combination of lanthanide triflates, 8-phenylmenthol, and related chiral auxiliaries gives absolute stereocontrol in the cyclization of β -keto esters. This has resulted in enantioselective syntheses of triptolide, triptonide, triptophenolide,³³⁹ triptocallol,³⁴⁰ and wilforonide.³⁴¹ The key step in the asymmetric synthesis of triptophenolide is shown in (50).³³⁹ Exposure of the β -keto ester **203** to MAN and ytterbium triflate in trifluoroethanol at -5 °C gave the tricyclic product **204** in 77% and 38:1 dr. The cyclization is believed to occur from the reactive conformation **205**. It is proposed that the ytterbium triflate promotes enolization of the substrate and, by chelation, renders the β -keto ester radical more electrophilic and holds it in a syn conformation (**205**) during cyclization. The use of ytterbium triflate allows the reaction to be conducted at a low temperature, thereby enhancing the stereocontrol.

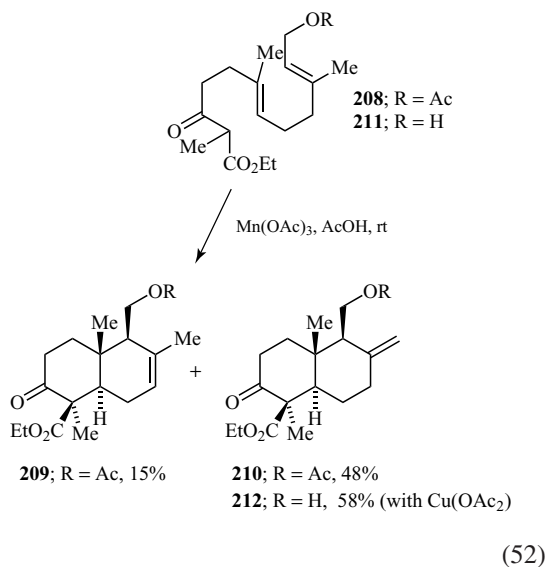
Tandem cyclizations of β -diketones onto alkenes have been used in a total synthesis of the anti-tumor antibiotics okicenone and aloesaponol III. Cyclization of **206** with MAN delivers the naphthol **207** in 60% yield (51).^{342,343} Here, the radical derived from **206** undergoes exclusive 6-*exo*-trig cyclization because of the presence of the chlorine atom. Treatment of the naphthol **207**



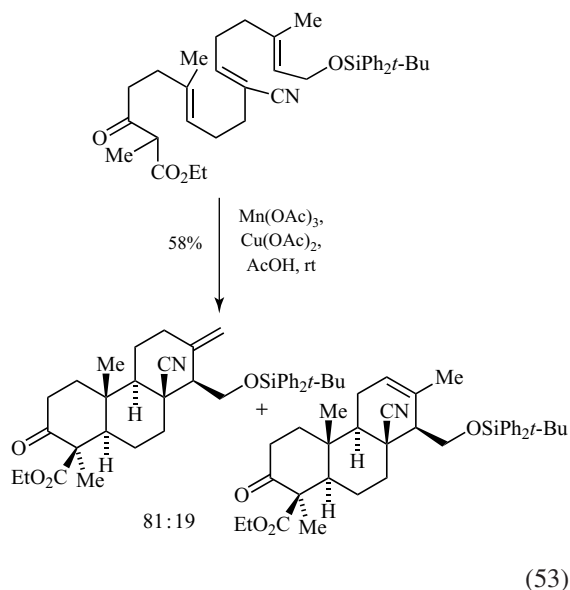
with boron tribromide delivered okicenone. A related cyclization has been used for the synthesis of a benzoxanthene for use in molecular recognition.^{344–346}



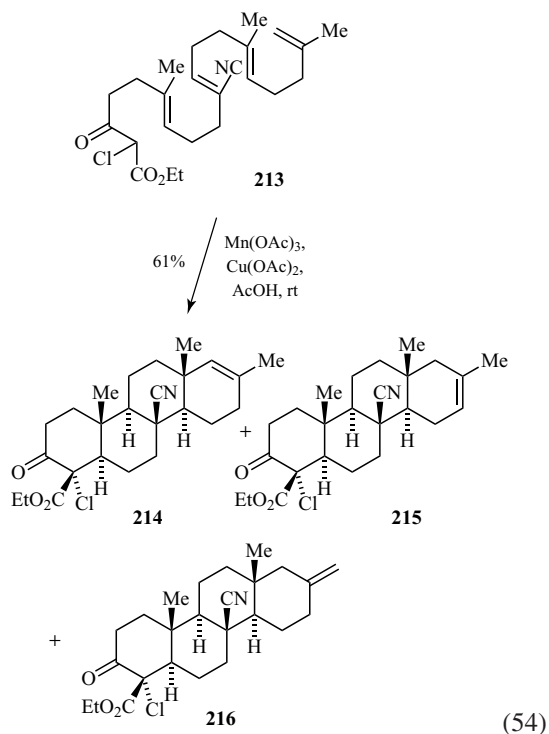
Cyclizations of β -dicarbonyl radicals involving two alkenes have also been widely studied. Cyclizations onto *E*-trisubstituted alkenes proceed exclusively by the 6-*endo*-trig mode as expected and have been widely studied by Zoretic^{347,348} and Snider^{237,256}; cyclizations involving *Z*-trisubstituted alkenes have been far less studied and give mixtures of products.³⁴⁹ In an early example that demonstrates the power of the methodology, treatment of the acetate **208** with MAN in acetic acid gave a mixture of the corresponding bicyclic compounds **209** and **210** with excellent stereocontrol (52).²³⁷ The formation of seven- and eight-membered rings in related reactions has been reported.^{259,260}



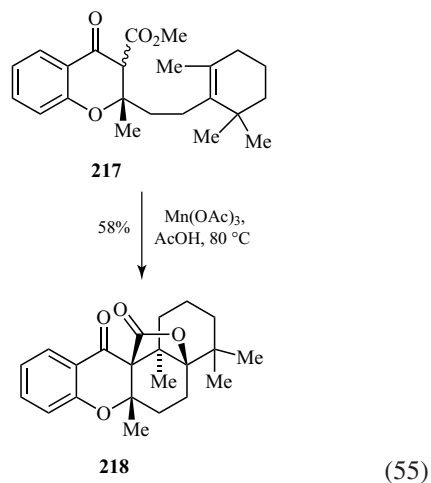
Zoretic has demonstrated the cyclization of a closely related substrate **211** in the presence of MAN and copper(II) acetate, which delivered the *exo*-cyclic alkene **212** as a single stereoisomer in 58% yield (52); the alkene **212** was used to synthesize norlabdane oxide.³⁵⁰ The same reaction of **211** to give **212** was recently used for the synthesis of the originally proposed structure of wentilactone B.³⁵¹ A MAN-mediated 6-*endo*, 6-*exo*-trig cyclization of β -keto esters reported by Zoretic³⁴⁷ has been used in studies toward the synthesis of heteroscyphic acid A.³⁵² Similar 6-*endo*, 5-*exo*-trig reaction sequences of β -keto esters give rise to *cis*-fused hydrindans.^{330,348} Triple^{353–356} and quadruple^{357,358} cyclizations of β -keto ester substrates are also feasible. A key step in the synthesis of spongiatriol is shown in (53).³⁵⁹ In this impressive transformation, three C–C single bonds and six stereocenters are formed.



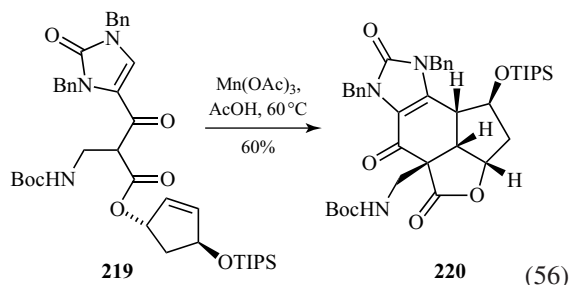
A quadruple cyclization has been used to prepare a D-homosteroid (54).³⁶⁰ Thus, the tetraene **213** delivered the tetracyclic double-bond regioisomers **214**, **215**, and **216** in 61% yield; treatment of the mixture with trifluoroacetic acid gave predominantly the alkene **215**. Complete control of the relative stereochemistry of the products occurs as a result of the chair-like nature of the cyclization transition state.



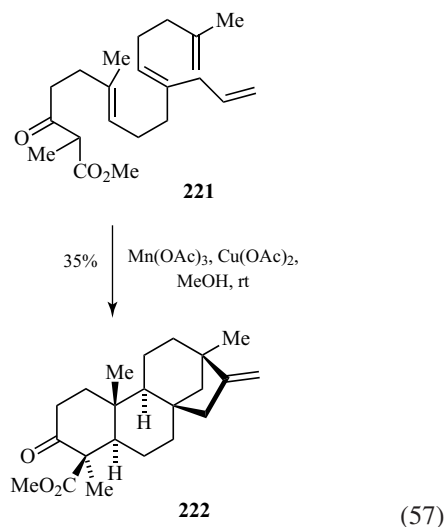
The termination of cyclization reactions does not always have to involve oxidative elimination to give alkenes. In an approach to sesquiterpene–phenol natural products, Wallace has demonstrated that treatment of the β -keto ester **217** with anhydrous MAN in acetic acid gave the γ -lactone **218** in 58% yield (55).³⁶¹ This is an impressive transformation, as it forges three adjacent quaternary stereocenters in a single step.



Chen has investigated 5-*exo*-6-*endo*-trig tandem cyclizations in highly complex systems as a potential route to the oriodin family of natural products which include palau'amine.^{362,363} In one example, the β -keto ester **219** gave the corresponding tetracyclic product **220** in 60% yield as a single stereoisomer on treatment with MAN in acetic acid (56).

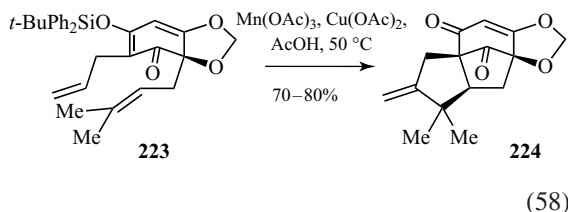


Cyclization reactions to give bridged bicyclic structures have also been investigated^{23,254,256,364–366} and have been used in the preparation of a gibberelic acid intermediate.²⁵⁴ A beautiful example of a quadruple cyclization to form both fused and bridged ring structures is demonstrated in the synthesis of isosteviol and beyer-15-ene- 3β ,19-diol (**57**). Here the tetraene **221** undergoes consecutive 6-*endo*, 6-*endo*, 6-*endo*, 5-*exo*-trig cyclizations to deliver a single stereoisomer of **222** in 35% yield.³⁶⁷

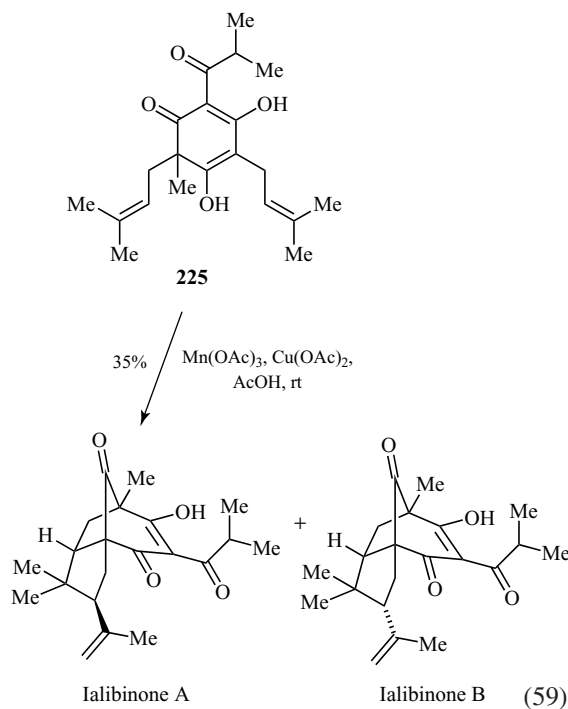


Danishefsky has used the tandem cyclization of a β -diketone as a key step in the synthesis of the

neurotrophic illicinones.^{368,369} Thus, treatment of the silyl enol ether **223** with MAN and copper(II) acetate delivers the tetracyclic product **224** in 70–80% yield (58). It is proposed that under the reaction conditions the silyl enol ether **223** is hydrolyzed to give a β -diketone from which radical formation occurs. A 5-*exo*, 5-*exo*-trig cyclization occurs which ultimately gives the alkene **224**.

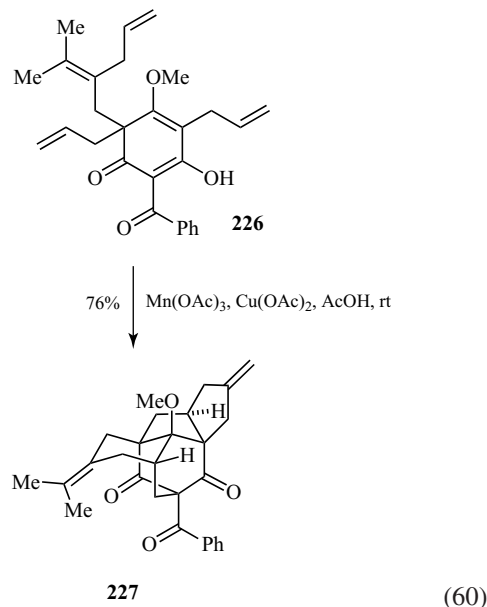


In related work, Simpkins has recently reported the synthesis of a 1:1 mixture of ialibinones A and B from the diketone **225** by a 5-*exo*, 5-*exo*-trig radical cascade (59).³⁷⁰



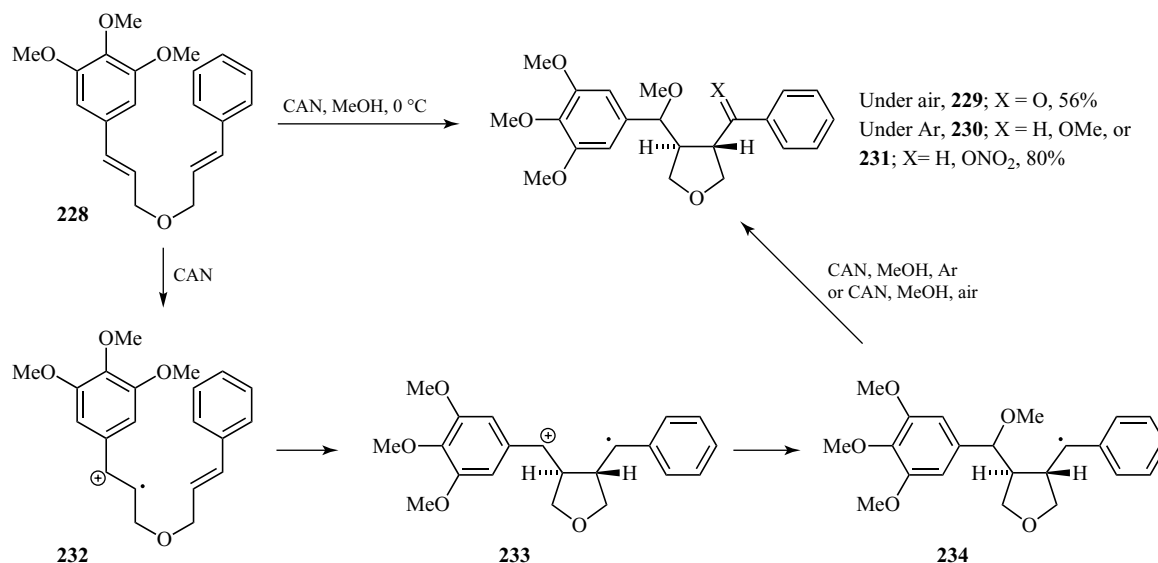
Porco has reported a most impressive synthesis of polycyclic triketones from dearomatized phloroglucinol.³⁷¹ One of many examples is shown in (60). Thus, treatment of the cyclohexadienone **226** gives the pentacyclic product **227** in 76% yield. In this reaction, four C–C bonds and four rings are formed

in a single step, illustrating the power of oxidative radical cyclizations in organic synthesis.

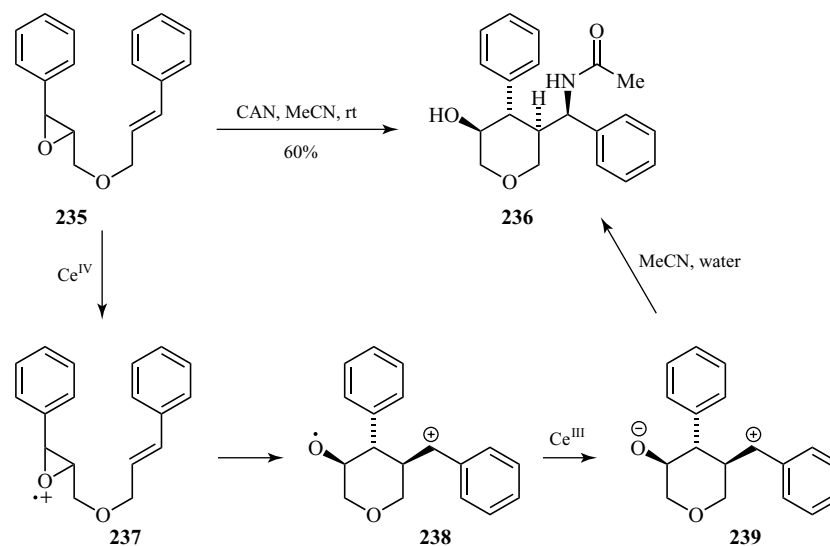


4.3 Ring-Opening and Other Reactions

From the above discussion, it is clear that MAN can mediate enormously powerful transformations in organic synthesis resulting in the formation of multiple C–C bonds frequently with control over multiple stereocenters. In almost all of the above transformations, in order to commence the reaction sequence it is necessary to form a manganese enolate or equivalent subsequent to oxidative SET. In contrast, CAN is able to mediate oxidative SET from substrates that cannot enolize. As with MAN, CAN is capable of single-electron oxidation of electron-rich aromatic rings. Indeed, one of the most widespread uses of CAN in organic synthesis is for the removal of electron-rich benzyl protecting groups such as the 4-methoxybenzyl and 2,4-dimethoxybenzyl groups, which Floreancig has developed into a mild procedure for the formation of oxocarbenium ions.^{372–376} The ability of CAN to form radical cations from electron-rich aromatic rings has been exploited by Nair in an elegant synthesis of disubstituted tetrahydrofurans.^{377,378} Thus, treatment of the ether **228** with CAN in methanol under air gave the ketone **229** in 56% yield,



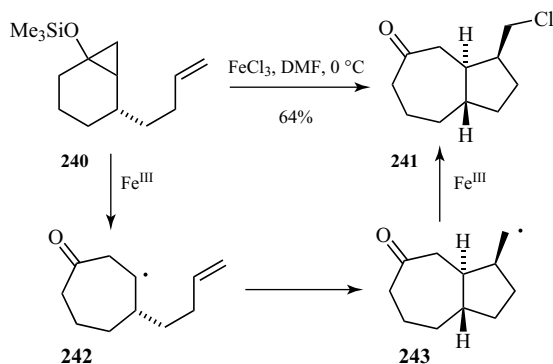
Scheme 24 Formation of THFs from radical cation cyclization.



Scheme 25 Synthesis of a tetrahydropyran.

whereas conducting the reaction under anaerobic conditions delivered a 2:1 mixture of the methyl ether **230** and the nitrate **231** in 80% yield (Scheme 24); only trans-disubstituted tetrahydrofuran (THFs) were formed. A plausible mechanism for the reaction is shown. Thus, oxidation of the electron aromatic ring in **228** occurs to give a radical cation **232**, which yields a second radical cation **233** on cyclization. Quenching of the cation

by methanol followed by further oxidation delivers the products. This reaction was applicable to a wide variety of bis-aromatic substrates, and cyclization was also achieved with a dimethallyl moiety as the radical acceptor; however, allyl, methallyl, or propargyl ethers failed to undergo cyclization. The synthesis of *N*-tosyl pyrrolidines, pyrrolidinones, and cyclopentanes by this method has been reported.^{379,380}



Scheme 26 Ring expansion of a cyclopropanol silyl ether.

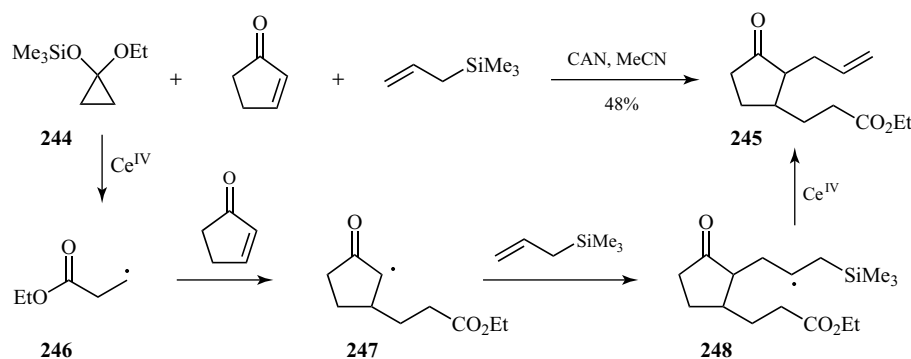
This work has been extended to the synthesis of diastereomerically pure tetrahydropyrans by the cyclization of epoxypropyl cinnamyl ethers. Thus, the epoxide **235**, on treatment with sub-stoichiometric quantities of CAN, gave the tetrahydropyran (THP) **236** as a single diastereomer, along with minor amounts of hydroxy nitrates formed by direct ring-opening of the epoxide **235** (Scheme 25).³⁸¹ The postulated mechanism is based on the work of Iranpoor, who has studied the ring-opening of epoxides with heteroatom-based nucleophiles catalyzed by CAN and garnered evidence for a radical-based pathway.^{382–385} It was proposed that oxidation of the epoxide **235** by CAN delivers the radical cation **237**, which undergoes stereospecific ring-opening to give the radical cation **238** followed by reduction with Ce(III) to give **239**. Ritter reaction of **239** gives the product **236**. The use of *tert*-butanol as the solvent gave the corresponding hydroxy *tert*-butyl ethers. This method

was extended to the stereoselective synthesis of piperidines.³⁸⁶

Other ring-opening reactions mediated by Mn(III), Fe(III), and Ce(IV) have been studied. Booker-Milburn has developed an efficient cyclopropane opening–C–C bond-forming reaction for the synthesis of fused bicyclic systems.^{387–393} As an example, treatment of the cyclopropyl silyl ether **240** with iron(III) chloride delivered the ring-expanded ketone **241** in 64% yield (Scheme 26).³⁸⁷ The reaction is believed to proceed by oxidative formation of the β -keto radical **242**, which undergoes 5-*exo*-trig cyclization to give the adduct radical **243**. Ligand transfer mediated by iron(III) chloride gives the product.^{387,392} The methodology is applicable to the formation of other bicyclic carbocycles. Moreover, if iron(III) nitrate is used in place of iron(III) chloride, the adduct radicals undergo H-atom abstraction instead of ligand transfer with the formation of a C–H bond.^{391,392}

Narasaka has used Mn(III) picolinate for analogous ring-expansion reactions of cyclopropanols,^{394,395} which has resulted in the synthesis of 10-isothiocyanoguaia-6-ene.^{396,397} Related ring-openings of aminocyclopropanes in the presence of CAN have been reported.^{398,399} In a similar manner, oxidative ring-expansion reactions of cyclobutanols mediated by MAN have been reported by Snider⁴⁰⁰ and used in the total synthesis of silphiperforin-6-ene and methyl cantabradienate.⁴⁰¹

Ring-opening of cyclopropyl acetals in the presence of CAN leads to β -carboxy radicals which undergo C–C bond formation. An example is shown in Scheme 27.⁴⁰² Here, the cyclopropyl acetal **244**



Scheme 27 Ring-opening C–C bond formation in the synthesis of disubstituted ketones.

yields the nucleophilic β -carboxy radical **246** on treatment with CAN. Addition of **246** to cyclopentenone occurs selectively to give the electrophilic adduct radical **247**, which reacts with nucleophilic allyltrimethylsilane to give the β -silyl radical **248**. Oxidative loss of the silyl group from **248** gives the product **245**. The ring-opening of cyclopropyl sulfides with concomitant C–X or C–C bond formation has been widely studied by Takemoto and Iwata.^{403–407}

5 CONCLUSIONS

The use of Mn(III), Ce(IV), and Fe(III) salts to mediate oxidative radical reactions has great utility in organic synthesis. In particular, MAN has been shown to mediate some exceptionally powerful stereocontrolled transformations of β -dicarbonyl compounds. It is certainly the case that similar chemistry mediated by CAN and particularly iron(III) salts is underdeveloped and much work remains to be done. Perhaps more exciting, though, are the highly enantioselective transformations that have recently been discovered by merging oxidative radical chemistry and organocatalysis which will likely provide a rich seam of research for years to come. Moreover, new and exciting transformations are being reported that involve oxidative radical reactions, and the development of oxidative radical reactions that are catalytic in metal are beginning to be explored.⁷ In summary, oxidative radical chemistry has delivered a range of exceptionally powerful synthetic methods and we confidently predict that in the future many new important developments will be forthcoming.

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Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA

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1 INTRODUCTION

Oxidation reactions that are initiated by the formation of superoxide radicals ($O_2^{\bullet-}$) during mitochondrial respiration, inflammation, or phagocytosis^{1–6} are present in living cells.^{6–9} Generation of $O_2^{\bullet-}$ may be followed by its enzymatic dismutation into H_2O_2 ,¹⁰ which does not exhibit significant reactivity toward DNA¹¹ with the exception of a rather minor and highly specific reaction giving rise to N^1 -oxide adenine.¹² Reduction of H_2O_2 by transition metals such as ferrous ions (Fe^{2+}) is known to lead through the Fenton reaction¹³ to the generation of the highly reactive hydroxyl radical ($\bullet OH$), the most deleterious reactive oxygen species (ROS), which reacts with proximal biomolecules at the site where it is generated. It is well documented that $\bullet OH$ undergoes addition to the double bonds of nucleobases^{11,14} and hydrogen atom (H) abstraction reaction from the methyl group of thymine^{11,14} and 5-methylcytosine¹⁵ the 2-amino group of guanine¹⁶ together with abstraction reactions from the 2-deoxyribose moiety¹⁷ at rates that are diffusion controlled.¹⁴ The reactions

of H_2O_2 with copper ions that are also present in cells¹³ have been shown to give rise at least partly to other ROS and oxidizing processes. Evidence has been provided for the generation of singlet oxygen (1O_2) by the $Cu(I)-H_2O_2$ system, whereas $Cu(II)-H_2O_2$ has been shown to degrade guanine by one-electron oxidation.^{18–20} Another possible reaction of $O_2^{\bullet-}$ is its radical combination with nitric oxide ($NO\bullet$), which is produced by nitric oxide synthase during inflammation reactions.^{6,13,21} The resulting peroxynitrite (^-OONO) may promote rather multiple types of reactions including nitration together with $\bullet OH$ -mediated and one-electron oxidation. The latter reaction is accounted for by the reaction of ^-OONO with bicarbonate leading to unstable nitrosoperoxycarbonate,^{6,22} which rapidly undergoes decomposition into nitrating NO_2 and the one-electron oxidizing carbonate ion ($CO_3^{\bullet-}$).²³ Among common exogenous oxidants, one may underline ionizing radiation as being able to generate $\bullet OH$ and promote the ionization of DNA components through indirect and direct effects, respectively.¹⁴ One-electron oxidation of the bases could be achieved in a milder way

either by using ultraviolet A (UVA) excited type I photosensitizers^{24,25} or on exposure to high-intensity UVC laser pulses as the result of biphotonic ionization.^{26,27} Another major environmental oxidant is the UVA component of solar radiation, which on excitation of the endogenous photosensitizers, is able to generate predominantly $^1\text{O}_2$ and to a lesser extent $\text{O}_2^{\cdot-}$ through type II and type I photosensitization mechanisms, respectively.²⁸

A large body of information is available on the oxidation reactions of DNA as discussed in several recent review articles.^{29–40} This article focuses on the survey and critical review of oxidative pathways mediated by $^1\text{O}_2$, $^{\cdot}\text{OH}$ and one-electron oxidants to nucleosides, oligonucleotides, and isolated DNA in aqueous solutions. Emphasis is placed on oxidation reactions that have been shown in most cases to occur in cells and that have been validated in model studies using aqueous systems through the detection of known final degradation products. In this respect, mostly single-radical-hit modifications, which include single-base lesions, tandem intrastrand cross-links, and clustered damage, are reported and discussed. One may point out that for lack of space, other types of base modifications induced by ozone^{41,42} or HOCl ^{43,44} or indirectly by breakdown products of lipid peroxides^{25,45–48} are not discussed in the article. The same applies to oxidized bases and nucleosides released in biological fluids such as urine^{49–51} or formed in ribonucleic acids.^{52,53}

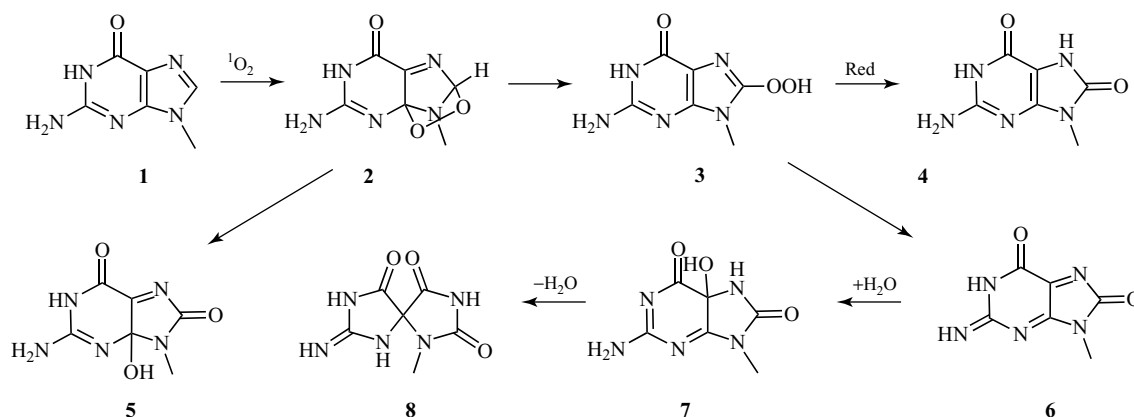
Information is also provided on several DNA oxidation products that have been shown to be generated in cells mostly using the accurate high performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) method.^{51,54–57} Numerous data obtained by using gas chromatography (GC), HPLC–MS, ^{32}P -labeling, and immunodetection assays are not reported because of the major drawbacks in these methods as discussed in a recent review article.⁵⁸ This is not the case of enzyme-based assays involving DNA repair enzymes such as the formamidopyrimidine DNA *N*-glycosylase and endonuclease III. The enzymes are used for recognizing base damage and strand breaks thus formed are measured with the alkaline comet assay,^{59,60} the unwinding method,⁶¹ or the alkaline elution technique.⁶² However, the latter indirect and more global assays do not provide accurate structural information because of the broad

substrate specificity of the repair enzymes used, and therefore, these assays will not be reported in the present survey.⁶³ As a final remark, the analysis of oxidation products has been confined to nuclear DNA because the quality or the amount of mitochondrial DNA is not sufficient at this time for accurately measuring oxidized bases and nucleosides.

2 SINGLE-BASE DAMAGE

2.1 Singlet Oxygen Oxidation of Guanine

Singlet oxygen ($^1\text{O}_2$) in the $^1\Delta_g$ state ($E = 22.4 \text{ kcal mol}^{-1}$) which is generated in cells by type II photosensitizers or enzymic reactions involving myeloperoxidase^{33,64} is a dienophile⁶⁵ that exclusively reacts at neutral physiological pH with guanine among the DNA components.^{66,67} This contrasts with molecular oxygen (O_2) in its triplet state, which as a biradical reacts efficiently with most carbon-centered radicals. The reaction of $^1\text{O}_2$ with 2'-deoxyguanosine (**1**; Scheme 1) and related guanine model compounds in aqueous solutions has been shown to yield, as the main primary oxidation products, the 4*R** and 4*S** diastereomers of spiroiminodihydantoin nucleosides **8**,^{68,69} initially misassigned as the position isomers of 4-hydroxy-8-oxo-7,8-dihydro-2'-deoxyguanosine **5**,⁷⁰ with a relatively minor contribution of 8-oxo-7,8-dihydro-2'-deoxyguanosine (**4**).^{70–72} More recently, evidence was provided on the basis of HPLC–MS/MS measurements for the generation of **5** as a minor degradation product of **1**.⁷³ The formation of stable oxidation products **4**, **5**, and **8** may be rationalized in terms of a Diels–Alder [4+2] cycloaddition of $^1\text{O}_2$ across the imidazole ring of the base moiety of **1** (Scheme 1) leading to a diastereomeric pair of 4,8-endoperoxides **2**. Evidence for the formation of the latter instable intermediate (**2**) was gained from the nuclear magnetic resonance (NMR) characterization of the related endoperoxides generated by $^1\text{O}_2$ oxidation of 2', 3', 5'-*O*-*tert*-butyldimethylsilyl-8-methylguanosine in CD_2Cl_2 at low temperature.⁷⁴ In a subsequent step, **2** is expected to rearrange giving rise to 8-hydroperoxy-2'-deoxyguanosine (**3**)^{74,75} as indirectly supported by low temperature NMR analysis of a type II photosensitized



Scheme 1 $^1\text{O}_2$ oxidation reactions of the guanine moiety (1) of nucleosides and DNA.

2',3',5-*O*-*tert*-butyldimethylsilyl derivative of 8- ^{13}C -guanosine in an organic solution.⁷⁶ Reduction of **3** is likely to lead to 8-hydroxy-2'-deoxyguanosine, which is in dynamic equilibrium with the predominant 6,8-diketo tautomer (**4**),⁷⁷ while competitive dehydration gives rise to the unstable quinonoid 2-amino-7,9-dihydropurine-6,8-dione (**6**),⁷⁸ which after the addition of water across the 5,7-double bond leads to **8** through the intermediacy of the unstable 5-hydroxy-7,8-dihydro-2'-deoxyguanosine (**7**).⁷⁹ It is worth mentioning that in isolated DNA, $^1\text{O}_2$ oxidation of **1** leads to the overwhelming formation of **4** at the exclusion of detectable amounts of **8** because of steric effects that favor linearization of **2** over dehydration.^{67,80}

Evidence was provided that, in cellular DNA, the reaction of $^1\text{O}_2$ with **1** occurs with the same selectivity and specificity as in aqueous solutions of DNA, generating **4** as the only detectable HPLC–MS/MS oxidized nucleoside.^{64,81} This was achieved using a clean source of $^1\text{O}_2$ that was released in the vicinity of nuclear DNA on incubation of cells at 37 °C with a suitably protected thermolabile naphthalene endoperoxide.⁸² It was confirmed using [^{18}O]-labeled $^1\text{O}_2$ that **4** arises from $^1\text{O}_2$ oxidation of **1** and not indirectly as the result of an oxidative stress induced by the incubation of cells with naphthalene endoperoxide. Several reports have shown that UVA irradiation of cells^{64,83} and human skin⁸⁴ leads through photodynamic effects⁷² to an increase in the level of **4** in nuclear DNA. This, at least in human monocytes, is explained on the basis of a detailed mechanistic study,⁸⁵ in terms of major

contribution of $^1\text{O}_2$ of up to 80% as the result of a type II photosensitized reaction promoted by endogenous photosensitizers. The remaining 20% of **4** was accounted for by $\cdot\text{OH}$ -mediated oxidation by a different mechanism as will be discussed later. Another clarification of a controversial issue concerning the putative DNA nicking activity of $^1\text{O}_2$ was provided by the almost total lack of generation of DNA strand breaks and/or alkali-labile sites as inferred from the results of a comet assay analysis of cells exposed to a specific chemical source of $^1\text{O}_2$: naphthalene endoperoxide.⁸⁶ It has been also shown that UVA irradiation of cells leading to the predominant formation of $^1\text{O}_2$ is not able to generate any detectable amounts of DNA double-strand breaks.^{87,88}

2.2 Hydroxyl Radical Reactions

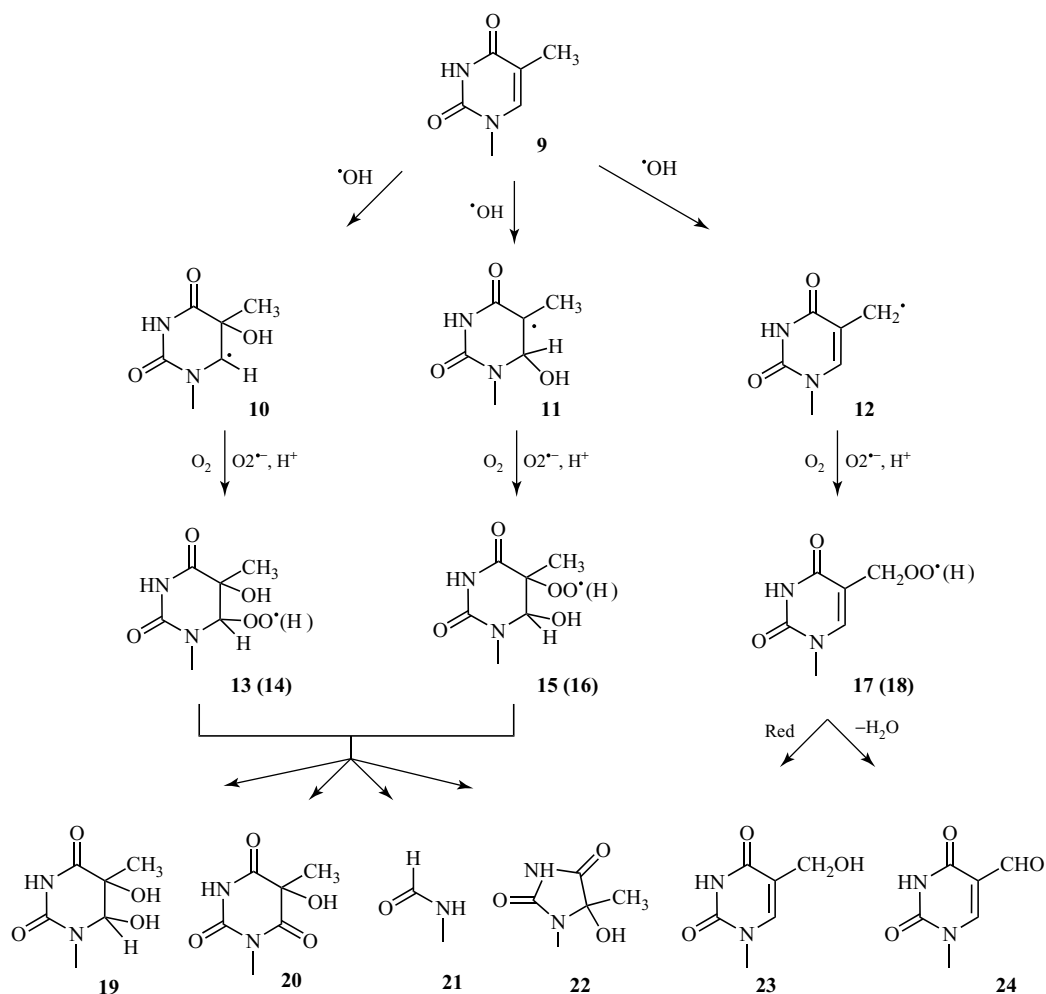
A convenient way to generate $\cdot\text{OH}$ under well-controlled conditions in model studies is to use the indirect effects of ionizing radiation. Thus, γ -radiolysis of aerated aqueous solutions gives rise to $\cdot\text{OH}$ and $\text{O}_2^{\cdot-}$ in 45 and 55% yields, respectively.^{14,89}

2.2.1 Thymine

The main oxidation products of the base moiety of thymidine (**9**; Scheme 2) mediated by

$\cdot\text{OH}$ in aerated aqueous solutions have been isolated and characterized on the basis of extensive ^1H and ^{13}C NMR, mass spectrometry, and X-ray diffraction measurements.^{90–96} Thus, nine hydroperoxides, which represent about 50% of the total oxidized nucleosides were assigned, consisting of the *cis* and *trans* diastereomers of 6-hydroperoxy-5-hydroxy-5,6-dihydrothymidine (**14**) and 5-hydroperoxy-6-hydroxy-5,6-dihydrothymidine (**16**)⁹⁷ together with 5-(hydroxyperoxy-methyl)-2'-deoxyuridine (**18**). The structures of hydroperoxides **14**, **16**, and **18** were confirmed by chemical synthesis using well-established methods.⁹⁸ In addition, the X-ray crystal structure of *cis*-5-hydroperoxy-6-hydroxy-5,6-dihydrothymine was solved and its electronic properties were inferred from *ab initio* theoretical investigations.⁹⁹ A mixture of the nine hydroperoxides **14**, **16**, and **18** was fully resolved by reverse-phase high-performance liquid chromatography (RP-HPLC) using a colorimetric based post-column reaction for hydroperoxides.¹⁰⁰ HPLC–MS/MS also appears to be a powerful method for detecting hydroperoxides as illustrated by the measurement of hydroperoxide **18** after enzymatic hydrolysis of calf thymus DNA that was exposed to γ rays in aerated aqueous solutions (Ravanat and Cadet, unpublished). The rest of the thymidine degradation products consist of stable nucleosides that are ranged in the following order of decreasing quantitative importance: *N*-(2-deoxy- β -D-*erythro*-pentofuranosyl) formylamine (**21**) > the four *cis* and *trans* diastereomers of 5,6-dihydroxy-5,6-dihydrothymidine (**19**) > the (*5R**)- and (*5S**)-forms of 1-(2-deoxy- β -D-*erythro*-pentofuranosyl)-5-hydroxy-5-methylhydantoin (**22**) > the (*5R**)- and (*5S**)-diastereomers of 1-(2-deoxy- β -D-*erythro*-pentofuranosyl)-5-hydroxy-5-methylbarbituric acid (**20**) > 5-(hydroxymethyl)-2'-deoxyuridine (**23**) > 5-formyl-2'-deoxyuridine (**24**). On the basis of indirect characterization of the primary pyrimidine radicals **10** and **11**, and the structural assignment of final oxidation products **14**, **16**, **18–24** (*vide supra*), a comprehensive mechanism for the $\cdot\text{OH}$ -mediated oxidation of thymidine (**9**) has been proposed (Scheme 2). The predominant reaction of $\cdot\text{OH}$ with the base of free nucleoside **9** is the addition at carbon C-5^{14,101,102} generating the reducing C-6 centered radical **10** in 60% yield. The oxidizing C-5 radical **11** that arises from the addition of $\cdot\text{OH}$ at C-6 is formed with a lower efficiency (35%). A third and minor process

(5%), at least for the free nucleoside, consists of hydrogen atom abstraction from the methyl group, generating the aromatic radical **12**. In a subsequent step, transients **10–12** are converted into the corresponding peroxy intermediates **13**, **15**, and **17** through a fast diffusion-controlled reaction with O_2 .¹⁰³ About half of the peroxy radicals **13**, **15**, and **17** are transformed after $\text{O}_2^{\cdot-}$ reduction and subsequent protonation into hydroperoxides **14**, **16**, and **18**.¹⁰⁴ The half-life of thymidine hydroperoxides varied from 1 to 35 hours at 37 °C for 5(6)-hydroxy-6(5)-hydroperoxides (**14**, **16**), with a much greater half-life for 5-(hydroperoxymethyl)-2'-deoxyuridine (**18**)⁹⁸. The decomposition of **14**, **16**, and **18** was quite specific in aqueous solution in the absence of transition metals. The *trans* and *cis* diastereomers of thymidine 6-hydroperoxides (**14**) initially undergo dehydration to give 5-hydroxy-5-methylbarbituric acid nucleoside (**20**), which in turn can transform by hydrolysis into an open-chain ureid: *N*³-tartronoylurea nucleoside (not shown). In a recent theoretical investigation, the thermal decomposition of 6-hydroperoxide (**14**) was found to be significantly facilitated by water molecules with dehydration being the most favorable initial reaction.¹⁰⁵ In contrast to thymidine 6-hydroperoxides (**14**), the main decomposition pathway of thymidine 5-hydroperoxides (**16**) involved initial cleavage of the 5,6-pyrimidine bond followed by either loss of formic acid and cyclization to give 5-hydroxy-5-methylhydantoin (**22**) or loss of a pyruvyl group to give formylamine (**21**). In the presence of trace or added metal ions, the decomposition of **14**, **16**, and **18** shifted to metal-catalyzed reduction of the hydroperoxides to the corresponding alcohols (**19** and **23**). In addition, aromatic hydroperoxide **18** has been shown to be converted partly into aldehyde **24** on dehydration. It may be added that in the case of free nucleoside **9**, thymine hydroperoxyl radicals **13**, **15**, and **17** may undergo competitive dismutation reactions giving rise to the corresponding highly reactive oxyl radicals.¹⁴ The latter radicals are expected to undergo hydrogen atom abstraction leading to the formation of **19** and/or β scission giving rise to **21** and **22**. However, these reactions are not possible in DNA where peroxy radicals are reduced to hydroperoxides and/or react with vicinal purine and pyrimidine bases leading in



Scheme 2 $\cdot\text{OH}$ -mediated oxidation reactions of the thymine (9).

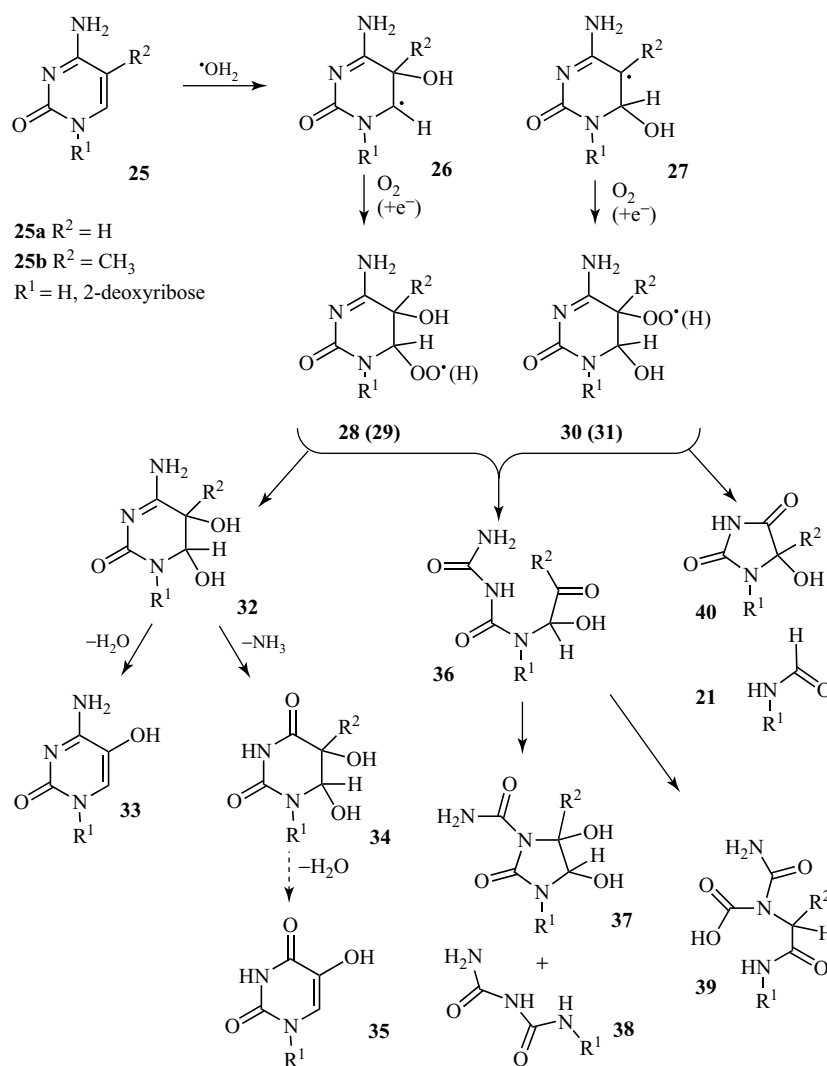
the latter case to tandem base modifications (see Section 3). Two single-base lesions including **19** and **22** were shown to be formed in double-stranded DNA (dsDNA) on exposure to $\cdot\text{OH}$ in aerated aqueous solutions.¹⁰⁶ In addition, evidence was provided for the $\cdot\text{OH}$ -mediated formation of **24** in DNA.¹⁰⁶ Subsequently thymidine glycols (**19**), 5-(hydroxymethyl-2'-deoxyuridine (**23**), and 5-formyl-2'-deoxyuridine (**24**) have been found to be generated by ionizing irradiation in either aerated aqueous solutions of DNA^{54,107} or cellular DNA in a dose-dependent manner. This was achieved in both cases by using the accurate HPLC-MS/MS method.^{108–110} The similarity between the degradation patterns of **9** in isolated DNA and nuclear

DNA is strongly indicative of the relevance of using aqueous solutions as model studies for investigating the effects of $\cdot\text{OH}$ on cellular DNA. It may be noted that the radiation yields of **19**, **23**, and **24** in cellular DNA are about three orders of magnitude lower than those measured in isolated DNA. Interestingly, a similar shielding effect that is exerted by the cellular components is observed on the levels of radiation-induced damage to the 2-deoxyribose moiety of DNA.¹⁷ As discussed further in Section 2.3, it may be pointed out that the degradative action of ionizing radiation on cellular DNA is mostly explained in terms of the indirect effect mediated by $\cdot\text{OH}$.

2.2.2 Cytosine and 5-Methylcytosine

The intermediates and stable products involved in the $\cdot\text{OH}$ -induced decomposition of cytosine derivatives **25a** are presented in Scheme 3; compounds denoted with the letter **a** refer to cytosine derivatives, whereas those with **b** refer to 5-methylcytosine derivatives. The initial reaction of $\cdot\text{OH}$ with the base moiety of cytosine derivatives proceeds by addition to the 5,6-double bond giving mainly 5-hydroxy-5,6-dihydrocytos-6-yl (**26a**) and partly 6-hydroxy-5,6-dihydrocytos-5-yl (**27a**) in a ratio

of approximately 9:1.^{111,112} Similar to thymine and uracil, the $\cdot\text{OH}$ -adducts of cytosine likely react rapidly with O_2 in aerated aqueous solutions to form the corresponding peroxy radicals: 5(6)-hydroxy- 6(5)-hydroperoxyl- 5, 6-dihydrocytosine radicals (e.g., **28a** and **30a**). The intermediate peroxy radicals of cytosine derivatives may undergo a number of reactions depending on the chemical environment: reduction, bimolecular decay, or reaction with either the flanking bases or sugar moieties of DNA. The formation of the radical cation of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine has been observed on pulse radiolysis of an aqueous



Scheme 3 $\cdot\text{OH}$ -mediated oxidation reactions of cytosine (**25a**) and 5-methylcytosine (**25b**).

oxygenated solution of cytosine, suggesting the formation and reduction of peroxy radicals.¹¹¹ Although the hydroperoxides of cytosine (**29a** and **31a**) have been tentatively characterized, they are not stable under aqueous and neutral conditions.¹¹³ The oxidation products of cytosine **25a** can be divided into three groups: 5,6-glycols and 5-hydroxypyrimidines (**32–35**; 40% of total); C4–C5 cleavage products (imidazolidine (**37**), biuret (**38**), and carbamate (**39**) products; 23%), and fragmentation products (5-hydroxyhydantoin (**40**) and formylamine (**21**; 15%).

The major decomposition pathway of alkoxy, peroxy, or hydroperoxide intermediates of cytosine derivatives involves the formation of cytosine 5,6-glycols (**32a**), which subsequently undergo either dehydration to 5-hydroxycytosine (**33**) or hydrolytic deamination to uracil 5,6-glycols (**34a**). The half-life of cytosine 5,6-glycols is approximately 1 hour at 37 °C and 5 hours at 22 °C in aqueous solution at pH 7 and they predominantly undergo dehydration from pH 2 to 8 (>90%) with an increase in deamination at higher pH (>8).¹¹⁴ In contrast, the half-life of **32a** in DNA was estimated to be 28 hours at 37 °C and pH 7, and the ratio of dehydration to deamination was 1.5:1 in favor of dehydration in oxidized calf-thymus DNA as estimated by acid hydrolysis and HPLC with electrochemical detection (HPLC–EC).¹¹⁴ Similar results were obtained for double-stranded poly(dG–dC) treated with KMnO₄, which more specifically induces the formation of the *cis* diastereomers of **32a**.¹¹⁵ Although these studies have utilized indirect methods to measure cytosine 5,6-glycols **32a** in DNA, they strongly suggest that the double-stranded structure of DNA substantially increases the half-life of **32a** and shifts the decomposition pathway toward deamination in comparison to the monomer. This is reminiscent of changes in the half-life of 6-hydroxy-5,6-dihydrocytosine in poly(dG–dC) (18 hours) compared to that of the monomer (25 min) in aqueous solution at 37 °C and pH 7.¹¹⁶ The yield of **33**, **34a**, and **35** as determined by enzymatic digestion and HPLC–EC, was 19, 16, and 24 lesions per million cytosine per Gy, respectively, in calf-thymus DNA exposed to ionizing radiation in aerated aqueous solutions.¹¹⁷ Again, these results point to an increase in the extent of deamination in dsDNA compared to the monomer. Interestingly, the yield of 5-hydroxyuracil (**35**) was comparable to that of

5-hydroxycytosine (**33**) on exposure of DNA to ionizing radiation, whereas **35** was not detected on exposure of DNA to KMnO₄. This suggests that **35** is not formed by consecutive deamination and dehydration (**32** → **35**). The average steady-state levels of endogenous DNA damage in human lymphocytes was 2.9 ± 1.4 for 5-hydroxycytosine (**33**) and 4.5 ± 1.8 for 8-oxo-7,8-dihydroguanine (**4**) per 10⁶ guanines ($n = 10^5$) as determined by HPLC–EC.¹¹⁸ The levels of 5-hydroxycytosine (**33**) in cellular DNA obtained by HPLC–EC compare closely to those obtained by HPLC–MS/MS. The results suggest that 5-hydroxycytosine (**33**) is generated in cellular DNA at comparable levels to 8-oxo-7,8-dihydroguanine (**4**), whereas the amount of 5-hydroxyuracil (**35**) is at least 10-fold lower.^{119,120}

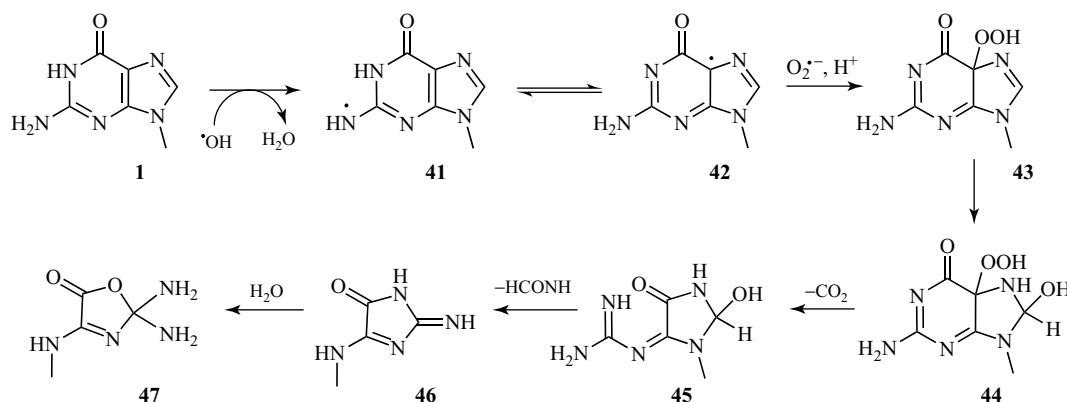
The formation of products **37a–39a** constitutes a novel pathway of 'OH-mediated decomposition for cytosine derivatives (Scheme 3). The imidazolidine products consist of four diastereomers with two chiral centers (C4 and C5 of the imidazolidine ring), which remarkably, undergo ring-chain tautomerism involving both N1–C5 and N3–C4 bonds of the ring, leading to epimerization of all four diastereomers.¹²¹ The rate of epimerization was much greater for *cis* diastereomers ($8.5 \times 10^{-4} \text{ s}^{-1}$ (half-life = 14 min) compared to *trans* diastereomers ($5.8 \times 10^{-6} \text{ s}^{-1}$; half-life = 33 hours) at 37 °C and pH 7. The mechanism of formation of **37a** likely involves intramolecular rearrangement of 5-hydroxy-6-hydroperoxides, **29a** into C6–C4 endoperoxides followed by O–O and C4–C5 bond cleavage to give intermediate **36a**. This was supported by the formation of imidazolidine products on the reaction of 5-bromo-6-hydroxy-5,6-dihydro-2'-deoxycytidine with H₂O₂, which proceeds by the initial formation of intermediate 5-hydroxy-6-hydroperoxides (**29a**). Additional evidence for the formation of an intermediate endoperoxide was provided by ¹⁸O₂-labeling experiments showing the incorporation of two ¹⁸O atoms into the structure of product **37a**, that is, one label on each at the sides of O–O bond cleavage.¹²² In addition to **37a**, two other nucleosides with a related structure were identified in the mixture of products: biuret (**38**) and aminocarbonyl[2-amino]-2-oxomethylcarbamic acid (**39a**). The open-chain intermediate resulting from C4–C5 cleavage of the endoperoxide may be proposed as a common precursor for all of

the products (**36** $\rightarrow$ **37–39**). The formation of biuret products (**38**), which exist in four different forms (α - and β -furanose, and α - and β -pyranose), due to protonation at N1 and ring-opening of 2-deoxyribose moiety, may be explained by either loss of glyoxal (CHO–CHO) from the intermediate (**36a**) or from the imidazolidine product (**37a**). The formation of **39a** may be explained by the subsequent α -hydroxyketone rearrangement of the precursor (**36a**), followed by dehydration and hydrolysis at C2. The *trans* diastereomers of **37a** have been detected on γ -irradiation of aerated aqueous solutions of dGpdC, dCpdG, and d(TpApCpG), as well as by the reaction of Fenton reagents with dCpC.^{123,124} Using LC–MS/MS, the endogenous steady-state level of a dinucleotide containing imidazolidine (**37a**) in DNA extracted from white extracted from white blood cells was estimated to be 7.7 lesions /10⁶ DNA bases, higher than the amount of either formylamine (**21**) or thymine 5,6-glycol (**19**).¹²⁵

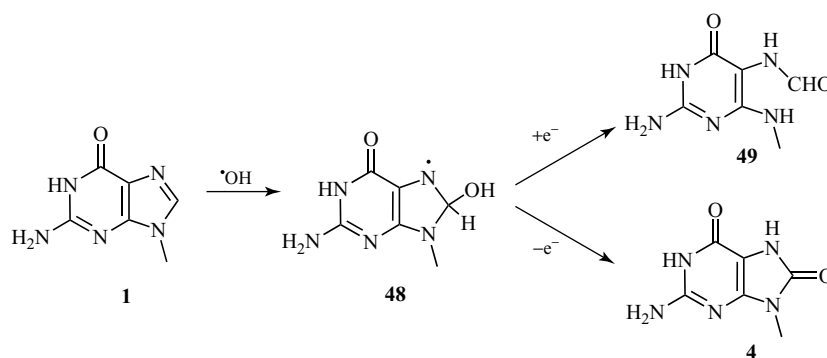
The chemistry of $\cdot$ OH-induced decomposition of 5-methylcytosine derivatives is similar in many respects to that of cytosine derivatives. The main products observed after γ -irradiation of an aerated aqueous solution of the nucleoside (**25b**; Scheme 3; R² = CH₃) included the corresponding derivatives of 5,6-dihydroxy-5,6-dihydro-5-methylcytosine (**32b**), 1-carbamoyl-4,5-dihydroxy-5-methyl-2-oxo-imidazolidine (**37b**), aminocarbonyl[2-amino]-carbamic acid (**39b**) and formylamine (**21**).^{126,127} The four *cis* and *trans* diastereomers of 5-methylcytosine 5,6-glycols (**32b**) undergo deamination to thymidine 5,6-glycols (**19**) with a half-life of 17 and 22 hours for *cis*-(5*S*, 6*S*) and *cis*-(5*R*, 6*R*) diastereomers, respectively, at 37 °C and pH 7; in contrast, the *trans* diastereomers undergo deamination more efficiently than the *cis* diastereomers. Thus, 5-methylcytosine 5,6-glycols **32b** are more stable than cytosine glycols **32a** by about 20-fold for the corresponding nucleosides. Interestingly, there was no marked difference in the half-lives for the deamination of 5-methylcytosine 5,6-glycols (**32b**) as a monomer compared to that in duplex DNA at 37 °C (half-life between 27 and 37 hours).¹²⁸

2.2.3 Guanine

The two main $\cdot$ OH-mediated degradation products of 2'-deoxyguanosine (**1**) in aerated aqueous solution have been identified as 2,2-diamino-4-[(2-deoxy- β -D-*erythro*-pentofuranosyl) amino] -5 (2*H*) -oxazolone (**47**) and its unstable precursor, 2-amino-5-[(2-deoxy- β -D-*erythro*-pentofuranosyl) amino]-4*H*-imidazol-4-one (**46**).^{129,130} In addition, traces of 8-oxo-7,8-dihydro-2'-deoxyguanosine (**4**), which is a ubiquitous DNA oxidation product since it is generated as well by ¹O₂, one-electron oxidants, ONOO[−]^{11,37,131}, and addition of vicinal intrastrand thymine 5(6)-hydroxy-6(5)-hydroperoxyl radicals^{132,133} were found to be formed in a manner independent of the γ radiation dose. The formation of **46** and **47** (Scheme 4) may be rationalized in terms of initial $\cdot$ OH-mediated H[•] abstraction from the 2-amino group of the guanine base¹⁶ and not from $\cdot$ OH addition at the C4 position as proposed earlier.^{134–136} The resulting aminyl radical **41** undergoes tautomerization to guanyl radical **42**, which has been shown to react in nucleosides and oligonucleotides with O₂^{•−}¹³⁷ and not with O₂, as in the case of other highly oxidizing radicals derived from the one-electron oxidation of tyrosine and tryptophan.³⁵ The 5-hydroperoxide **43** thus formed is likely to undergo a complex set of reactions and rearrangements (Scheme 4) including the initial addition of a water molecule addition across the 7,8-double bond giving rise to **44**, followed by opening of the pyrimidine ring at C5–C6 bond and decarboxylation.^{37,129,138} The intermediate **45** is likely to lose a formamide residue as shown by GC–MS analysis leading to the formation of poorly stable **46**. The latter compound has a half-life of 10 hours in neutral aqueous solutions at 20 °C when inserted into oligonucleotides with a quantitative hydrolytic conversion into **47**.¹³⁹ The formation of **4** is explained by $\cdot$ OH addition at C8 leading to the minor reducing 8-hydroxy-7,8-dihydro-7-yl radical **48** (Scheme 5), which represents only 17% of the total guanine radicals.^{135,136} One-electron oxidation of **48** gives rise to **4**, whereas competitive reduction, which is a minor process in aerated aqueous solution for isolated nucleoside, is accompanied by the opening of the imidazole ring at C8–N9 bond with subsequent formation of the 2'-deoxyribonucleoside derivative of 2,6-diamino-4-hydroxy-5-formamidopyrimidine



Scheme 4 Oxidation reactions of guanine (**1**) through $\cdot\text{OH}$ -mediated $\cdot\text{H}$ abstraction from the 2-amino group.



Scheme 5 Oxidation reactions of guanine (**1**) through $\cdot\text{OH}$ addition at C8.

(**49**).^{29,31,37} The low amount of $\cdot\text{OH}$ -mediated formation of **4** is accounted for by its efficient one-electron oxidation as soon as it is produced by the oxidizing guanine radical **42**. However, the presence of a reducing agent such as ascorbic acid in a mixture of H_2O_2 and Fe^{2+} ions, the so-called Udenfriend reagent, leads to the predominant formation of **4**¹⁴⁰ at the expense of **47**. This may be explained by the reduction of precursor radical **42**, which prevents the oxidation and consumption of **4**.

Exposure of DNA in aqueous aerated solution to the indirect effects of ionizing radiation has been shown to give rise to significant amounts of **4** with smaller amounts of **49**, both degradation products arising partly from initial $\cdot\text{OH}$ addition at C8 of **1**.⁵⁴ This contrasts with the low yield of formation of **4** on $\cdot\text{OH}$ oxidation of free **1**, which may be explained by the reduced possibility for the guanine oxidizing radical **42** to degrade **4** and also the presence of transition metals in

DNA. Both **4** and **49** were found to be generated in the DNA of human monocytes on exposure to γ rays and heavy ions^{109,110} at least partly according to the mechanisms depicted in Scheme 5. This was achieved using an accurate HPLC–MS/MS assay and a combined enzymatic/hydrolytic protocol that allows the quantitative release of **49** as a free base.¹⁴¹ An interesting feature of **49** is that it is generated in higher yield than **4**, whereas an opposite trend is noted in aerated aqueous solutions of isolated DNA. This may be explained by the lower concentration of O_2 and the presence of reducing agents in the nucleus. Further support for the predominant role of indirect effects in the radiation-induced degradation of cellular DNA is provided by the observation that an increase in linear energy transfer (LET) of $^{12}\text{C}^{6+}$ ($24.5 \text{ keV}/\mu\text{m}^{-1}$) and $^{36}\text{Ar}^{18+}$ ($250 \text{ keV}/\mu\text{m}^{-1}$) heavy ions with respect to γ photons leads to a decrease in the yield of both **4** and **49**. It may be added that **47**, the

main $\cdot\text{OH}$ -mediated degradation product of **1** in aerated aqueous solution has been detected by HPLC–MS/MS in the DNA of diabetic rats.¹⁴² It was proposed that the formation of **47** whose yield is about 10-fold lower than that of **4**, may be rationalized in terms of oxidative stress induced by diabetes with the concomitant release of $\text{O}_2^{\cdot-}$ and the subsequent generation of $\cdot\text{OH}$.

2.2.4 Adenine

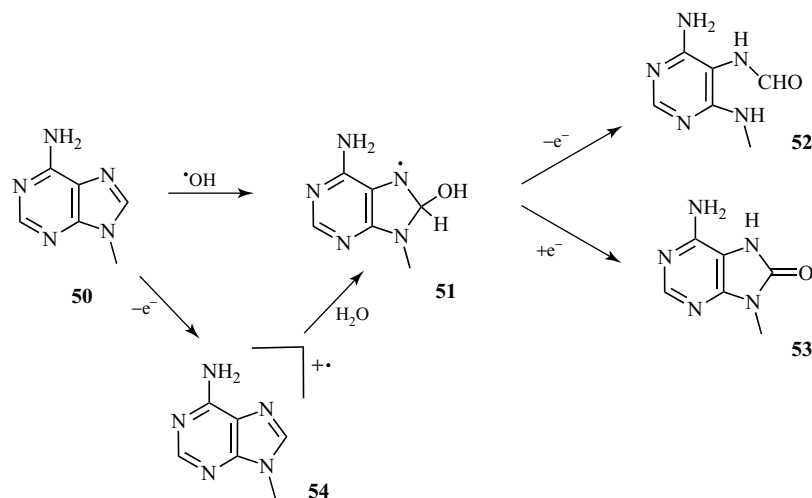
4,6-Diamino-5-formamidopyrimidine (**52**) and 8-oxo-7,8-dihydro-2'-deoxyadenosine (**53**) have been shown to be the two main $\cdot\text{OH}$ -mediated degradation products of adenine (**50**) as free nucleosides^{143,144} and within isolated DNA⁵⁴ in aqueous solutions. The mechanism of formation of **52** and **53** which is similar to that of **49** and **4**, for the two guanine analogs, is depicted in Scheme 6. Addition of $\cdot\text{OH}$ at C8 of **50** gives rise to transient 8-hydroxy-7,8-dihydroadenyl **51**, which is subsequently converted into **52** and **53** on one-electron reduction and one-electron oxidation, respectively. A similar degradation pathway is likely to explain the radiation-induced formation of **52** and **53** in cellular DNA via the indirect effect of γ rays.^{109,110} It should be mentioned that the yields of **52** and **53** in both naked and cellular DNA are about 10-fold lower than those of **49** and **4**, respectively. This is likely due to the

enhancement of the formation of **4** and **49** as the result of efficient charge transfer reactions, guanine being the sink of positive holes, and the formation of tandem base lesions with the participation of vicinal pyrimidine peroxy radicals.¹⁴⁵ Application of the accurate HPLC–MS/MS method has allowed revisiting the $\cdot\text{OH}$ -induced chemical reactions of **50** in isolated and cellular DNA. Thus, the formation of 2-hydroxy-2'-deoxyadenosine was not detected in γ -irradiated human monocytes up to doses of 200 Gy¹⁴⁶ This contrasts with previous GC–MS measurements, which have shown that 2-hydroxy-2'-deoxyadenosine is one of the predominant $\cdot\text{OH}$ -mediated degradation products in the DNA of γ -irradiated cells and mice.^{147,148}

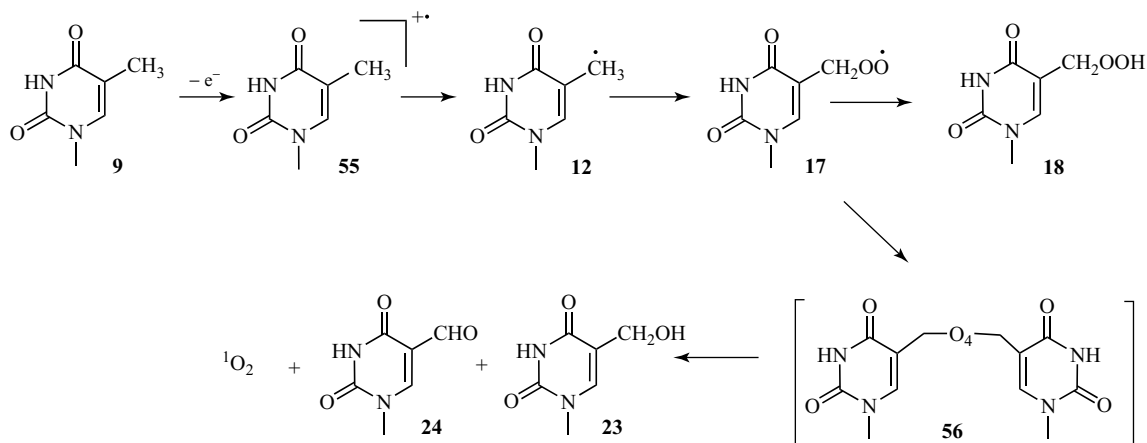
2.3 One-Electron Oxidation of Nucleobases

2.3.1 Thymine

A convenient and efficient method to induce one-electron transfer and generate pyrimidine radical cations in aerated aqueous solutions involves photosensitization with 2-methyl-1,4-naphthoquinone (MQ) on excitation by UVA radiation.¹⁰⁴ Using this approach, two main decomposition pathways of thymidine radical cations **55** have been identified^{24,149–151} (Scheme 7). The hydration of thymidine radical cations gives mainly



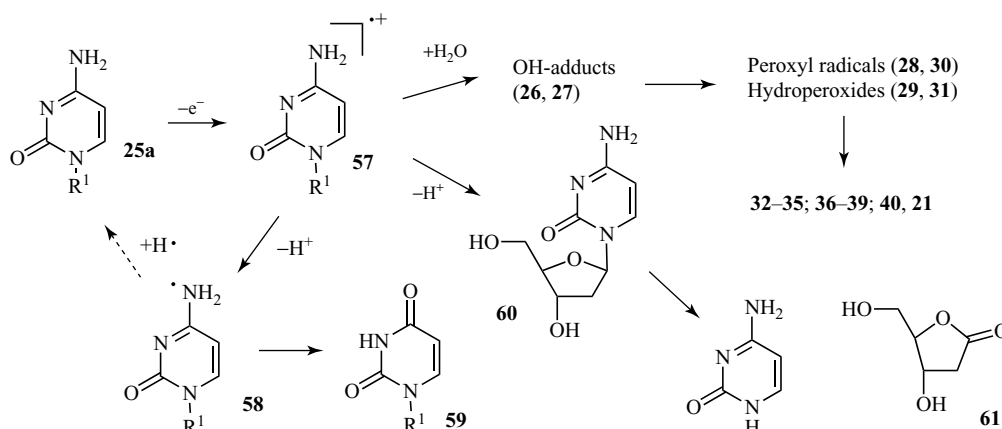
Scheme 6 $\cdot\text{OH}$ and one-electron oxidation reactions of adenine (**50**).



Scheme 7 One-electron oxidation reactions of thymine (**9**).

oxidizing 6-hydroxy-5,6-dihydrothymid-5-yl radicals (**11**) as inferred by spin trapping in electron spin resonance (ESR) experiments.¹⁵² These results were confirmed from the isolation of the four *cis* and *trans* diastereomers of 5-hydroperoxy-6-hydroxy-5,6-dihydrothymidine **16**^{150,151} (Scheme 2). The formation of stable thymidine degradation products including the four *cis* and *trans* diastereomers of 5,6-dihydroxy-5,6-dihydrothymidine (**19**), the 5*R** and 5*S** forms of 5-hydroxy-5-methylhydantoin (**22**), and formamide (**21**) nucleosides may be explained in part by thermal decomposition of hydroperoxides **16**. Altogether, the hydration pathway accounts for 60% of the total degradation products of isolated thymidine (**9**). The remaining stable products accounting for 40% of the total may be explained by the initial deprotonation of the thymidine radical cation **55** (Scheme 7). Interestingly, the relative importance of the two pathways is dependent on the photosensitizer used since deprotonation was significantly more favored on benzophenone-mediated photosensitization with UVA light compared to MQ-photosensitization. An influence of the pK_a of the radical anion of the sensitizer was proposed to account for this result.¹⁵³ Deprotonation of **55** gives rise to the allylic 5-methyl-(2'-deoxyuridylyl) radical (**12**).^{150,151} Efficient addition of O_2 to **12** is the first step of a sequence of reactions, that through the intermediacy of the corresponding peroxy radical **17** and its subsequent reduction, lead to the generation of highly stable 5-(hydroperoxymethyl)-2'-deoxyuridine (**18**) as the

precursor of **23** and **24**. The formation of the latter oxidized nucleosides may be also rationalized in terms of a Russell mechanism¹⁵⁴ in which the intermediate tetroxide **56** formed by combination of two 5-(hydroperoxymethyl)-2'-deoxyuridylyl radicals **17** decomposes with subsequent formation of alcohol **23** and aldehyde **24** products together with concomitant release of 1O_2 as recently proposed for the decomposition of peroxy radicals of linoleic acid.¹⁵⁵ Hydration and deprotonation reactions of **55** previously identified in 2'-deoxyribonucleosides (*vide supra*) have been shown to occur in isolated DNA and double-stranded oligonucleotides.^{156,157} This was achieved on suitable digestion of oxidized DNA to 2'-deoxyribonucleosides followed by HPLC to versatile and sensitive electrospray ionization MS/MS detection.⁵⁴ Thus, several oxidized nucleosides, including **19**, **23**, and **24** were generated in DNA and AT-containing oligonucleotides exposed to high-intensity UVC laser pulses^{27,149,156} and UVA excited anthraquinone,¹⁵⁷ respectively. It is interesting to note that, in the latter case, final damage was localized on thymine rather than on adenine, probably as the result of the higher reactivity of pyrimidine radical cations. Evidence for the one-electron oxidation-mediated formation of **23** and **24** in isolated DNA was gained from previous studies with menadione, riboflavin, and nitro derivatives of lysine, as type I photosensitizers.^{156,158} Interestingly, the formation of **19**, **23**, and **24** was observed in cellular DNA on exposure to high-intensity UVC laser pulses¹¹⁰



Scheme 8 One-electron oxidation reactions of cytosine (**25a**).

that have been able to photo-ionize pyrimidine and purine bases with a similar efficiency in isolated DNA.^{26,27}

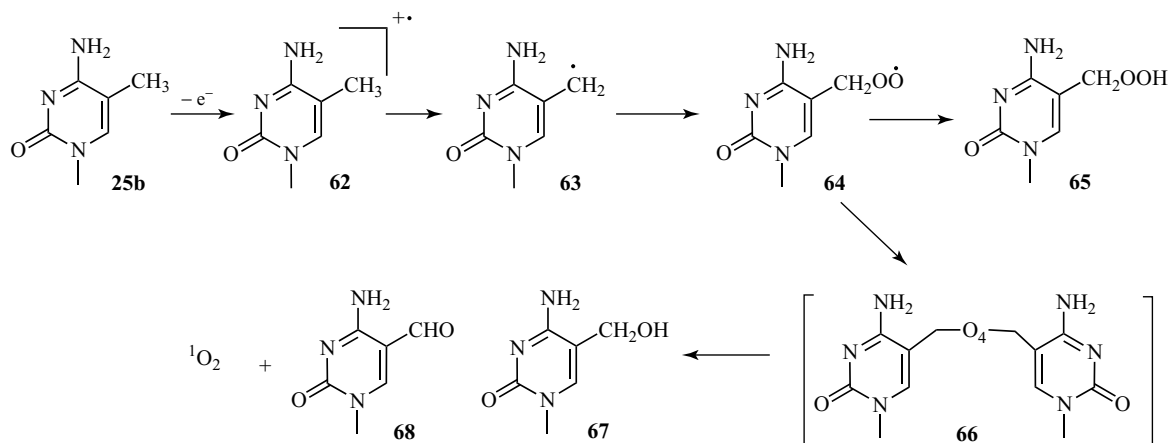
2.3.2 Cytosine

The radical cation of cytosine **57** is efficiently generated in aqueous solution by near-UV photosensitization of the nucleoside with 2-methyl-1,4-naphthoquinone (menadione, MQ).¹⁰⁴ On the basis of product analyses, the mechanism of formation of stable products of cytosine nucleoside may be divided into two competitive reaction pathways: hydration (**57** → **26a** + **27a** where “a” refers to cytosine derivatives; Scheme 3) and deprotonation (**57** → **58** + **60**; Schemes 8). Hydration of **57** leads to cytosyl radicals (**26a** and **27a**), which are identical to those generated by the addition of $\cdot\text{OH}$ to cytosine. Thus, the majority of stable products for the nucleoside are the same from both $\cdot\text{OH}$ -induced reactions and one-electron oxidation. Experiments in the presence of $^{18}\text{O}_2$ showed that the label is incorporated at C5 and C6 of the pyrimidine ring in a ratio of about 40 and 60%, respectively, on the basis of MS analysis of products **33**, **34a**, and **21**.¹²² These results suggest that the addition of H_2O occurs with similar efficiency at both C5 and C6 positions of cytosine radical cations (**57**). The greater yield of imidazolidine products (**37a**) in the reactions of $\cdot\text{OH}$ with cytosine (**25a**) compared to the reaction of cytosine radical cations

(**57**) suggests that **37a** is more efficiently produced from 5-hydroxy-substituted 6-hydroperoxyl radicals (**28a**) and/or the corresponding hydroperoxides (**29a**) than from 6-hydroxy-substituted derivatives (**30a** or **31a**). The deprotonation of **57** leads to 2'-deoxyuridine (**59**) as the major product in the MQ-photosensitized oxidation of cytosine nucleoside (**25a**) (Scheme 8).¹²² The formation of cytosine N^4 -aminyl radicals (**58**) was confirmed by ESR experiments in the photosensitization of 1-methylcytosine by triplet anthraquinone-2,6-disulfonic acid (AQ).¹⁵⁹ From a computational perspective, the lowest free energy barrier pathway for deamination involves the addition of water to the N3–C4 imine bond followed by cleavage of the C4–N4 bond.¹⁶⁰ Finally, cytosine radical cation (**57**) also undergoes deprotonation from the C1' position of the sugar moiety (**57** → **61**) leading to the release of cytosine and 2-deoxyribo-1,4-lactone (**61**) in equal amounts.¹⁶¹

2.3.3 5-Methylcytosine

5-Methylcytosine (**25b**) is more susceptible to single electron oxidation because of its lower oxidation potential compared to both cytosine and thymine. Indeed, the formation of 5-methylcytosine radical cation (**62**) as monitored by electron paramagnetic resonance was favored upon irradiation of crystals of cytosine that contained small amounts of 5-methylcytosine as an impurity.^{162,163}

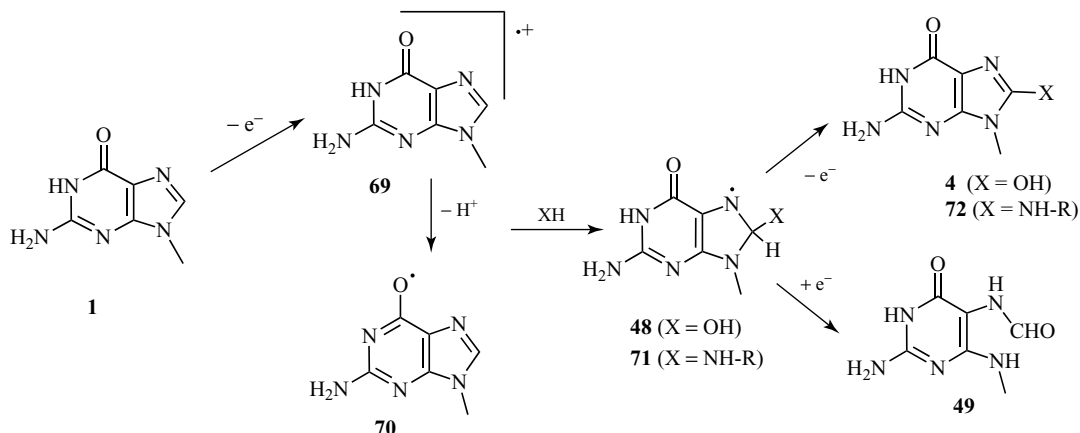


Scheme 9 One-electron oxidation reactions of 5-methylcytosine (**25b**).

Compound **25b** was also preferentially oxidized in oligonucleotides containing G by photosensitized electron transfer with naphthoquinone in aerated aqueous solutions.¹⁶⁴ The deprotonation of **62** to 5-methyl-(2'-deoxycytidylyl) radical (**63**) is a major reaction for the nucleoside in aqueous solution ($\sim 60\%$) (Scheme 9).¹²⁷ The methyl centered radical **63** likely transforms into the corresponding peroxy radical **64** and hydroperoxide **65** (half-life = 9.5 hours at 24°C). In turn, **65** can decompose into stable methyl oxidation products namely 5-(hydroxymethyl)-2'-deoxycytidine (**67**) and 5-formyl-2'-deoxycytidine (**68**) (Scheme 9). Interestingly, the one-electron oxidation of **25b** by UV photolysis of oligonucleotides tethered to naphthoquinone displayed an unusual pH dependence with a maximum production of **68** observed at pH 5–6 and lower yields at both extremes of pH (pH 4 and 8).¹⁶⁵ This phenomenon was explained by two competitive pathways: one involving deprotonation from the exocyclic amino group that cycles back to **25b**; and the other involving irreversible deprotonation from the methyl group leading to methyl oxidation products.¹⁶⁵ There is considerable interest today in the presence of **67** in cellular DNA because of its high levels (0.3–0.7% of cytosine) in brain and embryonic stem cells.^{166,167} In cells, the oxidation of **25b** may occur via Fe^{2+} -mediated oxidation of the methyl group by ten-eleven-translocation (TET) family enzymes.¹⁶⁸ This modification was previously shown to arise from the single electron oxidation of **25b** and subsequent deprotonation of the corresponding radical cation **62**.¹²⁷

2.3.4 Guanine

As observed for pyrimidine bases, deprotonation and hydration of the purine radical cations are the main competitive pathways that lead to the formation of several degradation products. Thus, one-electron oxidation of **1** gives rise to intermediate **69**, which undergoes deprotonation with a rate constant of $1.8 \times 10^7 \text{ s}^{-1}$ for the nucleoside¹⁶⁹ leading to the generation of oxidizing $\text{G}(-\text{H})^\bullet$ (**70**) (Scheme 10). The two predominant degradation products of the purine moiety of free 2'-deoxyguanosine (**1**) arising from the fate of **69** were identified as 2,2-diamino-4-[(2-deoxy- β -D-erythro-pentofuranosyl)amino]-5(2H)-oxazolone (**47**) and its precursor, 2-amino-5-[(2-deoxy- β -D-erythro-pentofuranosyl)amino]-4H-imidazol-4-one (**46**).^{129,130} The mechanism of their production as depicted in Scheme 4 has been rationalized in terms of multistep reactions of **70** or more likely of its isomeric C5 carbon-centered radical **42** that arises also from the initial 'OH -mediated hydrogen abstraction from the 2-amino group of **1** followed by tautomerization.¹⁶ Interestingly, the nucleophilic addition of a water molecule in the sequence of events leading to **47** has received support from the competitive formation of an anhydronucleoside on one-electron oxidation of **1**.¹⁷⁰ This constitutes a relevant model system for investigating the mechanism of oxidatively generated DNA–protein cross-links as proposed in the previous studies.^{171,172}



Scheme 10 Nucleophilic addition reactions at C8 of the guanine radical cation (**69**).

Hydration of **69** has been shown to lead to 8-hydroxy-7,8-dihydroguanyl radical **48** with a pseudo-first-order rate constant estimated to be $6 \times 10^4 \text{ s}^{-1}$ in dsDNA.¹⁷³ This was found to occur according to a counterion-assisted proton shuttle mechanism that was inferred from molecular dynamics and *ab initio* quantum simulations.¹⁷⁴ Evidence for the significant nucleophilic addition of H_2O to C8 of **69** in native calf thymus was provided by the incorporation of ^{18}O into **4** on riboflavin photosensitized oxidation reactions performed in H_2^{18}O solutions.¹⁷⁵ Two major competitive reactions of **48**, which are also generated by $\cdot\text{OH}$ ¹³⁶ (Scheme 4) have been shown to lead to **4** and **49** in a relative ratio that is strongly dependent on the redox status of the environment, and in particular, on the oxygenation of aqueous solutions. In this respect, product **4** is formed predominantly at the expense of **49** in aqueous solutions of dsDNA on one-electron oxidation.¹⁵⁶ This contrasts with the formation of only traces of **4**, which were detected on riboflavin-mediated photosensitized ionization of guanine (**1**) as the free 2'-deoxyribonucleoside.¹⁷⁶ This may be accounted for by an almost complete oxidation of **4** as soon as it is generated by the oxidizing $\text{G}(\text{-H})^\bullet$ radical **70** ($k = 0.46 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7.0) derived from **1**.¹⁷⁷ Another explanation for the lack of **4** in single-stranded DNA (ssDNA) involves efficient deprotonation of **69**, which occurs more readily owing to the absence of base stacking and pairing.¹⁷⁵

Several interesting examples of nucleophilic addition reactions at C8 of **69** have become available more recently as illustrated by the isolation and characterization of novel guanine adducts. As a striking observation, a guanine-lysine cross-link **72** was generated on riboflavin photosensitization of the tight complex formed between TGT trinucleotide and KKK trilycine peptide.¹⁷⁸ This was rationalized in terms of efficient addition of the central lysine residue of KKK to C8 of **69** leading to transient **71** followed by a one-electron oxidation step as proposed from the formation of **4** from **48** (Scheme 10). The alternative mechanism of formation of **72**, in which the lysine radical cation adds to the guanine moiety appears to be less likely.¹⁷⁹ The guanine radical cation **69** is also implicated in the formation of cross-links with either thymine or uracil bases separated from the guanine moiety by cytosine in single-stranded oligonucleotides.^{180,181} A reasonable mechanism for the formation of the base adducts involves nucleophilic addition between the N3 position of pyrimidine bases and the C8 position of **69**.

A major difference between the chemistry of base radical cations as free nucleosides compared to those within dsDNA is the occurrence of efficient electron transfer along DNA strands leading to a redistribution of the initially generated base radical cations (see **Charge Transfer in DNA**). Several mechanisms of transfer including polaron-mediated hopping, two-step hopping with superexchange, and coherent long-range tunneling have been proposed.^{182–185} This leads to

damage at a distance, mostly at guanines and to a lesser extent at adenines, from the initial site of radical cation generation.²⁶ This may be accounted for by the fact that guanine (**1**) bases have the lowest oxidation potential, and thus, act as preferential sinks for positive hole migration. On the basis of both experimental and theoretical investigations, intra- but not interstrand charge migration was shown to be implicated in the formation of damage at **1** following 193 nm laser pulse-mediated one-electron oxidation of nucleobases in dsDNA.¹⁸⁶ Kinetic information has been gained on the two competitive reactions of guanine radical cation **69**, namely hydration and hole transfer to other guanine sites.¹⁷³ Thus, the pseudo-order rate for the hydration of **69** was estimated to be about $6 \times 10^4 \text{ s}^{-1}$, a value that is two orders of magnitude lower than that of hole migration between two isolated guanines separated by two AT base pairs.¹⁷³

Evidence for hole transfer reactions within cellular DNA has been provided from the HPLC–MS/MS measurements of the preferential formation of **4** at the expense of thymidine oxidation products including **19**, **23**, and **24** in human cells on exposure to high-intensity UVC nanosecond laser pulses. A comparison of the product distribution obtained following ionization of DNA bases and that obtained on exposure to γ rays indicates the major contribution of the indirect effect mediated by $\cdot\text{OH}$ under the latter conditions.¹¹⁰

2.3.5 Adenine

One-electron oxidation reactions of adenine (**50**) in free nucleosides have been shown to lead to the formation of 8-hydroxy-7,8-dihydroadenyl radicals (**51**) through hydration of the initially generated adenine radical cation **54** (Scheme 6). In addition, competitive deprotonation of **54** gives rise to oxidizing the 6-aminyl radical, which is the likely precursor of hypoxanthine on deamination.^{187–189} The reducing radical **51** is able, as already discussed in Section 2.2.4, to undergo two competitive reactions in aqueous solutions. One-electron oxidation of **51**, mostly by molecular oxygen, gives rise to 8-oxo-7,8-dihydroadenine (**53**), whereas one-electron reduction leads to 4,6-diamino-5-formamidopyrimidine (**52**) through the transient formation of 8-hydroxy-

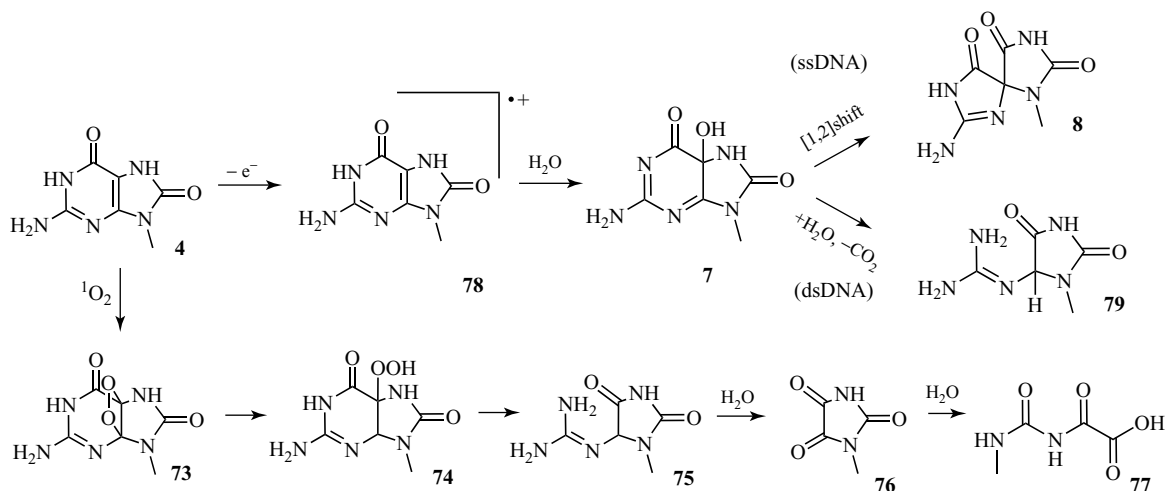
7,8-dihydroadenine.^{143,144} A similar degradation pathway would explain the formation of both **52** and **53** in the DNA of human THP1 cells on exposure to high-intensity nanosecond UVC laser pulses.¹¹⁰

2.4 Secondary Oxidation Lesions

2.4.1 8-Oxo-7,8-dihydroguanine

8-Oxo-7,8-dihydro-2'-deoxyguanosine (**4**) has been shown to be more susceptible to several oxidizing agents including $^1\text{O}_2$ and one-electron oxidants than the parent compound **1**.^{24,190} In that respect, it was found that the rate of reaction of $^1\text{O}_2$ with **4** is about two orders of magnitude higher than that with **1**.^{191,192} The reaction of $^1\text{O}_2$ with free nucleoside **4** predominantly leads to the formation of cyanuric acid together with 2,2,4-triamino-5-(2*H*)-oxazolone (**47**) and the 4*R** and 4*S** diastereomers of **8**.^{68,193–195} This is likely to be explained in terms of $^1\text{O}_2$ addition across the 4,5-ethylenic bond of **4** to yield the transient dioxetane **73**. The $^1\text{O}_2$ -mediated oxidation of **4** inserted within a single-stranded oligonucleotide was found to be more specific. Oxaluric acid (**77**) was the overwhelming $^1\text{O}_2$ oxidation product.¹⁹⁶ This was rationalized by the initial formation of dioxetane **73** on $^1\text{O}_2$ addition across the 4,5-ethylenic bond¹⁹⁰ followed by rearrangement into the transient **74** (Scheme 11). At this point, hydroperoxide **74** may be converted into a derivative of dehydro-guanidinohydantoin **75** after cleavage of the 5,6-bond and subsequent decarboxylation. The final degradation steps involve two successive hydrolytic steps that lead to the formation of **77** through transient parabanic acid (**76**). It may be pointed out that **75** is stable enough for its characterization, and therefore, it has been generated by two electron oxidation of guanine within d(GpT) using the Mn-TMPyp/KHSO₅ oxidizing system.¹⁹⁷

There are numerous examples showing that **4** whose oxidation potential is about 0.5 eV lower than that **1**¹⁹² is a preferential target for a large number of one-electron oxidants. These oxidants include Na₂IrCl₆, K₃Fe(CN)₆, CoCl₂/KHSO₅, high-valent chromium complexes, peroxy radicals, triplet ketones, oxyl radicals, ionizing radiation through the direct effect, and riboflavin.²⁴ The



Scheme 11 $^1\text{O}_2$ oxidation reactions of 8-oxo-7,8-dihydroguanine (**4**) in oligonucleotides.

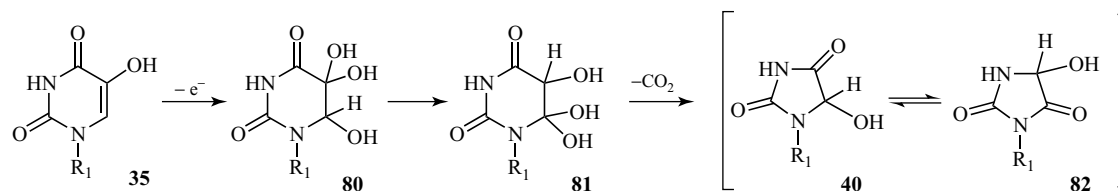
one-electron oxidative degradation pathway of **4** (Scheme 11) involves the transient formation of 5-hydroxy-8-oxo-7,8-dihydroguanine (**7**) through a still not completely elucidated mechanism after the initial formation of radical cation **78**. The rearrangement of **7** into the two diastereomers of **8** through an acyl shift was found to be favored in neutral and slightly alkaline aqueous solutions in the case of isolated nucleosides.^{79, 198–200} At pH lower than 6.5, a different decomposition pathway of **7** takes place by initial opening of the 5,6-pyrimidine ring followed by a decarboxylation reaction to give two diastereomers of guanidinohydantoin derivatives **79**.²⁰¹ Oxazalone nucleoside **47** together with its imidazolone **46** precursor was also found to be one-electron oxidation products of **4**, although generated in lower yields than **8** and **79**.²⁰² It is worth mentioning that **8** is preferentially formed in ssDNA, whereas the generation of **79** is favored in duplex DNA.²⁰¹

Two diastereomers of **8** were reported to accumulate in the DNA of Nei deficient *Escherichia coli* cells on exposure to chromate ion.²⁰³ The frequency of **8**, assessed by HPLC–MS operating in the selective ion monitoring (SIM) mode, was estimated to be 6 lesions per 10^3 guanines on treatment of TK3D11 bacterial cells with $500\ \mu\text{M}$ Cr(VI); this frequency is about 20-fold higher than that observed in the wild-type cells. It is intriguing that in both bacterial cells, the level of **4**, which is the likely precursor of **8**, is much lower. Other questionable issues

include the lack of accuracy of HPLC–MS for measuring low levels of base modifications⁵⁸ and the fact that **8** is formed only in ssDNA.²⁰¹ One may add that the proposed sacrificial role of **4** in protecting normal nucleobases within DNA against the damaging effects of one-electron oxidants^{204,205} has been recently questioned.²⁰⁶ This raises the question of how **4**, whose endogenously generated steady-state level does not exceed at best a few residues per 10^6 , can preferentially undergo one-electron oxidation in the presence of an overwhelming amount of **1** if one considers that hole transfer process within DNA helix does not likely occur at distances greater than 20 bp.

2.4.2 5-Hydroxypyrimidine Bases

The nucleosides of 5-hydroxycytosine (**33**) and 5-hydroxyuracil (**35**) are susceptible to secondary oxidation because of their relatively low oxidation potential. The oxidation potential of **33** is 70 mV, while that of **35** is 150 mV, versus the Pd reference electrode (in comparison, the oxidation of normal DNA bases is higher than 700 mV).^{117,120} Oxidation of **35** by either Br_2 or Na_2IrCl_6 leads to the quantitative formation of isodialuric acid (**35** $\rightarrow$ **80**; Scheme 12).^{206,207} Remarkably, the decomposition of **80** involved a sequence of three transformations in which



Scheme 12 One-electron oxidation reactions of 5-hydroxyuracil (**35**).

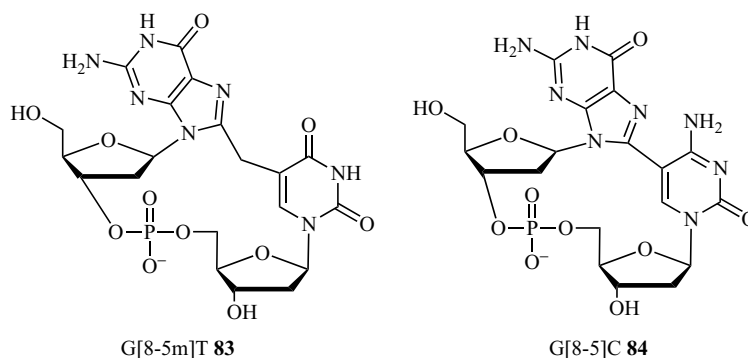
each product in the sequence (**80**, **81**, **40**, **82**) existed as a pair of diastereomers. After 2 hours at 37 °C in neutral aqueous solution, **80** transformed in a stereospecific manner into the corresponding dialuric acid product **81**. Both **80** and **81** assumed a fully hydrated hemiacetal form in aqueous solution as determined by NMR and MS. Further incubation at 37 °C for 72 hours resulted in the transformation of **81** into a mixture of four products consisting of two diastereomers of 5-hydroxyhydantoin (**40**) and two diastereomers of 5-hydroxy-3-methylimidazolidine-2,4-dione (**82**). The mechanism of decomposition of **81** probably involves initial ring-opening between N1–C6 followed by decarboxylation of an intermediate ureid. The four products likely interconvert by α -hydroxyketone rearrangement (**40** $\rightarrow$ **82**; half-life = 80–120 hours) accompanied with slow ring-chain tautomerism (12-fold slower than rearrangement), which accounts for the conversion between the diastereomers of **40** (tautomerism at N1–C5) and the diastereomers of **82** (tautomerism at N3–C4). In comparison, the oxidation of **33** by Br₂ resulted in the formation of analogous products (**80** and **81**) except that they retained the exocyclic amino group. These results indicate that the deamination of intermediate products (i.e., analogous to **80** and **81**) derived from **33** takes place on the same timescale as the decomposition of **80** and **81** (several hours).²⁰⁷ The treatment of trimers as well as longer oligonucleotides (<15 mer) containing **35** with Na₂IrCl₆ led to the quantitative formation of **80** within the oligomer as inferred by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) analysis.²⁰⁸ Interestingly, whereas the fully hydrated form of **80** existed as a free nucleoside in aqueous solution, the dehydrated carbonyl form appeared to prevail in single-stranded oligomers.

3 TANDEM BASE LESIONS

The pioneering work of Box and coworkers^{209–212} has highlighted the importance of the so-called tandem damage involving the formation of two adjacent DNA modifications. Formation of such damage is initiated by a single ionization event generating a single radical, which in oligonucleotides or DNA can react with neighboring bases creating the so-called tandem lesions constituted of two (at least) adjacent modifications. Indirectly, such an observation indicates that decomposition of initially produced base (or sugar) radicals may be influenced by their local environment, and thus, the decomposition reactions observed at the nucleoside level may be different, at least partly, in comparison to those in dsDNA.

3.1 Intrastrand Pyrimidine–Purine Cross-Links

Under anoxic conditions, Box and coworkers showed that tandem lesions involving intrastrand bases cross-links were produced in significant amounts in short oligonucleotides exposed to $\cdot\text{OH}$ generated by the radiolysis of aqueous solutions.²¹¹ Most of the lesions involved formation of a cross-link between a pyrimidine and a purine base, and among these, the majority of lesions implicated either the formation of a bond between the C8 of guanine and the C5 of a pyrimidine (with or without saturation of the C5–C6 double bond) or the exocyclic methyl group of thymine. Additional studies confirmed that such tandem lesions were generated in dsDNA exposed to ionizing radiation, and they were also detected in cells (Scheme 13). A detailed study²¹³ with tandem lesions involving a cross-link between the C8 of purines (for both adenine and guanine) and the methyl group of thymine showed that cross-links involving the guanine base



Scheme 13 Adenine–thymine (**83**) and guanine–cytosine (**84**) tandem lesions formed by initial $\cdot\text{OH}$ reactions on the pyrimidine moiety.

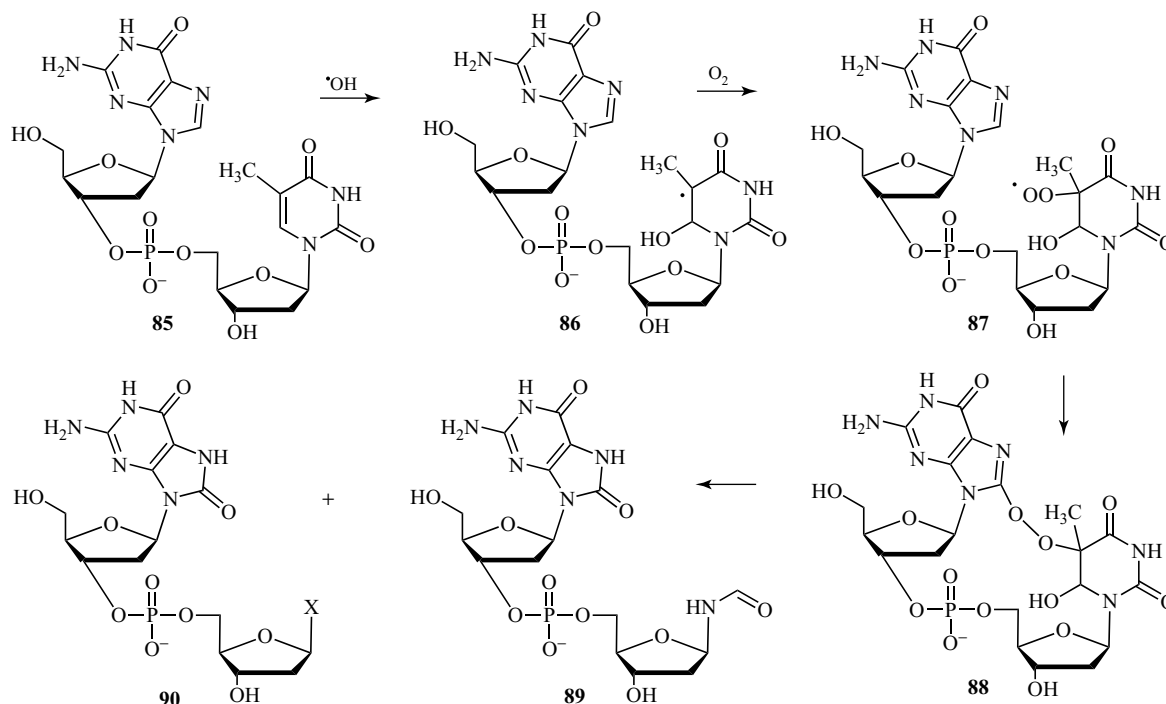
predominate in dsDNA. In addition, there was a strong sequence effect such that the adducts were generated most efficiently when the purine base was located 3' to thymine giving the so-called G[8-5 m]T **83** tandem lesion. The proposed mechanism of formation of such a lesion involved the formation of methyl radicals (**12**), which in turn add to the C8 of an adjacent purine base. The addition of methyl radicals is favored when the purine base is located 5' to the pyrimidine base since the distance between the radical (**12**) and the C8 of purines is shorter in the latter sequence, compared to the opposite one. Using HPLC–ESI–MS/MS, G[8-5 m]T (**83**) and G[8-5]C (**84**) were quantified in cells exposed to ionizing radiation.^{214,215} However, the yield of formation of such adducts was found to be significantly lower compared to that of single lesions including **4** and **24**. Indeed, the yield of formation of **84** was estimated to be around 0.037 lesions per 10^9 nucleosides per Gy, which is about 2–3 orders of magnitude lower than the reported yield of single lesions.

3.2 Lesions Involving Pyrimidine Hydroperoxyl Radicals

The low yield of formation of intrastrand cross-links between adjacent DNA bases may be explained, at least partly by the efficient competitive reaction of O_2 with the initially produced C-centered radicals. Interestingly, the generated peroxy radicals have been also shown to be able to produce tandem DNA lesions generating two adjacent oxidatively generated DNA lesions. With

dinucleoside monophosphates, Box and coworkers identified radiation-induced tandem lesions containing a formylamine (**21**) residue linked to **4**,²⁰⁹ the so-called 8-oxo-7,8-dihydroguanine/formylamine (8-oxodGuo/dF) lesion.¹³² Additional work performed on isolated dsDNA has provided a clear explanation for the mechanism of formation of this tandem lesion.^{216,217} Similarly, as reported for pyrimidine–purine cross-links, a strong sequence effect was observed since 8-oxodGuo/dF was found to be generated in higher amounts (about 20 times) compared to the opposite sequence dF/8-oxodGuo. Using ^{18}O -labeling, the tandem lesion was clearly shown to arise from the initial formation of 6-hydroxy-5,6-dihydrothymine-5-yl radicals (**86**) and, after the addition of molecular oxygen, the corresponding peroxy radicals in GpT (**87**; Scheme 14).¹³³ A key step is the addition of peroxy radicals (**87**) onto the C8 position of guanine to generate an intermediate endoperoxide (**88**), which decomposes to give two vicinal DNA lesions (**89**; 8-oxodGuo **4** adjacent to formylamine (**21**)) as well as several others (**90**; where X is an oxidation product of thymine or cytosine; *vide infra*). The formation of tandem lesions (**89** and **90**) is not a minor process since they represent about 15% of the total amount of generated **4** and additional results suggested the formation of other tandem lesions containing unidentified pyrimidine modifications **90** together with 8-oxodGuo **4**.

The yield of tandem lesions in dsDNA exposed to ionizing radiation in aqueous aerated solutions is estimated to be about 50% of the total amount of generated **4**.¹⁴⁵ Using polynucleotides containing specific DNA bases and an isotope-based



Scheme 14 Formation of tandem bases lesions between 3'-thymine and 5'-guanine arising from initial $\cdot\text{OH}$ addition across the 5,6-pyrimidine bond.

methodology, it was shown that pyrimidine peroxy radicals **13** and **15** are able to add to the C8 position of both guanine and adenine, but only when the purine bases are located on the same strand as the pyrimidine bases, thus generating tandem lesions containing oxidized purine bases such as either 8-oxodGuo **4** or 8-oxo-7,8-dihydro-2'-deoxyadenosine (**53**). It was determined that 50% of **53** is generated by a mechanism involving in tandem lesions, whereas the other 50% may be expected to arise by the direct addition of $\cdot\text{OH}$ produced by water radiolysis to the C8 of adenine (**50**). In dsDNA, three main mechanisms are involved in the formation of **4**. Interestingly, the addition of $\cdot\text{OH}$ to C8 of **1** (Scheme 5), which is the main reaction at the nucleoside level, accounted for only 5% of the generated **4**. As reported for **53**, 50% of the generated **4** is produced by the addition of a pyrimidine peroxy radical onto C8 of **1**, thereby generating 8-oxodGuo **4** containing tandem lesions (**89** + **90**). Of further interest, the remaining 45% of $\cdot\text{OH}$ -induced **4** was found to be produced by a one-electron oxidation mechanism, probably also involving peroxy radicals, a mechanism that favors

the formation of **4** compared to **53** likely due to the lower ionization potential of guanine and efficient electron transport of base radical cations in dsDNA to **1**. This provides an explanation for the higher formation yield (by about one order of magnitude) of **4** compared to that of **53** in dsDNA exposed to ionizing radiation. Work is in progress in order to identify the main pyrimidine modifications adjacent to **4** in tandem lesions **90** (Scheme 14). This is important because **4** within tandem lesions has been shown to be significantly refractory to repair by DNA glycosylases such as either the bacterial Fpg protein or human hOGG1.¹⁴⁵ Indeed, a high proportion of **4** involved in tandem lesions was resistant to excision by these two DNA glycosylases. Efficacy of excision may depend on both the sequence and on the nature of pyrimidine modifications adjacent to 8-oxodGuo **4** in **90**. Indeed, the presence of **21** does not significantly affect Fpg protein activity,²¹⁶ whereas the cleavage of **4** was considerably compromised by the presence of a 5' neighboring **19** (Scheme 2). In contrast, the presence of **19** as an adjacent 3' nucleoside enhanced **4** cleavage by hOGG1.^{217,218} It should also be taken into account

that tandem lesions containing two pyrimidine modifications may be generated through similar mechanisms involving the addition of peroxy radicals onto adjacent pyrimidine bases.²¹⁹

4 OTHER COMPLEX LESIONS

Other complex DNA lesions have been identified and quantified in DNA. Formation of such lesions arose from the initial formation of sugar radicals which, following different pathways, leads to different types of lesions involving purine 5',8-cyclonucleosides and several base-to-sugar adducts derived from the transient formation of reactive aldehydes.

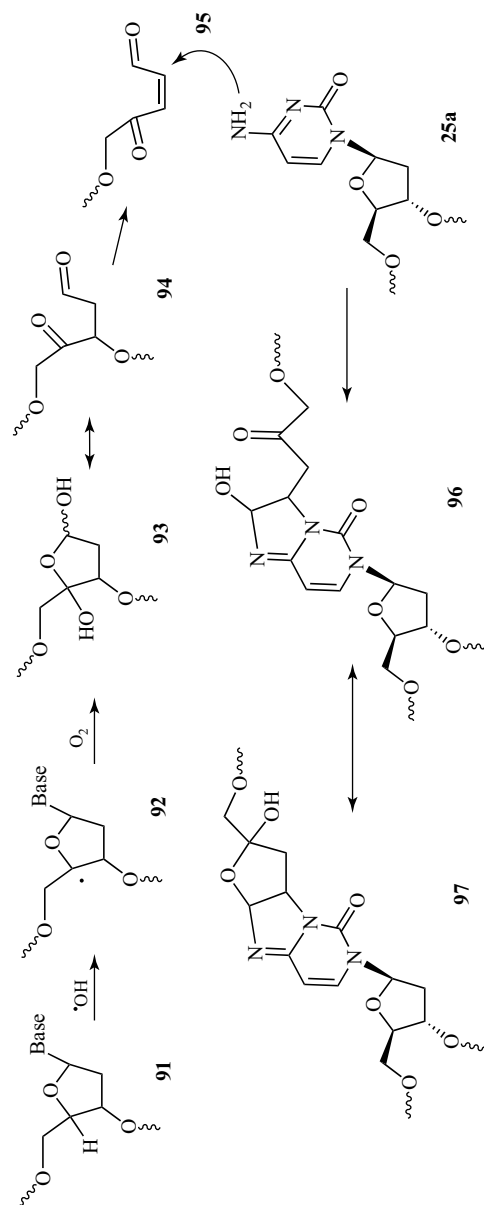
4.1 Cytosine Adducts Arising from C4' Radical

Following an attempt to search for the radiation-induced formation of novel DNA lesions,²²⁰ high molecular weight modifications were detected in the DNA of THP1 cells exposed to ionizing radiation, or to bleomycin, a radiomimetic drug. Identification of these lesions,²²¹ consisting of four diastereomers, revealed that these are cytosine adducts. The mechanism of their formation involves a complex cascade of events initiated by C4' hydrogen abstraction on the 2-deoxyribose moiety (**91**) in dsDNA (Scheme 15). Reaction of the C4' centered radical (**92**) with molecular oxygen gives rise to a C4' oxidized abasic site **93**, which may exist in a dynamic equilibrium with the open form **94**. Following β -elimination, the keto-aldehyde thereby generated **95** is able to react with a surrounding cytosine base (**25a**) producing the four diastereomers of 6-(2-deoxy- β -D-*erythro*-pentofuranosyl)-2-hydroxy-3-(3-hydroxy-2-oxopropyl)-2,6-dihydroimidazo[1,2-c]-pyrimidin-5(3*H*)-one, which exist in either an open chain (**96**) or closed ring (**97**) probably depending on the stereochemistry of the isomers. Interestingly, using a photochemical precursor of C4' oxidized abasic site **93**, Greenberg's group²²² has shown that the reaction of aldehyde **94** occurs preferably with a cytosine base (**25a**) located onto the opposite strand.²²³ Therefore, the unusual complex lesion **97** involves a strand break together with an interstrand cross-link. Moreover, it can

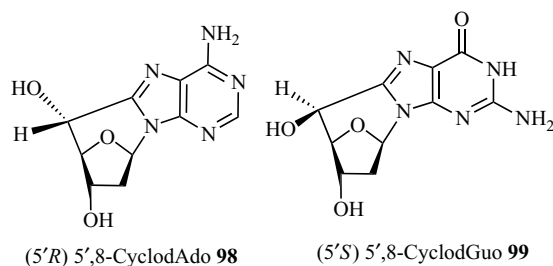
not be excluded that the reactive aldehyde **94** may also react with other DNA constituents containing nucleophilic amino groups such as the purine bases, creating similar types of complex lesions. Indeed, it was recently shown that the reaction of nucleophilic amino acids with the above-mentioned aldehyde **94** can also give rise to the formation of DNA-protein cross-links.²²⁴ In cells, the yield of radiation-induced formation of **97** was found to be similar to that of double-strand breaks.²²¹ In view of the relatively slow kinetics of removal of **97** from cellular DNA (half-life of about 10 hours), the DNA repair of **97** probably involves nucleotide excision repair rather than base excision repair that removes single lesions. In addition, the repair of such complex damage by the UvrABC nucleotide excision repair system was found to give rise to double-strand breaks.²²⁵ It should also be mentioned that following the generation of abasic sites on spontaneous depurination, the formation of adducts with cytosine have also been reported²²⁶ highlighting the importance of such nucleophilic reactions of DNA bases with transiently produced aldehydes to generate complex DNA lesions.

4.2 Purine 5',8-cyclonucleosides

The initial step in the formation of 5',8-cyclonucleosides (Scheme 16) involves $\cdot\text{OH}$ -mediated generation of C5' radical followed by intramolecular addition onto C8 of the purine base.^{36,40,227} Detailed information on the mechanism of formation of such complex DNA lesions including those derived from both adenine (**98**) and guanine (**99**), as well as on their relative importance has been reviewed recently.⁴⁰ The radiation-induced yield of such damage in isolated dsDNA was inversely correlated with the oxygen content because O_2 can trap C5' radicals and divert the reaction pathway to other products. During the last decade, several attempts were made to determine whether such complex DNA lesions including both **98** and **99** can be generated in significant amounts in cellular DNA. Since these unusual lesions are refractory to removal by base excision repair,^{228,229} it was proposed that **98** and **99** may accumulate in nucleotide excision repair (NER) deficient cells, and thus, be implicated in biological disorders observed in patients with Xeroderma pigmentosum (XP). Earlier determinations



Scheme 15 Formation of intrastrand cross-links (97) involving cytosine and the 2-deoxyribose through initial $\cdot\text{OH}$ -mediated hydrogen abstraction at C4'.



Scheme 16 (5'R)-5',8-cyclo-2'-Deoxyadenosine (**98**) and (5'S)-5',8-cyclo-2'-deoxyguanosine (**99**) formed by initial $\cdot\text{OH}$ -mediated hydrogen abstraction at C5'.

of the cellular level of **98** and **99** obtained by GC-MS and HPLC-MS (single MS) have given elevated levels of the purine 5',8-cyclonucleosides in control and γ -irradiated cells.^{230,231} Using a more accurate tandem mass spectrometry approach, it was found that the radiation-induced yield of these cyclonucleosides is significantly lower²³² than previously reported^{230,231} and even not detectable in untreated cells. It was estimated that the endogenous steady-state level of either **98** or **99** is below 1 modification per 10^9 normal bases. However, in a recent study using a HPLC-MS³ approach, the background level of **98** and **99** in rat tissues was determined to be about 0.1 lesion per million nucleosides.⁵⁷ Therefore, additional work is required to circumvent this apparent discrepancy, and the reported results highlighting the possible biological importance of this damage should be considered at the moment with caution.^{40,232}

5 CONCLUSIONS

In the last decade, there has been major progress toward elucidating the mechanisms of formation of oxidatively generated damage in isolated DNA and model compounds. In particular, there have been significant advances with single-oxidized nucleosides formed on exposure to $\cdot\text{OH}$, one-electron oxidants, and singlet oxygen. Evidence has been provided for the occurrence of tandem base modifications that are mostly induced next to either 5'-guanine or 5'-thymine by pyrimidine peroxy radicals on the 3' end. Other complex lesions arise from the nucleophilic addition of lysine residues and

opposite cytosine with guanine radical cations giving rise to DNA-protein adducts and intrastrand DNA cross-links. In addition, evidence has been provided for the formation of complex damage between cytosine and reactive aldehydes derived from initial oxidation of the 2-deoxyribose moiety. The development of accurate analytical methods such as HPLC-MS/MS has permitted the measurement of 14 single and complex oxidatively generated base lesions in cellular DNA. It is expected that the oxidation products of cytosine, tandem lesions, and DNA-protein cross-links will be the subjects of further investigations at the cellular level.

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Oxidatively Formed Sugar Radicals in Nucleic Acids

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1 INTRODUCTION

Chemical modifications of DNA in the form of strand breaks and nucleobase modifications are known to be caused by reactive oxygen species (ROS), in particular the $\cdot\text{OH}$ radicals derived from the metabolism of oxygen.¹ However, the majority of cells also possess defense mechanisms against oxidative damage, such as base excision repair (BER) and nucleotide excision repair (NER) enzymes, which remove these lesions to maintain the integrity of the genome.² As a result of poorly repaired oxidative damage, some lesions may accumulate in cells over time through errors in repair, replication, and recombination, and the levels of repair proteins may decrease with the cell aging.³ In addition to the DNA damage caused by the metabolism of oxygen, damage may also be induced through other environmental insults such as ionizing radiation, UV light, and chemical mutagens. Although the majority of DNA lesions induced through oxidative metabolism are single lesions, there are also types of multiple lesions such as tandem DNA lesions and clustered DNA damage that may challenge the repair machinery of the cell.

Diffusible hydroxyl radicals ($\text{HO}\cdot$) are known to react with DNA either by hydrogen abstraction from the 2-deoxyribose units or, more often, by addition to the base moieties (see **Oxidatively**

Generated Nucleobase Modifications in Isolated and Cellular DNA). However, there is growing evidence that the oxidation of 2-deoxyribose in DNA plays a critical role in the genetic toxicology of oxidative stress and inflammation.⁴

There are five sp^3 -hybridized carbons on a 2'-deoxyribose residue containing seven hydrogen atoms that are, in theory, available for abstraction by an oxidizing agent. The hydrogens are designated (IUPAC rules) as H-5', H-5'', H-4', H-3', H-2', H-2'', and H-1', although the designation H-2' β and H-2' α (above and below the sugar plane, respectively) is frequently adopted for the 2'-hydrogens. X-ray crystallographic data from oligonucleotide duplexes indicate that H-5', H-5'', H-4', H-2' α , and H-1' are accessible from the minor groove, whereas H-3' and H-2' β are accessible from the major groove of a typical B-form duplex DNA (Figure 1). It is apparent from Figure 1 that H-5'' and H-4' are the most solvent-accessible hydrogen atoms within B-form duplex DNA.

The relative reactivity of a diffusible reactive species, such as the $\text{HO}\cdot$ radical, toward the various hydrogen atoms of the 2-deoxyribose moiety is generally accepted to follow the order of the 2-deoxyribose hydrogen atom exposure to solvent (i.e., $\text{H5}' > \text{H4}' > \text{H3}' \approx \text{H2}' \approx \text{H1}'$),⁶ although this is currently under debate.⁴ Experimental data on the reaction of $\text{HO}\cdot$ radicals with simple nucleosides such as 2'-deoxyadenosine and 2'-deoxyguanosine indicate that $\sim 25\%$ of H-atom abstraction occurs

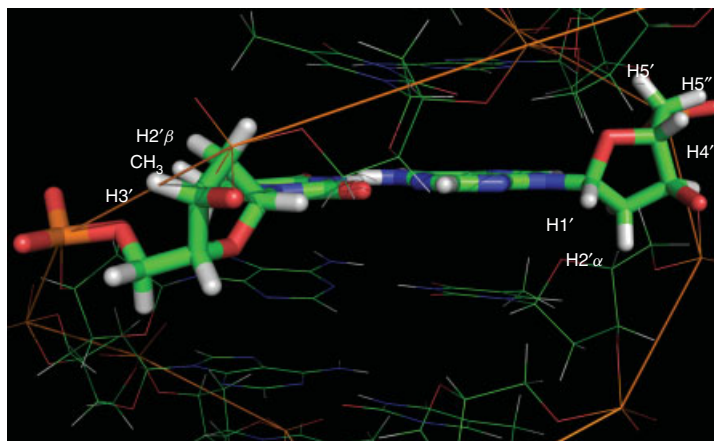


Figure 1 An AT pair within a B-form double DNA helix. The hydrogens directed toward the viewer point toward the minor groove (between the orange ribbons), whereas the hydrogens directed away from the viewer point toward the major groove. The methyl group proton (CH_3), also pointing toward the major groove, belongs to the thymine base directed toward the back. This image was prepared with PyMol and contains a typical B-form double helix oligomer from the Protein Data Base (3EIL).⁵

at the sugar moiety, $\sim 40\%$ of which is at the $\text{H5}'$ position.⁷ On the other hand, $\text{C1}'$ -, $\text{C4}'$ -, and $\text{C5}'$ -hydrogen atoms are abstracted by several minor groove-binding molecules.^{8–10}

Abstraction of a hydrogen atom from 2-deoxyribose produces a carbon-centered radical whose fate depends upon the environment. Recent studies emphasize the selective generation of these species that allow quantitative data to be obtained. While the chemistry of all possible sugar radicals (i.e., $\text{C1}'$, $\text{C2}'$, $\text{C3}'$, $\text{C4}'$, and $\text{C5}'$) from nucleosides to DNA are discussed in this article, only the literature from the last decade is discussed in depth, with support from seminal work. The reader is referred to some excellent reviews^{8–14} and books^{15–17} for more details of earlier work. The chemistry of 2-deoxyribose oxidation in DNA was first addressed in studies of the effects of ionizing radiation on DNA, as summarized in two books by von Sonntag.^{15,16}

2 OXIDATION OF THE $\text{C5}'$ POSITION

2.1 Generation of the $\text{C5}'$ Radical

The chemistry of the $\text{C5}'$ radical **1** (Scheme 1) was one of the first to be studied in detail.⁸ Both $\text{C5}'$ hydrogens are the most accessible from the minor groove in B-DNA, one of which points

away from the groove toward the solvent.^{18,19} As a result, diffusible species such as the hydroxyl radical $\cdot\text{OH}$ generated by Fenton chemistry or gamma radiolysis, or the hydroperoxyl radical $\cdot\text{OOH}$,²⁰ has been reported to preferentially oxidize the $\text{C5}'$ position.²¹ On the other hand, other metal complexes, such as $\text{Cu}(\text{phen})_2$ derivatives²² or $\text{Mn}(\text{TMPyP})/\text{KHSO}_5$,^{23,24} which do not produce diffusible species, have exhibited $\text{C5}'$ oxidation chemistry. Finally, enediyne derivatives, such as neocarzinostatin, which are known to bind in the minor groove of DNA, produce this type of oxidation with some sequence selectivity.⁸

2.2 Fate of the $\text{C5}'$ Radical

The chemistry of the $\text{C5}'$ radical is peculiar compared to that of the other 2-deoxyribose positions since (i) the peroxy radical **2** does not generate an abasic site, which is interesting in the polymerase bypass and mutagenesis,⁴ and (ii) unique cyclic base-sugar adducts are formed (Scheme 1). For example, the 5',8-cyclo-2'-deoxyadenosine and 5',8-cyclo-2'-deoxyguanosine moieties, generally referred to as 5',8-cyclopurines, are the result of the $\text{C5}'$ radical attack at the purine moiety to give **3** more rapidly than its reaction with oxygen. These lesions are observed among the DNA modifications^{25,26} and have also been identified in mammalian cellular DNA *in vivo*.^{27,28}



2-phosphoryl-1,4-dioxo butane residue **8** represents a second lesion produced in lower yield by the cleavage of the C4'–C5' bond. Several mechanistic aspects of the 5'-oxidation pathways under aerobic conditions are not well understood. All the proposed intermediates are based on rationalization of the products observed in DNA degradation by neocarcinostatin chromophore (NCS-Chrom) in the

A 5'-aldehyde-terminated DNA, or oligonucleotide **13**, has been observed during the analysis of DNA oxidized by chemical nucleases such as Mn(TMPyP)/KHSO₅^{23,24} or natural products such as enediyne compounds⁸ (Scheme 2). The



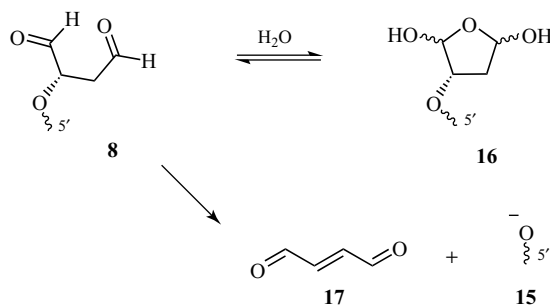
presence of glutathione (**4**).^{8,9,12} The forming C5' radical **6** (where B = thymine) reacts with oxygen to generate the peroxy radical **7**, which should partition between two reaction channels to give the corresponding hydroperoxide after reaction with glutathione (GSH) (**4**) and the corresponding alkoxy radical by disproportionation. The hydroperoxide produces the 5'-aldehyde terminus **13** and fragment **12**, while the alkoxy intermediate could be responsible for the 3'-formyl phosphate residue **9** and the 5'-(2-phosphoryl-1,4-dioxobutane) residue **8** with the concomitant loss of base (Scheme 2). In other studies, a 5'-aldehyde-terminated oligonucleotide, resulting from the C5' hydroxylation of a 2-deoxyribose, led to **11**, where B is guanine.²⁹ This hydroxylation favors the spontaneous elimination of the attached phosphate group and the cleavage of DNA accompanied by the formation of the two DNA components, a 5'-aldehyde end (**13**) and a 3'-phosphate end (**12**).

Upon heating at 90 °C for 30 min or with alkaline treatment, the 5'-aldehyde **13** undergoes β,δ -elimination reactions with the release of furfural **14** and of the corresponding nucleobase, resulting in the formation of a one-nucleotide shorter 5'-phosphate DNA fragment (**15**, Scheme 2).²⁹ Furthermore, the 5'-aldehyde **13** is found to give adducts with nucleophiles.

The 5'-(2-phosphoryl-1,4-dioxobutane) residue **8** may exist in a hydrated form, which is expected to be in equilibrium with the cyclic form **16** (Scheme 3). The dialdehydic structure and β -elimination reaction that gives *trans*-1,4-dioxo-2-butene **17** and 5'-phosphate-terminated oligomers **15** were investigated in detail,^{30,31} and two analytical methods were developed for their detection and quantification of **17**.³⁰ It was recently shown that **17** forms adducts with dA and dC in oxidized DNA.³¹

The synthesis of oligonucleotides containing 5'-aldehyde or 2-phosphoryl-1,4-dioxo butane termini, resulting from the C5'-oxidation of thymidine in DNA, has been performed and the cleavage labilities of these species have been determined.³² Unlike thymidine, 5'-aldehyde **13** does not destabilize duplex DNA, whereas **8** affects the thermal stability of a duplex to an extent similar to that of a tetrahydrofuran model of an abasic site.

The reactivity of purine-substituted C5' radicals **18** under aerobic conditions has also been studied in some detail (Scheme 4).⁷ Using a 13–266 μ M

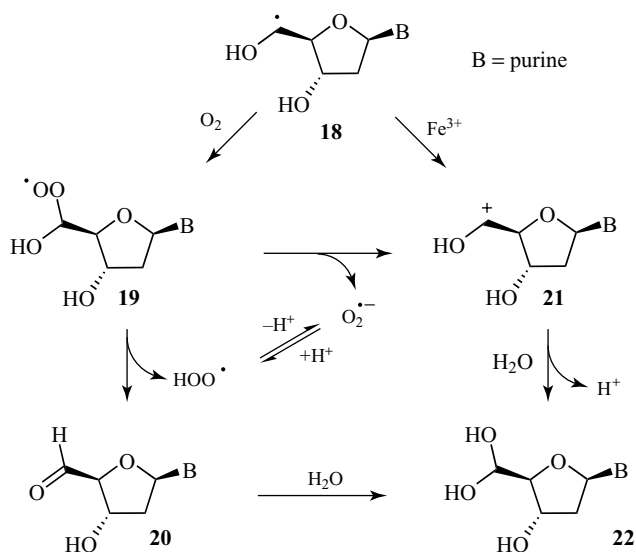


Scheme 3 Hydration and decomposition of the 5'-(2-phosphoryl-1,4-dioxobutane) fragment **8**.

oxygen concentration (typical for oxygenated tissues), the hydrated 5'-aldehyde **22** is accompanied by a 5',8-cyclopurine nucleoside (Figure 2). 5',8-Cyclopurine formation (see Section 2.2.2) was observed in all experiments, and the yields increased with decreasing O₂ concentration. The proposed mechanism involving the formation of peroxy radical **19**, which decays either via a cyclic transition state leading to HOO[•] radical and aldehyde **20** or via heterolytic cleavage to generate carbocation **21** and superoxide radical anion, is given in Scheme 4. The two pathways are formally identical. Trapping C5' radicals with Fe(CN)₆³⁻ gave the corresponding hydrated 5'-aldehydes **22** in good yield (Scheme 4).⁷ Similar experiments and results were reported for the 2'-deoxyinosin-5'-yl radical.⁷

2.2.2 Fate of the C5' Radical under Anaerobic Conditions: 5',8-Cyclopurines

The classic 5'-*tert*-butyl ketone modification for the site-specific generation of model sugar radicals, which was initially developed by Giese and coworkers in their studies of C4' radical chemistry (see below),^{33,34} has recently been extended to the C5' position. Photolysis of derivatives **27** and **30** leads to the formation of thymidin-5'-yl (**28**) and 2'-deoxyguanosin-5'-yl (**31**) radicals, respectively (Schemes 5 and 6).³⁵ In the thymidine system, the C5' radical **28** is fully quenched to give **29** in the presence of physiological concentrations of thiols. In the 2'-deoxyguanosine system, the C5' radical **31** is partially quenched to give **32** and undergoes competitive intramolecular attack onto



Scheme 4 Fate of the C5' radical in purine nucleosides.

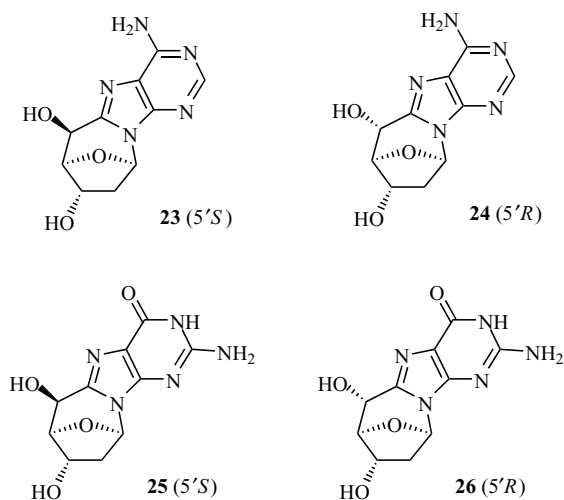
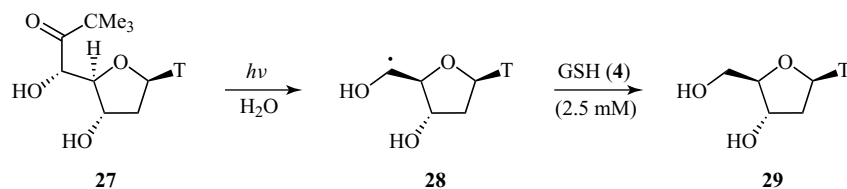


Figure 2 Structures of four possible 5',8-cyclopurine nucleoside diastereomers.

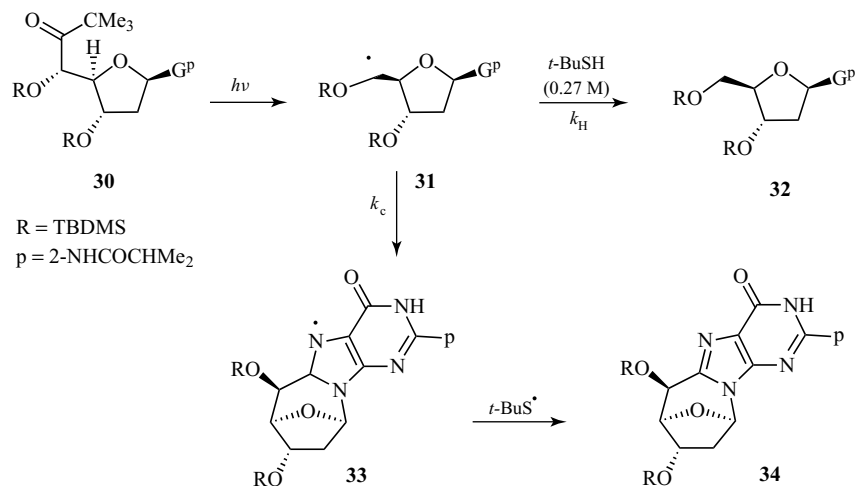
the C8–N7 double bond of guanine, leading ultimately to the 5',8-cyclo-2'-deoxyguanosine derivative **34**. The **30** $\rightarrow$ **33** cyclization occurs with a rate constant of circa $1 \times 10^6 \text{ s}^{-1}$ (based on $k_H = 5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) and is highly stereoselective, affording only the (5'S)-isomer.

Both 5',8-cyclo-2'-deoxyadenosine (**23**, **24**) and 5',8-cyclo-2'-deoxyguanosine (**25**, **26**) have two diastereoisomeric forms, the (5'S) and (5'R)

isomers, which differ in the C5' position configuration (Figure 2). Both the 5'S and 5'R forms have been synthesized and fully characterized. The first report involves a multistep synthesis but in overall poor yield.^{36,37} A one-pot synthesis was developed starting from the commercially available 8-bromopurine derivatives under continuous radiolysis or photolysis,^{38–42} featuring a radical cascade reaction that mimics the DNA damage leading to these lesions. The mechanism of these reactions was investigated by time-resolved spectroscopy to provide important information on the fate of C5' radicals.^{39,40} Some of these findings are summarized in Scheme 7. Specifically, 8-bromo-2'-deoxyadenosine **35** captures electrons and rapidly loses a bromide ion to give the corresponding C8 radical **36**.³⁹ Radical **36** can also be obtained by homolytic cleavage of C–Br bond under photolysis.⁴⁰ This intermediate intramolecularly abstracts a hydrogen atom selectively from the C5' position to give the 2'-deoxyadenosin-5'-yl radical **37**, which can undergo cyclization with a rate constant of $k_c = 1.6 \times 10^5 \text{ s}^{-1}$ to produce the heteroaromatic radical **38**. The reactivity of the C5' radical **37** toward GSH ($k = 4.9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$), O_2 ($1.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), and $\text{K}_3\text{Fe}(\text{CN})_6$ ($4.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) was examined in competition with the cyclization process as shown in Scheme 7.^{7,39}



Scheme 5 Photolysis of 5'-(*tert*-butylketo)-derivatives of thymidine.



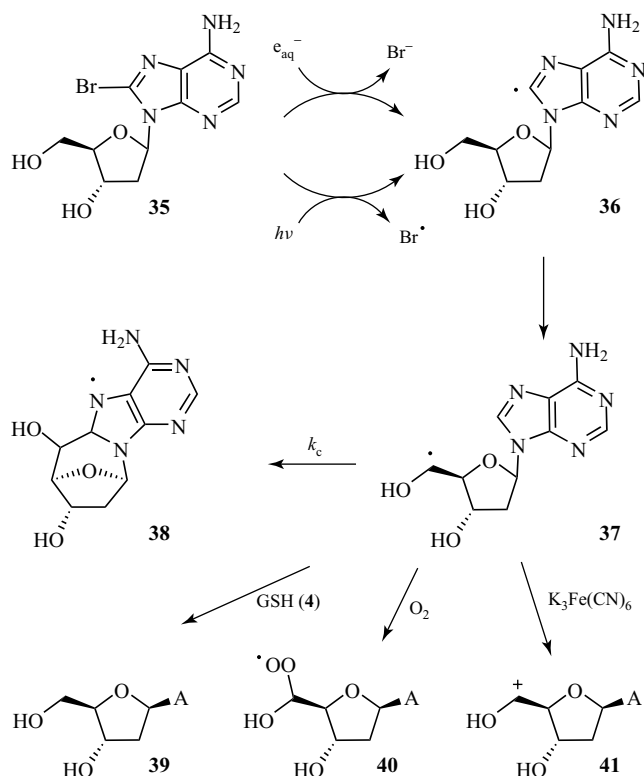
Scheme 6 Photolysis of 5'-(*tert*-butylketo)-derivatives of protected guanosine.

Similar experiments and results were reported for the 2'-deoxyinosin-5'-yl radical.⁴³

The isomeric ratio (5'*S*)/(5'*R*) substantially changes in all the above cases, depending on both the substrate structure and the experimental conditions. The effect of the solvent and the nature of the substituents at the O5' position play important roles in the stereoselectivity of the C5'-radical cyclization.^{35,41,42} The (5'*S*)/(5'*R*) ratio depends on the bulkiness of the C5'-OR substituent and the water solvation through intermolecular hydrogen bonding. The chair transition states of the pro-(5'*S*) and pro-(5'*R*) conformers, with the 5'-OH in the equatorial or the axial position, respectively, are illustrated by structures **42** and **43** (Figure 3). In aqueous solution, only the pro-(5'*R*) conformer may be stabilized by hydrogen bonding, involving either the N3 of the base (**43**) or the oxygen of the sugar ring (not shown). The (5'*R*)/(5'*S*) ratios obtained in water for 5',8-cyclo-2'-deoxyadenosine and 5',8-cyclo-2'-deoxyguanosine isomers were 6:1 and 8:1, respectively. In contrast, the (5'*S*) stereoselectivity of the cyclization reaction in

Scheme 6 is due to the steric hindrance between the guanine moiety and the 5'-*O*-*tert*-butyldimethylsilyl (TBDMS) substituent, which forces the 5'-*O*-TBDMS into the equatorial position. The (5'*R*)/(5'*S*) ratios of approximately 4 and 3 were reported for 5',8-cyclo-2'-deoxyadenosine and 5',8-cyclo-2'-deoxyguanosine lesions, respectively, in double-stranded DNA (dsDNA).^{14,44}

A study of (5'*S*)-5',8-cyclo-2'-deoxyadenosine (**23**, Figure 2) stability in aqueous medium revealed (i) that the glycosidic bond was >40-fold more resistant to acidic hydrolysis than that in 2'-deoxyadenosine and (ii) that no adenine was released, as evidenced by the intact C5'–C8 covalent bond.⁴⁵ Under sunlight irradiation, **23** photoisomerizes to the (5'*R*) isomer **24**, whereas the latter compound does not isomerize under the same conditions.⁴⁶ This one-way photoisomerization of **23** to **24** has been explained by invoking a heterolytic cleavage of the C–O bond to afford benzyl-type cations, which subsequently undergo nucleophilic trapping by water with concomitant isomerization. The isomer **24** is more easily



Scheme 7 Photolysis or one-electron reduction of 8-bromoadenosine.

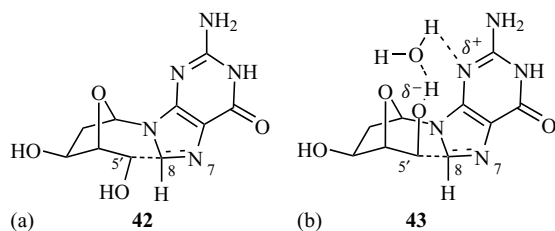


Figure 3 Proposed transition state structures leading to 5'S (a) or 5'R (b) 5',8-cycloguanosines.

repaired when these cyclopurine lesions are formed in DNA (see below), and an extension of this study in single-stranded DNA (ssDNA) or dsDNA would be of value.

The C5' radicals of pyrimidine nucleosides may also cyclize to give the analogous diastereomeric mixtures of 5',6-cyclopyrimidines.^{47,48} Several of these derivatives have been incorporated in oligonucleotides and their properties investigated.^{48,49} However, there is no evidence of 5',6-cyclopyrimidine

formation *in vitro* or *in vivo* either in ssDNA or dsDNA. In this context, the rate constant of the cyclization of the substituted thymid-5'-yl radical was measured and found to be 2–3 orders of magnitude slower than the analogous substituted 2-deoxyguanosin-5'-yl radical (cf. Scheme 5).⁴⁷ Thus, the cyclization of C5' radicals in the pyrimidine series remains an important reaction for its synthetic applications in medicinal chemistry,⁵⁰ while the chemistry of C5' peroxyl radicals in oxidative DNA damage is better understood (see above).

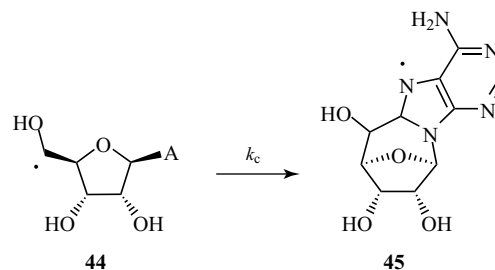
2.3 Repair and Mutagenicity Studies on 5',8-Cyclopurine Lesions

Synthetic oligonucleotides containing (5'S)- and (5'R)-5',8-cyclo-2'-deoxyadenosine at selected sites were prepared by solid-phase synthesis in order to elucidate the biochemical features of such lesions.^{51,52} In 2000, (5'S)- and (5'R)-5',8-cyclo-2'-deoxyadenosine were reported

by two groups to be substrates of the NER pathway, but not of other repair pathways.^{51,52} Neither the (5'*S*)- nor the (5'*R*)-isomer is recognized by human DNA glycosylases active in the BER pathway. Furthermore, both isomers were found to be relatively poor substrates for the NER pathway, where the (5'*S*) isomer is repaired more efficiently than the (5'*R*) isomer. The (5'*S*) isomer was found to strongly block gene expression⁵² and to cause transcriptional mutagenesis.⁵³ It was also reported that stereospecific differences between the (5'*S*) and (5'*R*) isomer residues affect the relative resistance to exonucleolytic activity and give rise to different efficiencies of translesion synthesis by human polymerase η .⁵⁴ On the basis of these findings, both groups proposed that these lesions may be responsible for the neurodegeneration in patients suffering from xeroderma pigmentosum (XP) who lack the capacity to carry out NER.^{51,52} The clinical and neuropathological aspects of the XP disease were recently described, and the sound set of criteria presented indicate the 5',8-cyclopurine lesion as the most likely DNA lesion to play a role in this neurological disease.^{27,55} The 5',8-cyclopurine lesions have also been identified in mammalian cellular DNA *in vivo*, where their levels are enhanced by oxidative stress.^{27,28}

2.4 C5' Radicals in Ribonucleosides

The chemistry of 5',8-cyclopurine nucleosides was originally investigated in ionizing radiation studies, and these nucleosides were first observed as products in the reaction of HO $\cdot$ radicals with adenosine.^{15,16,28} One-electron reduction of 8-bromoadenosine in pulse radiolysis experiments has led to the site-specific generation of adenosin-5'-yl radical **44** (Scheme 8).⁵⁶ 8-Bromoadenosine captures electrons and rapidly loses a bromide ion to give the corresponding C8 radical, which intramolecularly abstracts a hydrogen atom (cf. **36** in Scheme 7 for the analogous 2'-deoxyadenosine). The reaction is partitioned between the C5' and C2' positions in a 60:40 ratio, leading to adenosin-5'-yl radical **44** and adenosin-2'-yl radical (see below). Radical **44** cyclizes intramolecularly to give the aromatic aminyl radical **45**. The reported rate constant of $1.0 \times 10^4 \text{ s}^{-1}$ is more than one order of magnitude slower than the analogous cyclization of



Scheme 8 Cyclization of the adenosin-5'-yl radical.

the 2'-deoxyadenosin-5'-yl radical, probably due to the conformational changes in going from *ribo* to 2'-deoxyribo derivatives. Product analysis of these reactions evidenced the formation of 5',8-cycloadenosine in a (5'*R*)/(5'*S*) diastereomeric ratio of 3.5:1. Similar experiments and results were reported for the inosin-5'-yl radical.⁴³

3 OXIDATION OF THE C4' POSITION

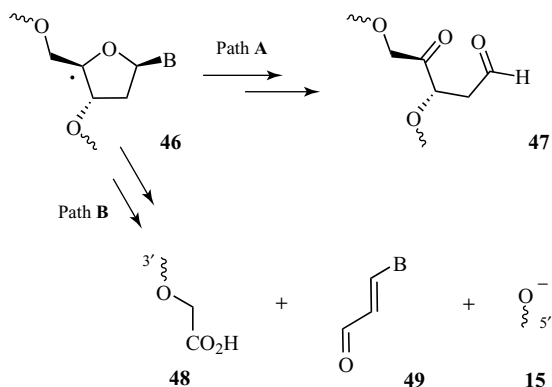
3.1 Generation of C4' Radicals

The C4' is probably the most well-studied position on the deoxyribose and it was the first position for which model studies were performed. Oxidation of C4' position has been observed in the presence of iron bleomycin,^{57–59} Cu(phen)₂,²² and enediyne antibiotics,⁸ as well as under conditions that generate reactive hydroxyl radicals.

3.2 Model Studies and Fate of the C4' Radical

Depending on experimental conditions, 4' oxidation chemistry can follow several pathways. For example, only 4'-hydrogen abstraction to give **46** has been observed with duplex DNA and iron bleomycin, and resulted mainly in two paths (Scheme 9).⁶⁰ Path A affords the C4'-oxidized abasic site **47** (or 2-deoxypentose-4-ulose lesion) and free base, whereas path B leads to a strand break and subsequent formation of 3'-phosphoglycolate (3'-PG) residue **48**, base propenal **49**, and 5'-phosphate terminus **15**.

The fate of the C4' radical, either in nucleosides or oligonucleotides, has been investigated in some



Scheme 9 Main degradation pathways for the C4' radical.

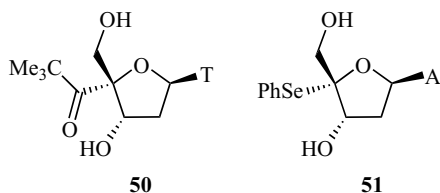


Figure 4 Photolabile precursors of the C4' radical.

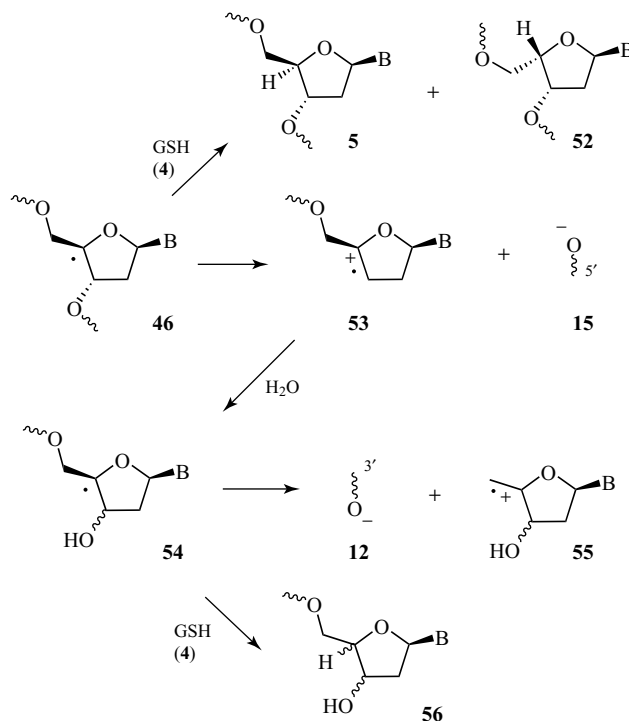
detail under oxygen-free and aerobic conditions.³³ Oligonucleotides functionalized with a modified unit **50** or **51** (Figure 4), which promoted the selective generation of the C4' radical under photolytic conditions, were synthesized.

In the absence of added traps, the C4'-radical **46** in ss- or ds-oligonucleotides yields the oligonucleotide phosphates **15** and **12** as main products (Scheme 10). A heterolytic cleavage gives radical cation **53** and 5'-phosphate **15** with a rate constant of about 10^3 s^{-1} for an ss-oligonucleotide and about 10-fold slower for the corresponding reaction in a ds-oligonucleotide.³⁴ Spectroscopic evidence for the radical cation intermediate was obtained by electron spin resonance (ESR) and chemically induced dynamic nuclear polarization (CIDNP) techniques.^{61,62} This oxidizing radical cation is capable of oxidizing a neighboring guanine base.⁶³ The heterolytic cleavage is favored over a homolytic β -cleavage owing to the effective solvation of the ensuing ions.⁶⁴ Trapping of **53** by H_2O generates radical **54**, which undergoes a second heterolytic cleavage to give phosphate

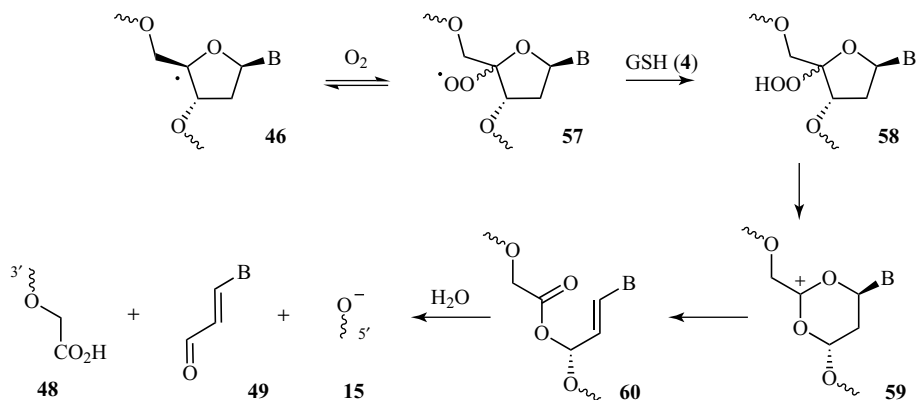
12 and radical cation **55**. In the presence of GSH at millimolar levels, the heterolytic cleavage of radicals **46** and **54** competes with hydrogen abstraction from GSH (Scheme 10), and radical **46** abstracts hydrogen from a thiol with a rate constant of $1.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.⁶⁵ The stereoselectivity of the H-trapping reaction is remarkable. Radical **46** in ss-oligonucleotides reacts nearly unselectively with GSH (**5:52** ≈ 1.5), while in ds-oligonucleotides the same species leads predominantly to the natural 2'-deoxyribonucleotides (**5:52** ≈ 9).³⁴

In the presence of O_2 , C4' radical **46** is trapped very rapidly ($2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) to give peroxy radical **57** (Scheme 11). However, this reaction was found to be reversible. The rate constant from ss-4'-DNA peroxy radical is 1.0 s^{-1} at ambient temperature.⁶⁵ As detected by ESR,⁶⁴ peroxy radicals abstract hydrogen from GSH with a rate constant of $\leq 400 \text{ M}^{-1} \text{ s}^{-1}$,⁶⁶ and the resulting hydroperoxide **58** has been isolated and characterized.^{65,67} Subsequently, the hydroperoxide **58** is converted to cation **59** (Criegee rearrangement), which, following β -elimination (**60**) and subsequent hydrolysis, leads to the oligomeric fragments 5'-phosphate **15** and 3'-PG **48** as well as base propenal **49**. Therefore, strand cleavage depends on the concentration of the hydrogen donor. At low GSH concentration, strand scission is the result of a spontaneous heterolytic cleavage that occurs even under aerobic conditions. It should be emphasized that the 5'-phosphate strand terminus (**15**) is formed under both aerobic and anaerobic conditions (cf. Schemes 10 and 11). However, at the 3' terminus, the 3'-PG fragment product **48** is characteristic of aerobic conditions, whereas the 3'-phosphate **12** is characteristically formed under anaerobic conditions.

According to the mechanism proposed by Stubbe *et al.*, the 2-deoxypentose-4-ulose lesion **47** is produced by oxidation of the C4' radical **46** to cation **61**, which is trapped by H_2O to give the cyclic hemiacetal **62**. Hydrolysis of **62** affords the observed lesion (Scheme 12).^{10,68} After H-abstraction from DNA, the bleomycin/ $\text{Fe}^{2+}/\text{O}_2$ complex was considered to effect the oxidation step to cation **61**. The subsequent partition ratio (between Path A and B in Scheme 9) depends on the concentration of O_2 . Model studies confirmed that the new oxygen atom at C4' does not come from oxygen but instead comes from the solvent, while



Scheme 10 Fate of the C4' radical under anaerobic or reducing conditions.



Scheme 11 Fate of the C4' radical under aerobic conditions.

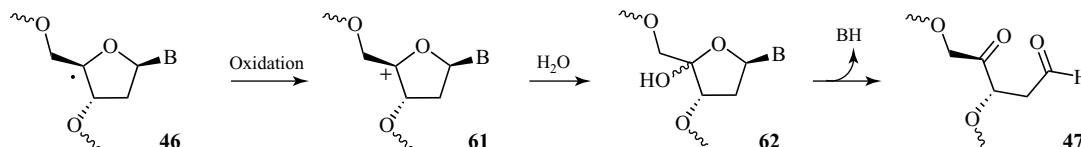
metal oxides can easily induce the oxidation step⁶⁹ to cation **61** and corroborated the mechanism in Scheme 12.

The 2-deoxypentose-4-ulose residue **47** also exists in the hydrated form **63**, which is expected to be in equilibrium with the cyclic form **64** (Scheme 13). It is an abasic site, also called a 4'-keto abasic site and is abbreviated as **C4-AP**.

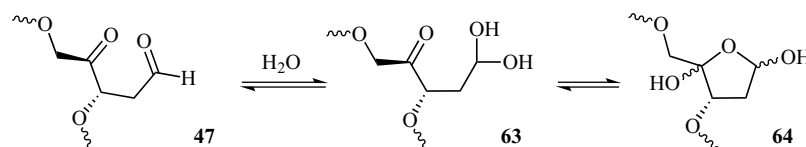
3.3 Biochemical Studies Involving the C4-AP Lesion

3.3.1 Incorporation of Caged C4-AP in Oligonucleotides

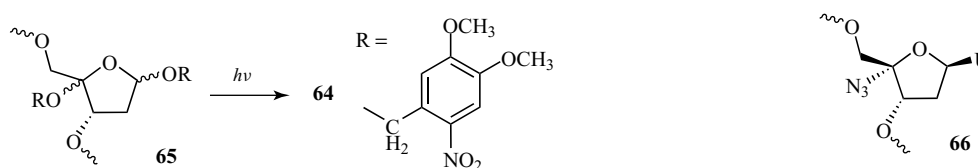
This C4'-oxidized abasic site is the result of a variety of DNA damaging agents, accounting for ~40%



Scheme 12 Proposed mechanism of 2-deoxypentos-4-ulose formation.



Scheme 13 Hydration and cyclization of the 2-deoxypentos-4-ulose (C4-AP) lesion.



Scheme 14 Independent generation of C4-AP in model oligonucleotides.

Figure 5 A biochemical precursor of C4-AP.

of the lesions produced by the antitumor agent bleomycin. This lesion also exhibits unique biochemical and biological effects in DNA. Oligonucleotides containing the C4'-oxidized abasic site at a defined position along the sequence have been prepared and the effects of this lesion on DNA have been reported. Greenberg and coworkers reported the first general method for the synthesis of oligonucleotides containing this lesion.⁷⁰ Modified oligonucleotides **65**, incorporating nitroveratryl, a photosensitive protecting group, were prepared, and subsequent photolysis of the desired ss- or ds-oligonucleotides independently generated the C4'-oxidized abasic site **64** (Scheme 14). This concept has also been studied by others.⁷¹

An alternative general method for the preparation of the C4'-oxidized abasic site was also reported.⁷² Here, 4'-azido-2'-deoxyuridine-5'-triphosphate is incorporated into duplex DNA using a primer and HIV-1 reverse transcriptase. The two strands of the duplex are separated on the basis of size after cleavage with a restriction enzyme. After treatment with uracil-DNA glycosylase, an enzyme that hydrolyzes uracil from the 2'-deoxyribose anomeric position, the ssDNA containing 4'-azido-2'-deoxyuridine **66** (Figure 5) resulted in the quantitative release

of uracil and azide and the generation of ssDNA containing the C4'-oxidized abasic site. This lesion was characterized directly by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and indirectly by subsequent reduction, enzymatic digestion, and gas chromatography-mass spectrometry (GC/MS). Synthetic methods for the preparation of gapped 3'-PG/5'-P lesions and the study of their structures by two-dimensional (2D) nuclear magnetic resonance (NMR) methods have also been reported.⁷³

The stability of the C4'-oxidized abasic site in both ss- and dsDNA has been determined. A half-life of 7.8 hours (37 °C, 100 mM NaCl at pH 7.5)⁷⁰ was found in ssDNA and 26 hours (37 °C, 100 mM NaCl at pH 7) in dsDNA.⁷² The rate constant in ssDNA is three times faster, suggesting that duplex DNA stabilizes the lesion, although pH conditions and the sequences were different in the two studies. A similar effect due to DNA structure has recently been reported for the 2-deoxyribonolactone lesion, whose half-life was found to be 20 hours in ssDNA and 32–54 hours in dsDNA. Thus, sugar lesion stability appears to be sensitive to both sequence and sequence context (ssDNA vs dsDNA).

3.3.2 Analytical Detection and Quantification of the C4-AP Lesion

A GC-MS approach was proposed for the quantification of 2-deoxypentos-4-ulose and 3'-PG pathways.⁷⁴ Another selective method for detecting femtomole amounts of the C4'-oxidized abasic site in DNA exploits the selective reactivity of the 1,4-dicarbonyl groups in the lesions with a biotinylated probe.⁷⁵ The adducts are quantified using a fluorescent assay.

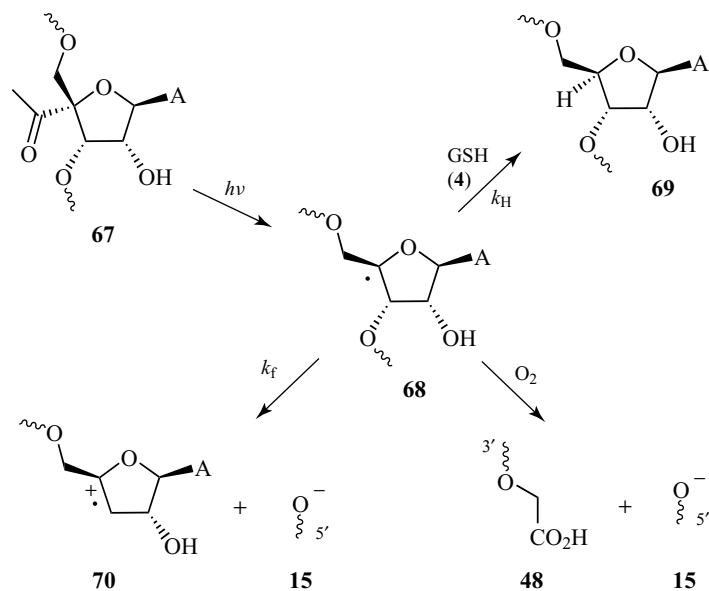
Mass spectrometry was employed to detect the C4-AP from intrastrand or interstrand cross-links in cellular DNA,⁷⁶ as well as at specific positions in DNA fragments.⁷⁷ In particular, cyclic adducts were formed with deoxycytidine. DNA interstrand cross-links are deleterious to cells because they block replication and transcription.⁷⁸ By means of duplexes in which **64** is produced from a synthetic precursor, the lesion was shown to produce interstrand cross-links where both strands were intact, as well as cross-links where the strand containing C4-AP was cleaved.⁷⁹ The yields of these products depend upon the surrounding nucleotide sequence. When C4-AP lies opposite dA, cross-linking occurs exclusively with the adjacent dA on the 5'-side.^{80,81}

3.3.3 Repair of the C4-AP Lesion

The ability to generate the C4-AP or the 3'-PG/5'-P lesions in any sequence context could elucidate the lesion structure (in both ss- and dsDNA lesions). The efficiency of *in vitro* C4-AP repair by the Ape1 protein (the major human abasic site endonuclease) and β -polymerase has been studied.⁸² Ape1 catalyzed effective incision at C4-AP at a rate that may be only a few times less than that for the incision of hydrolytic native abasic (AP) sites at the same location. Ape1 hydrolyzed 3'-PGs 25 times more slowly than the abasic site. The repair of C4-AP has also been studied with a variety of DNA polymerases *in vitro*.⁸³

3.4 C4' Radicals in Ribonucleotides

The site-specific generation of C4' radical in ribonucleosides and RNA has received much less attention than its DNA counterpart, and it should be noted that iron bleomycin cleaves RNA much less efficiently than DNA.⁸⁴ An oligonucleotide containing the modified methyl ketone **67** as photolytic precursor of the C4' radical (Scheme 15) has been synthesized.⁸⁵ In the presence of GSH and in competition with hydrogen abstraction from GSH to give **69**, the



Scheme 15 Generation of C4' radical in ribonucleotides.

4'-RNA radical **68** cleaves heterolytically to give the radical cation **70** and phosphate **15**. Assuming a $k_H = 1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of radical **68** with GSH, a rate constant of $k_f = 5 \times 10^2 \text{ s}^{-1}$ is calculated for the heterolytic cleavage of **68**. The cleavage rate of the corresponding 4'-DNA radical is more than three times faster. A destabilizing effect of the additional 2'-OH group⁸⁶ is considered to be responsible for the lower cleavage rate of the ribonucleotide radical.

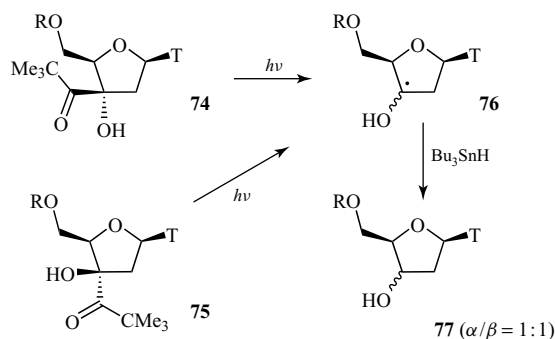
Under aerobic conditions, the expected products **15** and **48** were produced (Scheme 15).³³ However, their ratio changes substantially, since the value of **48/15** goes from 0.33 for the 4'-DNA radical to 3.0 for the 4'-RNA radical **68**. This effect was attributed to the retardation of β -elimination after the Criegee rearrangement (cf. Scheme 11).

4 OXIDATION OF THE C3' POSITION

4.1 Generation and Model Studies

Metallointercalators generally bind to the minor groove of dsDNA and abstract mainly C1', C4', and C5' H atoms from the sugar backbone. However, phenanthrenequinone diimine complexes of rhodium(III) intercalate in the major groove of dsDNA and have been postulated to abstract C3' H atoms from deoxyribose upon photoactivation,⁸⁷ although evidence suggests that H2' may be abstracted during photocleavage.⁸⁸ Under aerobic conditions, the C3' chemistry of **71** has thus been linked to the generation of 3'-phosphoglycolaldehyde (3'-PGA) **72**, base propenoate **73**, free base, as well as the oligonucleotide 3'-phosphate and 5'-phosphate termini at the site of strand scission (Scheme 16).

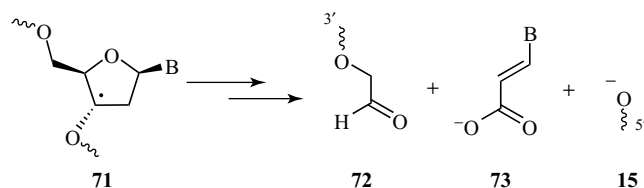
Site-specific radical-generating systems have been examined in some detail. The synthesis of *tert*-butyl ketone **74** or **75** and the conditions



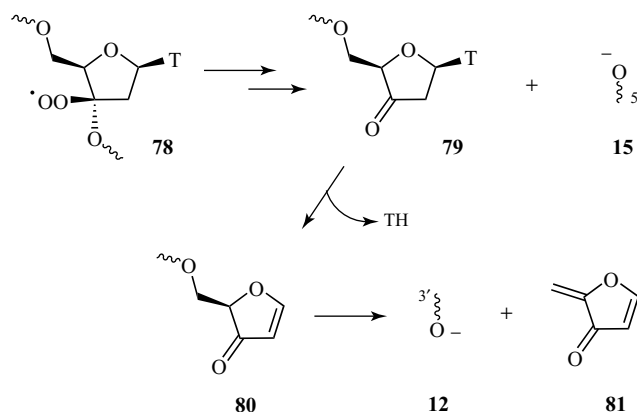
Scheme 17 Independent generation of C3' radical in model studies.

in which Norrish-type I photocleavage gave the desired C3' radical **76** were the subject of initial work.⁸⁹ In the presence of Bu_3SnH as a hydrogen donor, both derivatives gave **77**, a 1:1 mixture of isomers (Scheme 17).

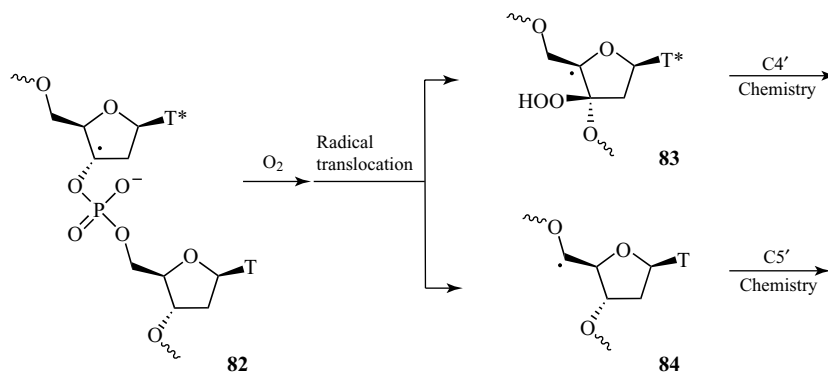
The *tert*-butyl ketone **75** (or its analogous acetyl derivative) has been incorporated into oligonucleotides and used as a photoactivated precursor of C3' radicals in ssDNA.^{90,91} While some products have been successfully identified, the mechanism of their formation is far from being understood. The thymidin-3'-yl radical abstracts hydrogen from GSH to give the reduced product in an undetermined β : α anomeric ratio.⁹⁰ Under aerobic conditions, the same radical was found to produce the labile 3'-ketodeoxynucleotide **79**, which led to **80** and free base, as well as the 5'- and 3'-phosphate-terminated oligomers (**15** and **12**) (Scheme 18).⁹¹ The expected 3'-PGA was accompanied by 3'-PG as well as 5'-aldehyde-terminated oligonucleotides. The formation of these fragments has been rationalized by oxidation of the C4' radicals of the same nucleotide and by oxidation of the C5' radicals of the 3'-adjacent nucleotide. The authors suggested the radical translocations from **82**, shown in Scheme 19, with formation of radicals **83** and **84**,



Scheme 16 Fate of the C3' radical in DNA.



Scheme 18 Fate of the C3' radical under aerobic conditions.

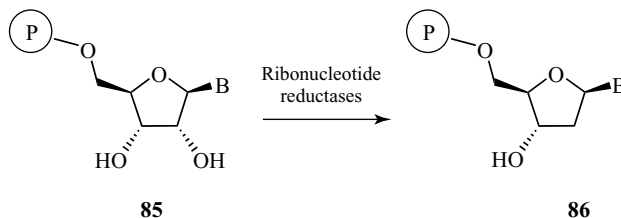


Scheme 19 Postulated radical translocation from C3' to C4' and C5' positions.

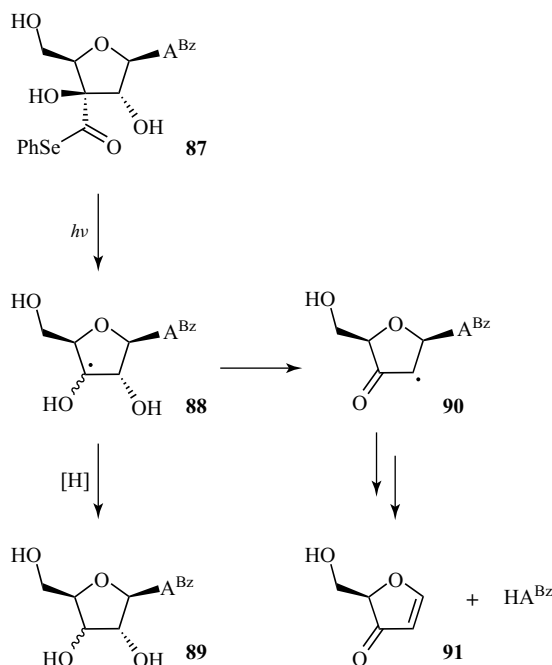
respectively. It should be noted that these findings are based on ss-oligonucleotide experiments. The mechanism of the transformation of peroxy radical **78** to 3'-ketodeoxynucleotide **79** has not yet been elucidated. The fate of this peroxy radical may be similar to that observed in the oxidation of C1' radicals: that is, release of O₂^{•−} from the peroxy radical, trapping of the corresponding cation by water, and β-elimination of the phosphate. Since the electronic environments of the C1' and C3' cations differ, the O₂^{•−} release in radical **78** should be much slower, rendering the intramolecular processes depicted in Scheme 19 plausible.

The mechanism of 3'-PGA (**72**) formation has not been clarified. It was suggested that, following hydroperoxide formation, a molecular rearrangement occurs with insertion of an oxygen atom into the deoxyribose ring, which further decomposes to

form 3'-PGA together with other products.⁸⁷ C3' radical degradation may not be the only pathway leading to 3'-PGA, and a method for the quantification of 3'-PGA residues has also been reported. After DNA irradiation and enzymatic digestion, the aldehyde moiety in 3'-PGA is derivatized to a stable oxime with pentafluorobenzylhydroxylamine, followed by extraction and characterization by GS/negative chemical ionization/MS.^{92,93} A stable isotopically labeled [¹³C₂]PGA was synthesized and used as an internal standard. In the presence of DNA, the detection limit was 30 fmol per sample, corresponding to two molecules of PGA in 10⁶ nucleotides for 170 μg of DNA. The application of this method for quantifying 3'-PGA residues revealed different yields for γ and α radiations.⁹²



Scheme 20 2'-Deoxygenation by ribonucleotide reductases.



Scheme 21 Independent generation and fate of C3' radical in ribonucleosides.

4.2 C3' Radicals in Ribonucleotides

The ribonucleotide reductase enzymes catalyze the conversion of 5'-(di or tri)-phosphate esters of ribonucleosides **85** to 2'-deoxynucleotides **86** in all organisms (Scheme 20). A radical-based mechanism for their action, derived from the results of several biological studies, has been established.^{94,95} The key steps involve formation of C-3' radical via hydrogen atom abstraction by a cofactor-induced thiyl radical and elimination of water prior to return of a hydrogen atom.

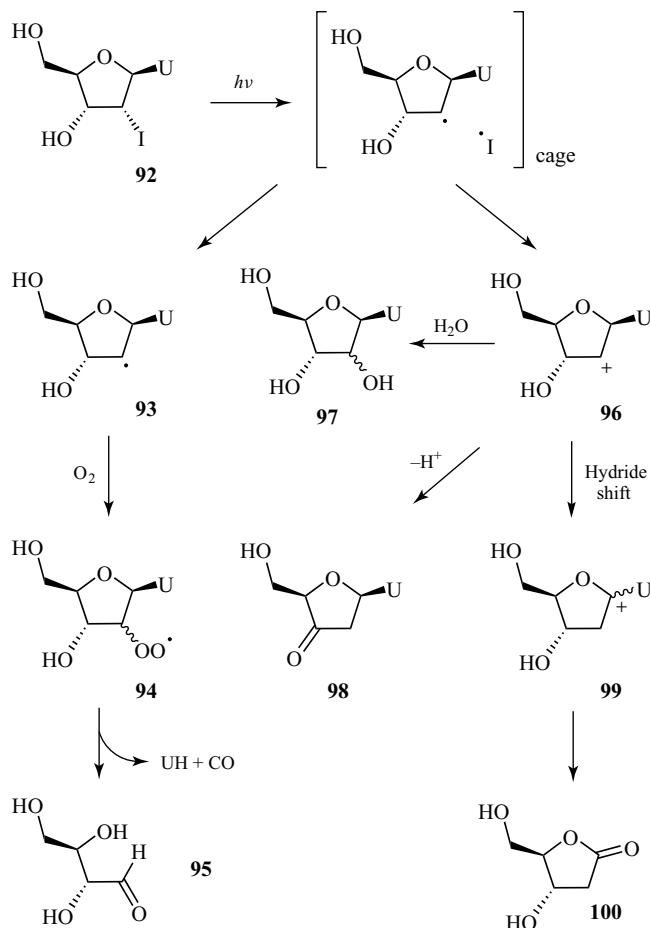
Biomimetic simulations of the free radical-initiated cascade reactions, postulated to occur at

the active site of ribonucleoside reductases, have also been performed.^{96,97} Synthesis of selenol ester **87** and subsequent photolysis (Scheme 21)⁹⁶ led to the site-specific generation of adenosin-3'-yl radical, and, with competition kinetic methods, it could be demonstrated that this radical effects the rapid elimination of the 2'-hydroxy group, leading to **91**, a reaction subjected to general base catalysis. The rate coefficient was determined as $1.5 \times 10^6 \text{ s}^{-1}$ by competition kinetics in the presence of 1 M triethylammonium acetate buffer at pH 7, and the elimination rate is about 10^3 times slower in the absence of the catalyst. A similar mechanism may also be feasible for the key steps of the enzyme-catalyzed reaction. A radical similar to **90** was also observed by pulsed electron paramagnetic resonance (EPR) and electron nuclear double resonance (ENDOR) spectroscopy in the deoxygenation of cytidine diphosphate by a mutant *Escherichia coli* ribonucleotide reductase.⁹⁸

5 OXIDATION OF THE C2' POSITION

5.1 Generation and Model Studies

Oxidation of the C2' is less common owing to the relatively higher C–H bond strength in DNA. Nevertheless, C2' oxidation in DNA has been observed under conditions that generate reactive hydroxyl radicals²¹ as well as in the photoirradiation of 5-halopyrimidine containing DNA.^{99,100} It is also expected that the C2' position in RNA would exhibit the same reactivity with the other positions of the deoxyribose. The photoreaction of 2'- α -iodo-2'-deoxyuridine (**92**) as a site-specific radical-generating system has also been explored. The reaction leads to a plethora of products that involve the formation of C2' radical **93** and C2' cation **96** (Scheme 22).¹⁰¹ Photoinduced



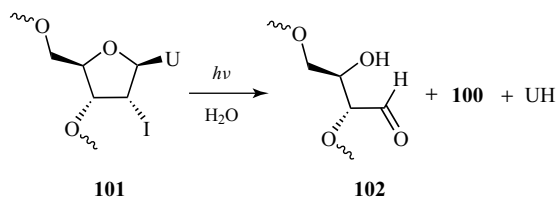
Scheme 22 Generation of C2' radical from 2'- α -iodo-2'-deoxyuridine.

homolytic cleavage of the C–I bond is followed by single-electron transfer in the cage before the diffusion of some reactive species. Under anaerobic conditions, the solvolysis product **97** as an anomeric mixture prevails with other proton elimination or cation translocation products to give **98** and **99**, respectively. In the presence of oxygen, the conversion of the C2' radical to the corresponding peroxy radical **94** is a consistent path that ultimately leads to the formation of erythrose **95** and uracil as well as to the C2'-hydroxylated product **97**.

The photoirradiation of **101** in a ds-oligonucleotide produced **102** (11%) and **100** (5.6%) under aerobic conditions, while the yield of **102** decreased with the yield increase of **100** in the absence of oxygen (Scheme 23).¹⁰¹ The photochemical dehalogenation of 5-halouracil-containing

DNA, where the hydrogen abstraction from the resulting uracil-5-yl radicals is atom-specific and highly dependent on the DNA structure, has been studied in detail.⁹⁹ Competitive C1' and C2' hydrogen abstraction was observed from the 2-deoxyribose at the 5' side in B-form DNA, affording the oligonucleotides **102** and **100**.^{101,102} In analogous experiments with Z-form DNA, product **100** is significantly suppressed and the formation of **102** is accompanied by C2' α -hydroxylation.¹⁰³

Therefore, the formation of D-erythrose abasic site (C2-AP, **102**) and the hydroxylation at C2' position are considered to be the key C2' oxidation products. Early studies on the γ irradiation of DNA also included a report of the formation of erythrose-containing sites.¹⁰⁴ The formation of **102** from the C2'-OO• radicals has been explained by



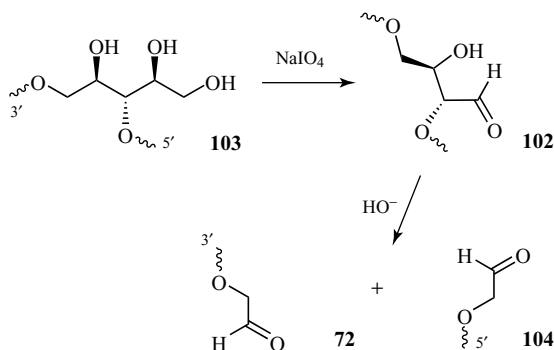
Scheme 23 Generation of C2' radicals in oligonucleotides.

several mechanistic pathways, although a definitive confirmation is not yet available.^{102,103}

5.2 Biochemical Studies with C2-AP

In addition to the 5-halouracil photochemical system described above for the synthesis of oligonucleotides containing an erythrose abasic site (C2-AP), the selective *in situ* generation of the lesion at a defined oligonucleotide site has been described.¹⁰⁵ A phosphoramidite derivative of a protected ribitol was prepared, which, following oligonucleotide incorporation and deprotection, afforded **103**. Periodate oxidation of the vicinal diol affords C2-AP (**102**), as shown in Scheme 24. Although incorporation of the precursor into oligonucleotides has only 50% efficiency, *in situ* conversion of the precursor to C2-AP was nearly quantitative.

This lesion is rapidly cleaved by piperidine at 90 °C.¹⁰⁵ Heating of this abasic site under alkaline conditions causes a retroaldol reaction, resulting in a strand break with subsequent formation of oligonucleotides 3'-PGA **72** and 5'-phosphoglycolaldehyde



Scheme 24 Independent generation of the C2-AP lesion in oligonucleotides.

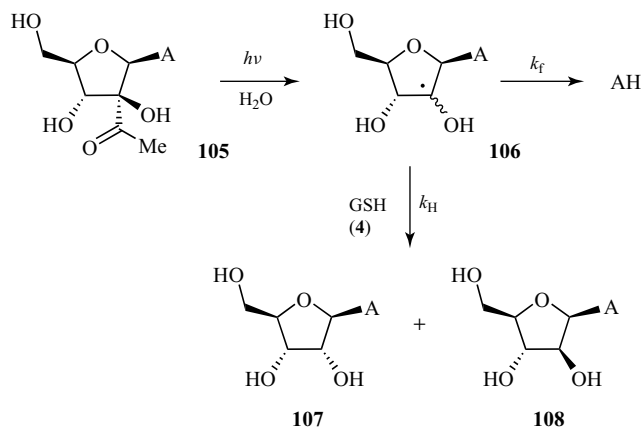
104 (Scheme 24).^{102,106} However, cleavage by 0.1 M NaOH at 37 °C reveals that the erythrose abasic site is considerably less labile to hydrolysis (half-life of 3.3 h) than other abasic lesions.¹⁰⁵ The 3'-residue (**72**) is chemically identical, but mechanistically unrelated, to the 3'-PGA residue product of the C3' radical oxidation (see above).

The results of two *in vitro* studies suggest possible biological consequences for the erythrose abasic lesion.^{106,107} Like other abasic lesions, deoxyadenosine is preferentially incorporated opposite to the abasic site, but is a strong inhibitor to polymerase extension. This lesion is incised by phosphodiesterases but is not a substrate for endonuclease III, even though a Schiff base is formed. Ape1 (see Section 3.4) incises C2-AP, but the 5'-phosphorylated fragment is not a substrate for the lyase activity of DNA polymerase β .¹⁰⁸ Excision of the lesion is achieved by strand displacement synthesis in the presence of flap endonuclease during which C2-AP and the 3'-adjacent nucleotide are replaced. C2-AP is also a substrate for the bacterial UvrABC NER system.¹⁰⁸

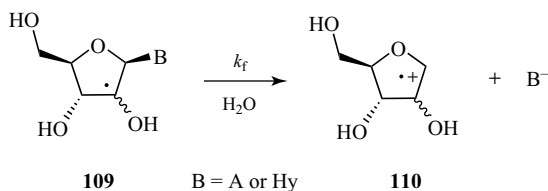
5.3 C2' Radicals in Ribonucleosides

Compound **105** was synthesized as a site-specific adenosin-2'-yl radical-generating system upon photolysis. The radical **106** was generated and was trapped by GSH (Scheme 25),⁵⁶ leading to the ribo and arabino products **107** and **108**, respectively, in a 1:3.5 ratio. The preferred attack of the thiol from the α -face of the C2' radical is due to the efficient β -face shielding by the adenine moiety. Adenine was also a reaction product. The ratio $k_H/k_f = 4.3 \text{ M}^{-1}$ was determined by competition kinetics and indicates a relatively rapid β -elimination.

The same adenosin-2'-yl radical was obtained by one-electron reduction of 8-bromoadenosine (see above) in pulse radiolysis experiments (Scheme 26).⁵⁶ A k_f value of $1.1 \times 10^5 \text{ s}^{-1}$ is obtained by measuring the oxidizing radical formed upon adenine release. Heterolysis of the glycosidic bond in radical **109** was suggested to produce both the radical cation **110** and the adenine. Similar experiments and results were reported for inosin-2'-yl radical, which also gives **110** and hypoxanthine (Hy) upon heterolysis of the glycosidic bond.⁴³



Scheme 25 Independent generation of C3' in ribonucleosides.



Scheme 26 Postulated heterolysis of the glycosidic bond of C2' radical.

6 OXIDATION OF THE C1' POSITION

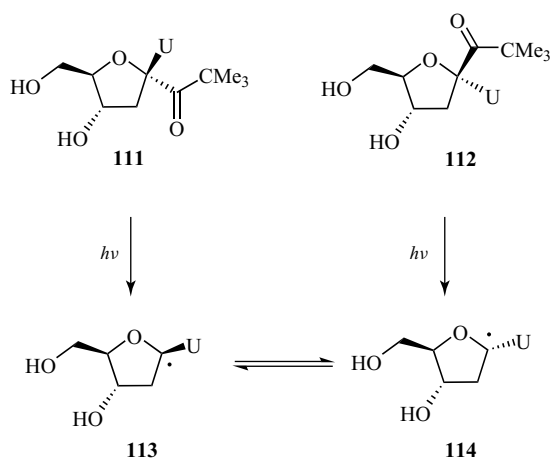
6.1 Generation and Fate of the C1' Radical

The 2-deoxyribonolactone lesion (or C1'-oxidized abasic site) is the outcome of the oxidation of the C1' position of DNA nucleotides and has been implicated in DNA strand scission, mutagenesis, and covalent cross-linking to DNA-binding proteins.^{3,4,8–10} The deoxyribonolactone lesion is known to be the result of a variety of toxic agents, including enediyne antibiotics (e.g., NCS-Chrom), bis(phenanthroline) copper, cationic manganese porphyrins, oxoruthenium complexes, ultraviolet irradiation, and ionizing irradiation.^{8–10,12,15,16} The chemical mechanisms for oxidized abasic site generation by these agents have been the subject of intensive investigation, and, while the details vary among damage reagents and conditions, key features of the damage process include hydrogen abstraction at the C1' position, nucleotide oxygenation,

and extrusion of the nucleobase to produce the 2-deoxyribonolactone (L) lesion in duplex DNA.

6.2 Model Studies for the Independent Generation of C1' Radicals

Significant efforts have been devoted to creating a site-specific radical-generating system and to incorporating the L lesion in duplex DNA. The specific generation of the C1' radical has been achieved by two independent synthetic routes involving the photoinduced cleavage of the corresponding *tert*-butyl ketone **111** (Scheme 27).^{109,110} The 2'-deoxyuridin-1'-yl radical, generated by photolysis of *tert*-butyl ketone **111** or **112** in water, was studied spectroscopically by EPR and laser flash photolysis (LFP) methods.^{110,111} Density functional theory (DFT) calculations at the UB3LYP/6-311G** level have also revealed structural properties of this radical, and hyperfine coupling (hfs) constants determined by EPR as well as optical transitions observed in the ultraviolet–visible (UV–vis) region of the LFP spectrum have been defined.^{110,111} The radical center is not planar, and the energy profile for the interconversion of the two anomeric forms **113** and **114** (Scheme 27) was determined computationally. A broad band in the 290–370 nm region with $\lambda_{\text{max}} = 320$ nm is characteristic of the 2'-deoxyuridin-1'-yl radical. The vertical optical transitions [spin] singly occupied molecular orbital (SOMO) $\rightarrow \pi^*(\text{uracil})[\alpha]$ and $\pi(\text{uracil}) \rightarrow \text{SOMO}[\beta]$ were computed at

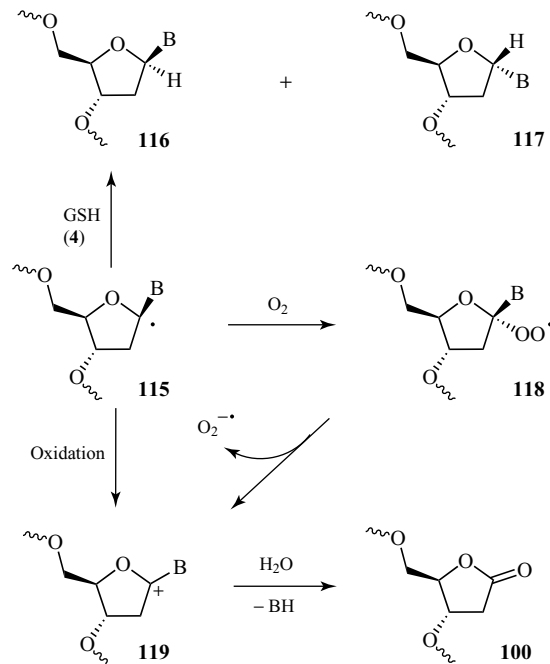


Scheme 27 Independent generation of C1' radicals.

296 nm (oscillator strength $f = 0.010$) and 378 nm ($f = 0.06$), respectively.¹¹¹

The 2'-deoxyuridin-1'-yl radical abstracts hydrogen from β -mercaptoethanol, cysteine, and GSH with rate constants of and 2.3×10^6 , 2.9×10^6 , and $4.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, respectively, to give a β : α anomeric ratio in the 1.3–2.0 range.¹¹¹ Since the β : α ratio was insensitive to the initial concentration of thiol and the precursor, it was suggested that the C-1' radical rapidly inverts (Scheme 27), and that the β / α distribution depends on the degree of the shielding effect of the two γ substituents in the sugar ring: that is, OH versus CH_2OH . The *tert*-butyl ketone **111** has been incorporated into oligonucleotide sequences, and the reactivity of the C1'-nucleotide radical toward thiols has been addressed.¹¹² Using β -mercaptoethanol, β : α ratios of 4.2 and 6.5 were determined for radical **115** (B = uracil) trapping in ss- and ds-oligonucleotides, respectively (Scheme 28). This increase in stereoselectivity favors the restoration of the naturally occurring β -deoxynucleotide. Those α -deoxynucleotides produced during γ radiolysis of DNA under anaerobic conditions have been shown *in vitro* to be premutagenic.^{113,114} The C1' radical **115** has been suggested to abstract a hydrogen atom from a thiol to give a mixture of β -anomer **116** and α -anomer **117** (Scheme 28).

In the presence of O_2 , radical **115** leads to abasic site damage with the formation of the 2-deoxyribonolactone residue (**100**).^{4,9,12,115} The reaction of selectively generated 2'-deoxy-uridin-1'-yl



Scheme 28 Fate of the C1' radical under reducing and oxidative conditions.

radical with molecular oxygen gives the corresponding peroxyl radical with a rate constant of $1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (cf. structure **118** in Scheme 28).¹¹¹ The fate of this peroxyl radical has been investigated in some detail by ^{18}O labeling and LFP experiments.^{116,117} The labeling experiments demonstrated the partition between two channels, where the ribonolactone carbonyl oxygen is derived from molecular oxygen and a water molecule.¹¹⁷ In the LFP experiment, the rapid release of $\text{O}_2^{\cdot-}$ from the peroxyl radical corresponds to a rate constant of $1.5 \times 10^4 \text{ s}^{-1}$.¹¹⁷ Similar reactions in dsDNA have been previously reported.¹¹²

Under physiological conditions, oxygen and GSH trapping of C1' radicals are competitive processes, because of the low O_2 concentration in the nucleus. Since the rate constant for reaction of the DNA peroxyl radicals with GSH is $\leq 400 \text{ M}^{-1} \text{ s}^{-1}$,⁶⁶ superoxide release from C1' nucleotide peroxyl radicals is orders of magnitude faster than peroxyl trapping at physiological GSH concentrations ($\sim 5 \text{ mM}$). Once formed, the C1' peroxyl radicals **118** expel superoxide radical anion to give C1' cations **119**, affording

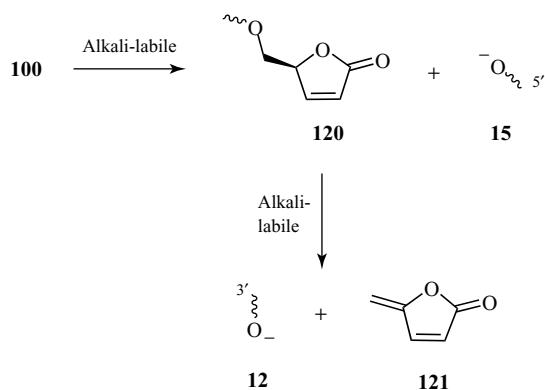
100 much faster than the respective trapping by GSH to give hydroperoxides.¹¹⁸

In the presence of metal complexes, the strongly reducing C1' radical **115** undergoes oxidation to the corresponding cation **119** (Scheme 28).^{11,12} Rate constants for the reaction of the 2'-deoxyuridin-1'-yl radical **113** with CuCl₂ and FeCl₃ are reported as 7.9×10^7 and $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, respectively.¹¹¹

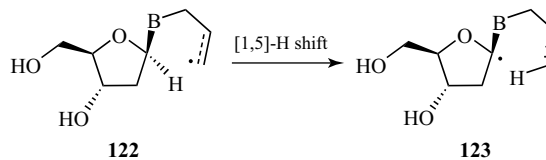
Therefore, 2-deoxyribonolactone (**L**) has been identified as the only C1' oxidation product. Radical translocation from the base unit to C1' position has been suggested in many radical-based DNA studies as the route to **L** formation. For example, the photochemical dehalogenation of 5-halouracil-containing DNA (see also oxidation of the C2' position) has been investigated in detail.⁹⁹ Hydrogen abstraction from the resulting uracil-5-yl radicals is atom-specific and highly dependent on the DNA structure, suggesting that this approach could also be applied as a probe for the DNA conformations in living cells.

6.3 Independent Generation of the 2-Deoxyribonolactone Lesion in Oligonucleotides

2-Deoxyribonolactone (**L**) is an alkali-labile lesion and, under alkaline conditions, results in strand scission (Scheme 29) with formation of 3'-phosphate **15** and 5'-phosphate **12** termini. Thus, **L** cannot be incorporated into chemically synthesized deprotected oligonucleotides under basic conditions.



Scheme 29 Products of alkali treatment of the **L** lesion.



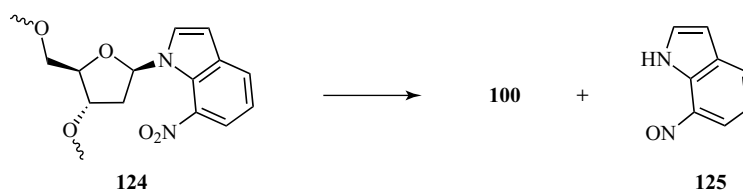
Scheme 30 Radical [1,5]-translocation to the C1' position.

In addition to the photolysis of the corresponding oligonucleotides containing the *tert*-butyl ketone **111**,^{112,118} a general method has been developed for the *in situ* generation of the lesion at a defined site of oligonucleotides using known radical translocation approaches.^{119–121} Efficient 1,5-radical translocation protocols for the selective generation of C1' radicals **123** (Scheme 30) and their subsequent trapping in nucleosides have been proposed.^{119,120} In particular, a synthesis has been reported,^{122,123} which is based on the photochemical conversion of the nitroindole nucleoside **124** (selectively incorporated in an oligonucleotide) to **100** with simultaneous expulsion of nitrosoindole **125** (Scheme 31). The single **L**-containing strands were hybridized with the complementary strand for biophysical and biochemical studies. NMR structural studies have illuminated aspects of the conformation of the DNA containing this lesion.¹²⁴ The procedure was also extended to double-strand synthesis by irradiation of the duplex in which one strand contains the nitroindole residue.¹²⁵

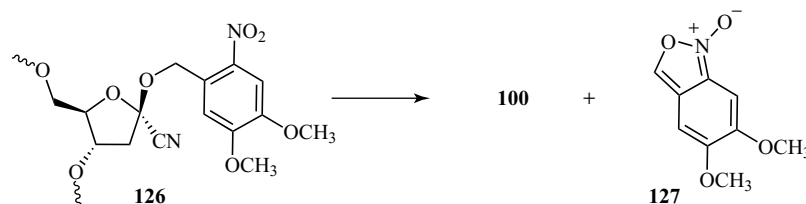
An alternative photochemical approach for the introduction of **L** in ds-oligonucleotides has also been developed,^{126,127} where a C1' nitroveratryl cyanohydrin phosphoramidite analog (**126**, Scheme 32) was synthesized and used for the preparation of ss-oligonucleotides. Irradiation at 350 nm quantitatively converted **126** to the 2-deoxyribonolactone lesion.

6.4 Biochemical Studies

The degradation of **L**-containing DNA was investigated in some detail.^{125,126} The cleavage through α,β - and γ,δ -elimination at the site of the lesion has been established with identification of the reaction products (Scheme 29). The degradation kinetics was investigated as a function of pH, temperature, length, and ionic strength.¹²⁵ Incubation of **L**-containing DNA under simulated



Scheme 31 Independent L-lesion formation under photochemical conditions.



Scheme 32 Photochemical (nonradical) generation of L lesion.

physiological conditions led to DNA fragmentation after two consecutive elimination reactions. DNA cleavage occurred with a half-life of ~ 20 hours in ssDNA and of 32–54 hours in duplex DNA, depending on the identity of the deoxynucleotide paired opposite to the lesion site ($A > C > G > T$).¹²⁷ The initial α,β -elimination reaction was the rate-determining step for the formation of methylene furanone and phosphorylated DNA products.

In the case of the minor groove-binding copper phenanthroline ($\text{Cu}(\text{phen})_2$) conjugate, the formation of 5-methylene furanone (**121**) and 3'- and 5'-terminus phosphates occurs without alkali-labile conditions in a much faster kinetic regime than expected (cf. Scheme 29).¹¹⁸ An L-containing ds-oligonucleotide resulted from photolysis of the corresponding oligonucleotide containing the *tert*-butyl ketone **111** (Scheme 27).^{112,118} $\text{Cu}(\text{OP})_2$ was shown to produce direct strand scission by effecting α,β -elimination from **100** (Scheme 29).¹²⁸

The approaches for the synthesis of L-containing DNA lesions described above have led to a better understanding of the toxicity, mutagenesis, and biochemical fate of the L lesion. This lesion is incised by AP endonucleases, suggesting a BER pathway for L removal.¹²⁹ The L lesion was also found to induce DNA polymerase-mediated mutagenesis¹³⁰ and transcriptional inhibition.¹³¹ These lesions form covalent adducts with DNA repair

proteins that metabolize AP sites, implying potential toxicity mechanisms,^{132,133} and long-patch base excision DNA L lesion repair prevents the formation of DNA–protein cross-links with DNA pol β .¹³⁴ The L lesion has been shown to have mutagenic properties unlike those of native abasic sites,^{135,136} although caution is needed for the interpretation of the experiments.⁴ The development of analytical methods for quantifying 2-deoxyribose oxidation products in isolated DNA and cells has been reported.^{137,138}

7 CONCLUSIONS

Oxidation of the sugar moiety in DNA is biologically relevant since, in most cases, it leads to an unstable or altered biomolecule that puts the repair machinery of the cell to test. DNA damage involving the 2-deoxyribose is caused by ROS and chemical mutagens. The ensuing DNA lesions involve either ss breaks repaired by NER enzymes, or deleterious ds breaks resulting from tandem and clustered DNA lesions and leading eventually to cell apoptosis or cell death.

The study of sugar DNA damage was initiated by studies on the effects of ionizing radiation involving mainly diffusible ROS and has progressed to the study of chemical nucleases and metal complexes which, through DNA binding, induce sequence-specific and position-specific damage.

Table 1 DNA fragments arising from sugar radicals.

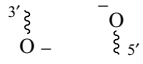
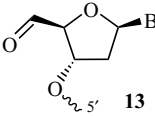
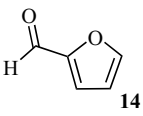
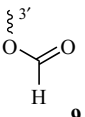
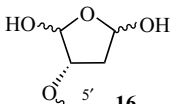
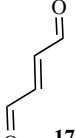
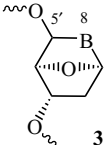
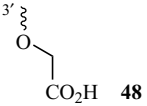
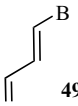
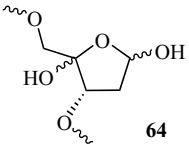
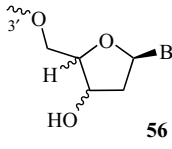
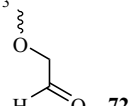
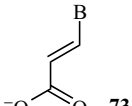
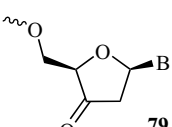
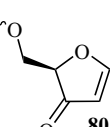
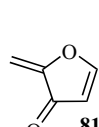
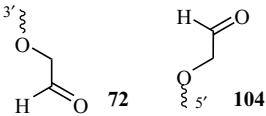
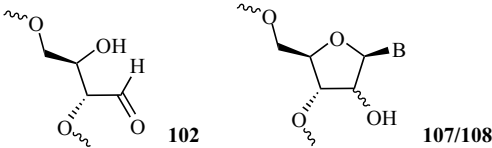
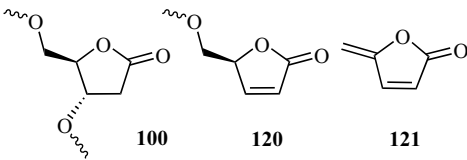
Fragments			Origin
BH			All positions
10	12	15	
			C5'
			C5'
			C5'
			C4'
			C4'
			C3'
			C3'

Table 1 (continued)

Fragments	Origin
	C2'
	C2'
	C1'

Research in the area has been aided by model systems capable of photochemical-independent generation of a nucleosidyl or nucleotidyl radical in monomeric state or inserted in ss or dsDNA. Finally, these studies have more recently been extended to photosensitive precursors of specific damage products inserted in oligonucleotides. Independent generation of these lesions in DNA has allowed biochemical studies of their stability and mutagenic potential within the frame of the double helix as well as the elucidation of other biologically important events involving modification of nearby nucleobases and the formation of DNA–DNA and DNA–protein cross-links.

The small molecule and DNA fragments that arise from an initial H-atom abstraction from one sp^3 -hybridized C–H sugar bond are listed in Table 1 and have been described above, together with the assignment of the position of initial attack. As previously mentioned, there are still open questions, especially involving the less studied positions, which will continue to draw the attention of researchers in the field and the study of which will hopefully bring a thorough understanding of the biological significance of oxidatively formed sugar radicals in nucleic acids.

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NOTE

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Reactions of Small Reactive Species with DNA

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1 INTRODUCTION

The major source of endogenous reactive oxygen species (ROS) is aerobic metabolism,¹ while both ROS and reactive nitrogen species (RNS) and oxidizing halogen derivatives are secreted by macrophages and neutrophils, respectively, that arise at sites of inflammation.² These intermediates include small molecular reactive species such as hydrogen peroxide (H_2O_2), peroxynitrite (ONOO^-), hydrochlorous acid, and HOCl , as well as free radicals such as superoxide radical anion ($\text{O}_2^{\bullet-}$), nitric oxide ('NO), the hydroxyl radical ('OH), and the carbonate radical anion ($\text{CO}_3^{\bullet-}$).^{1–6} Molecular reactive species have even pairs of electrons, while free radicals have one unpaired electron, and therefore an odd number of electrons. Because of the presence of unpaired electrons, free radicals are typically more reactive than molecules with even numbers of electrons. In normal tissues, ROS/RNS are present at low concentrations and play a role in regulating the activation of transcription factors, cell proliferation, and apoptosis.^{7,8} Reactive oxygen and nitrogen species play a critical role in eliminating viral and microbial infections and thus function as an efficient cellular defense mechanism. However, under conditions of acute or chronic inflammation developed in response to a variety of pathogens, environmental pollutants, tobacco smoke, and other exogenous factors, the damage inflicted by this intrinsic physiological defensive mechanism becomes harmful to

biological macromolecules and tissues.^{9–11} Thus, the overproduction of ROS/RNS during the inflammatory response has been linked with the etiology of various diseases¹ and the inflammatory response.^{2,3}

In normal and healthy tissues, the potentially harmful impact of ROS/RNS is mitigated by detoxification reactions catalyzed by catalase and superoxide dismutase (SOD) as well as by nonenzymatic mechanisms that involve glutathione and other antioxidants.¹ The overexpression of ROS/RNS results in the development of oxidative stress, which is accompanied by a series of signaling events that trigger the generation of cytokines and chemokines. Furthermore, chemical reactions of ROS/RNS with cellular DNA generate lesions, which, if not repaired by cellular DNA repair mechanisms, can induce mutations and genomic instability. Chronic inflammation can also stimulate cell-proliferating growth factors that enhance the frequencies of mutations that foster the progressive transformation of cells to the malignant state.^{9,10,12}

2 REACTIVE SPECIES IN CELLULAR ENVIRONMENTS

2.1 Molecular Pathways of ROS/RNS Generation

The pathways that generate the spectrum of ROS and RNS during the inflammatory response are

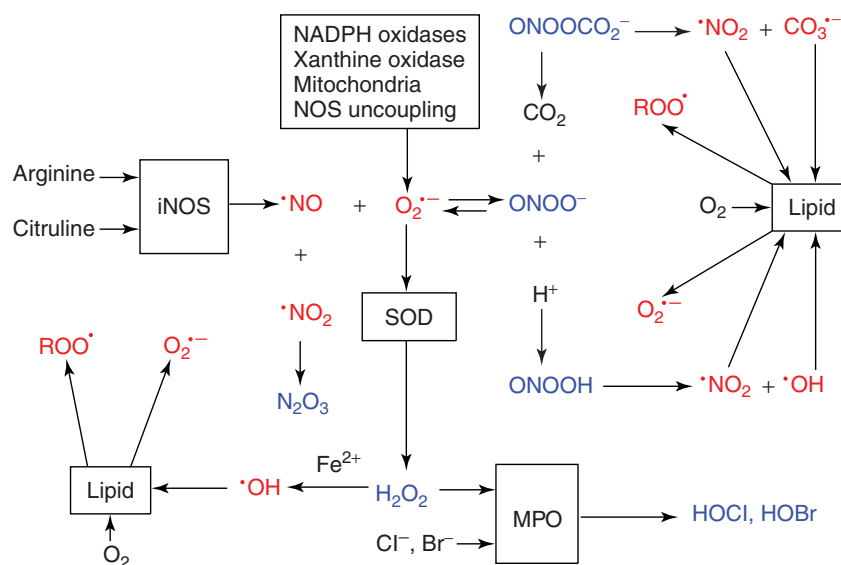


Figure 1 Molecular pathways of generation of molecular (blue) and free-radical (red) species in living systems.

shown in Figure 1.^{2,3,5} The upregulation of inducible nitric oxide synthase (iNOS) in macrophages plays one of the key roles in the inflammatory response. This enzyme catalyzes the oxidation of arginine to citrulline to form nitric oxide, a unique intracellular messenger that modulates blood flow, thrombosis, and neural activity.¹³ The physiological concentrations of $\cdot\text{NO}$ are at a level of ~ 10 nM, which is sufficient to activate guanyl cyclase, but can rise to levels of ~ 1 μM in highly inflamed tissues.⁵ The level of $\cdot\text{NO}$ is regulated by the extremely rapid conversion of $\cdot\text{NO}$ to nitrate by oxyhemoglobin in red cells, which prevents the direct oxidation of $\cdot\text{NO}$ by O_2 and the formation of potentially toxic intermediates such as $\cdot\text{NO}_2$, N_2O_3 , and N_2O_4 .^{14,15}

In 1990, Beckman and coworkers showed that $\cdot\text{NO}$ is highly toxic even at very low concentrations if superoxide radical anions are simultaneously produced and react with $\cdot\text{NO}$ to form the powerful oxidant peroxynitrite, ONOO^- .¹⁶



This reaction is extremely rapid and occurs with a close to diffusion-controlled rate constant of $6.7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.¹⁷ *In vivo*, the concentration of the $\text{O}_2^{\cdot-}$ radical is tightly regulated (basal level of 0.1 nM) by SOD. The latter exists as distinct isoforms located in the mitochondria, cytoplasm,

and extracellular compartments of cells.⁵ The SOD enzymes catalytically convert $\text{O}_2^{\cdot-}$ radicals to oxygen and hydrogen peroxide:



The reaction of SOD and $\text{O}_2^{\cdot-}$ is very rapid and occurs with the rate constants of $\sim 2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for both half-reactions of the catalytic cycle at 25°C over the pH range 5.0–9.5.^{18,19} Thus, $\cdot\text{NO}$ is a unique species produced in cells in sufficiently high concentrations to compete with SOD for $\text{O}_2^{\cdot-}$.⁵ In inflamed tissues, superoxide is overproduced as a result of the upregulation of NADPH oxidase and xanthine oxidase, electron leaks from mitochondria, and the uncoupling of the nitric oxide synthases leading to production of $\text{O}_2^{\cdot-}$ instead of $\cdot\text{NO}$.^{1,5} The H_2O_2 , derived from the dismutation of $\text{O}_2^{\cdot-}$ radicals, is regulated by catalase and peroxidase to levels of ~ 10 nM.²⁰ Neutrophils release large quantities of myeloperoxidase (MPO) which catalyzes the oxidation of halogen anions (Cl^- , Br^-) by hydrogen peroxide, thereby forming the highly reactive hypohalous acids (HOCl , HOBr).⁵ MPO also rapidly reacts with peroxynitrite to produce $\cdot\text{NO}_2$ radicals.^{21,22} *In vivo* $\cdot\text{NO}_2$ radicals rapidly react with an excess $\cdot\text{NO}$ to form N_2O_3 ,²³ a powerful nitrosating agent generated by macrophages.²⁴ Free radicals

generated at sites of inflammation initiate efficient lipid peroxidation associated with the formation of secondary radicals such as peroxy (ROO[•]) and hydroperoxy (HO₂[•]), as well as DNA-damaging reactive unsaturated aldehydes and epoxides.^{25,26}

2.2 General Aspects of ROS/RNS Reactivity

2.2.1 Molecular Reactive Species

In living systems, the inflammatory response is associated with the generation of a wide spectrum of molecular reactive species.^{1–3} Here we focus on small molecular reactive species such as ONOO[−], H₂O₂, and HOCl (Figure 1), which are present *in vivo* in extremely low concentrations under conditions of normal metabolism, and are overproduced at sites of inflammation. These molecular reactive species are strong oxidizing agents with two-electron reduction potentials^{27,28} in the range 1.08–1.37 V versus normal hydrogen electrode (NHE) (Table 1) and can potentially damage a wide spectrum of biomolecules. The oxidative processes initiated by molecular reactive species occur by two principal pathways: (i) two-electron oxidation without intermediate formation of free radicals and (ii) one-electron oxidation by highly reactive free radicals derived from the decomposition or the one-electron reduction of parent molecular reactive species.^{5,20}

Peroxynitrite (ONOO[−])

In neutral solutions, peroxynitrite exists in equilibrium with unstable peroxynitrous acid ONOOH (pK_a = 6.6), which spontaneously decomposes with the rate constant of 1.25 s^{−1} (25 °C).²⁹

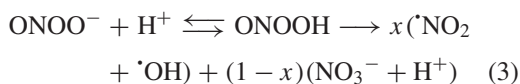
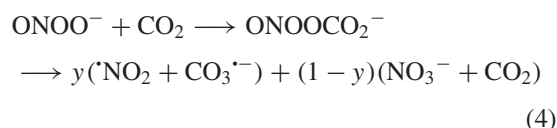


Table 1 Two-electron reduction potentials (*E*₇ vs NHE) of molecular reactive species at pH 7.

Reaction	<i>E</i> ₇ (V)	Reference
H ₂ O ₂ + 2H ⁺ + 2e [−] ⇌ 2H ₂ O	1.32	27
HOCl + 2H ⁺ + 2e [−] ⇌ H ₂ O + HCl	1.08	27
ONOOH + 2H ⁺ + 2e [−] ⇌ HNO ₂ + H ₂ O	1.37	28

The decomposition products are nitrate anions, nitrogen dioxide, and hydroxyl radicals formed with a yield of $x \sim 0.28$.³⁰ In neutral solutions, the lifetime of peroxynitrite ($\tau_e = 1/k_a$), estimated from the equation $k_a = k_1[\text{H}^+]/(\text{H}^+ + K_a)$, is about 4 s at pH 7 (24 °C).³¹ However, *in vivo*, the formation of [•]OH radicals plays only a minor role because of the rapid reaction of ONOO[−] with CO₂, which is ubiquitous in tissues due to the high levels of bicarbonate (10–30 mM) in biological fluids.³² This reaction occurs with a rate constant of $2.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ (24 °C)³¹ and results in the formation of a highly unstable nitrosoperoxycarbonate (ONOOCO₂[−]) species, which rapidly decomposes (<100 ns) to form carbonate radical anions, CO₃^{•−}, and [•]NO₂ radicals with a yield of $y \sim 0.33$.³³



In aqueous solutions, carbon dioxide coexists in equilibrium with bicarbonate anions and its concentration can be estimated using the equilibrium constant of $1.1 \times 10^{-6} \text{ M}^{-1}$ for the reaction $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$.³⁴ In neutral solutions (pH 7) containing 25 mM NaHCO₃, the lifetime of peroxynitrite is reduced to ~20 ms as a result of (4).³¹

The toxic effects of peroxynitrite are most likely associated with free radicals derived from its decomposition.⁵ The classic example is the oxidation/nitration of tyrosine (1) (Figure 2).^{35,36} In this case, the lifetime of peroxynitrite calculated from the decay of its characteristic absorbance ($\lambda_{\text{max}} = 302 \text{ nm}$, $\epsilon = 1670 \text{ M}^{-1} \text{ cm}^{-1}$),³⁷ either in the absence of CO₂/HCO₃[−] or in the presence of 25 mM NaHCO₃ (pH 7.5), is independent on the tyrosine concentration. This observation is a clear indication that mechanisms that invoke a direct electrophilic attack by peroxynitrite or nitrosoperoxycarbonate on the tyrosine aromatic ring are inconsistent with the reaction kinetics. In turn, the yields of the major end products derived from the combination of tyrosyl radicals (2) with [•]NO₂ radicals to form 3-nitrotyrosine (3), and the recombination of tyrosyl radicals (2) to form 3,3'-dityrosine (4), are in complete agreement with the free-radical mechanisms summarized in Figure 2.^{35,36}

A two-electron oxidation mechanism without the intermediate formation of free radicals

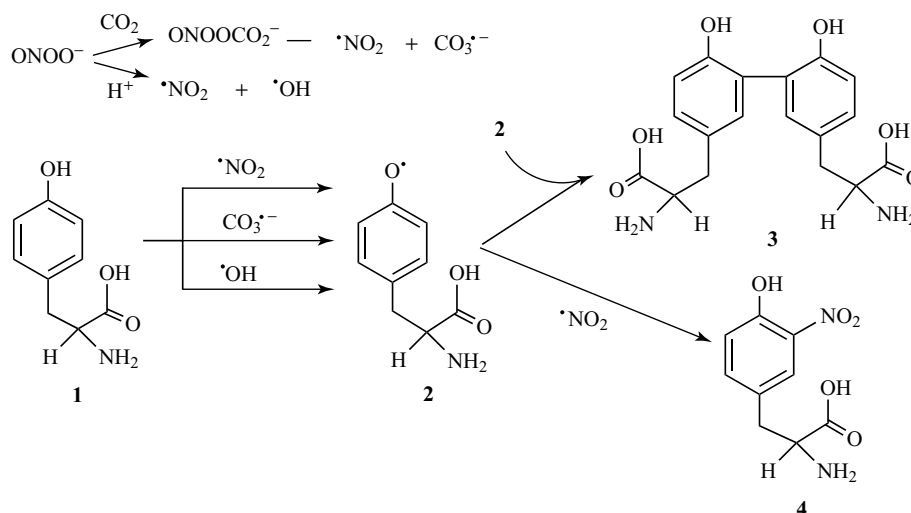
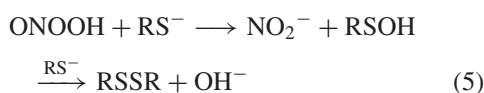


Figure 2 Free-radical mechanism of oxidation/nitration of tyrosine by peroxynitrite and nitrosoperoxycarbonate. [Adapted from Refs 35 and 36.]

has been reported for the oxidation of typical two-electron donors such as thiols (RSH) and thiolates (RS^-)^{38,39}:



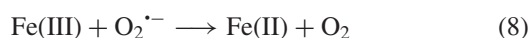
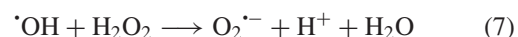
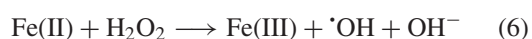
Here, increasing the concentration of the substrate is associated with a reduction of the peroxynitrite lifetime, and the decay of peroxynitrite in (5) follows second-order kinetics.³⁸ The value of the rate constant of (5) depends on the thiol structure and varies within the range of $2.8 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ for glutathione³⁸ to $\sim 2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for thiols and thiolates in proteins.³⁹

Hydrogen Peroxide

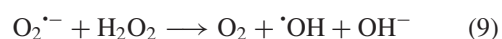
In pure aqueous solutions, hydrogen peroxide is quite stable and exists in the form of H_2O_2 , which is a very weak acid with $\text{p}K_a = 11.7$.⁴⁰ Two-electron oxidation reactions of hydrogen peroxide are typically very slow. For instance, the two-electron oxidation of glutathione by H_2O_2 at pH 7.4 occurs with the rate constant of $0.9 \text{ M}^{-1} \text{ s}^{-1}$.⁴¹

The transformation of H_2O_2 to highly reactive radicals can be initiated by traces of transition-metal ions.^{42,43} In 1876, Fenton demonstrated that mixing tartaric acid with H_2O_2 and low concentrations

of Fe(II) generates a colored product,⁴⁴ which was later identified as dihydroxymaleic acid, the oxidation product of tartaric acid.⁴⁵ Further studies have shown that the Fe(II)/ H_2O_2 system (Fenton reagent) efficiently oxidizes a variety of organic molecules.^{42,43} In neutral solutions, the catalytic effect of iron ions can be illustrated by the following simple scheme developed by Haber and Willstätter,⁴⁶ Haber and Weiss,^{47,48} and Baxendale and coworkers.^{49,50}



The reduction of H_2O_2 generates highly reactive hydroxyl radicals (Fenton reaction), which rapidly react with most organic molecules. The Fe(II) ions are regenerated by reduction of Fe(III) ions by superoxide radicals derived from the oxidation of H_2O_2 by $\cdot\text{OH}$ radicals. The direct reaction of $\text{O}_2^{\cdot-}$ (or $\text{HO}_2^{\cdot}$) with H_2O_2 (Haber–Weiss reaction) is very slow and its rate constant is in the range $0.1\text{--}0.5 \text{ M}^{-1} \text{ s}^{-1}$.⁵¹



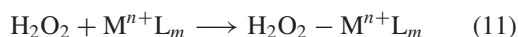
In 1932, at the same time as Haber and Weiss were investigating the Fe(II/III)/ H_2O_2 system, Bray

and Gorin⁵² proposed an alternative mechanism of the Fenton reaction:



where FeO^{2+} is “ferryl,” an iron(IV) species, which has a “free $\cdot\text{OH}$ -radical-like” reactivity. Over 70 years after Haber’s group proposed hydroxyl radicals as intermediates in the Fenton system, considerable controversy remains about the existence of free hydroxyl radicals.^{42,43} However, a full discussion of this problem is beyond the scope of this article.

Further studies have demonstrated that diverse metal ions and their complexes in lower oxidation states such as Cu(I), Ti(III), Cr(II), and Co(II) in mixtures with H_2O_2 are characterized by oxidative properties similar to those of the Fenton reagent.^{42,43} Extensive studies of “Fenton-like” reagents have shown that typical reactions of metal complexes with H_2O_2 do not occur via an outer-sphere electron transfer mechanism and involve the formation of the intermediate complexes:

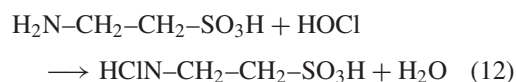


These complexes can produce $\cdot\text{OH}$ radicals or higher oxidation states of the metal (e.g., Fe(IV) and Cu(III)), which can exhibit “Fenton-like” reactivities with organic substrates.^{42,43}

Another set of problems is associated with complex formation between transition-metal ions and substrate molecules (e.g., DNA). Indeed, negatively charged DNA molecules can site-specifically bind positively charged metal ions (e.g., Fe^{2+}).⁵³ In this case, the Fenton reaction of H_2O_2 with the bound metal ions (or their complexes) generates reactive species (e.g., $\cdot\text{OH}$ and FeO^{2+}) in the vicinity of these sites, and the distributions of oxidatively modified nucleobases can differ from those generated by radiolytically generated $\cdot\text{OH}$ radicals. To address this problem, Tullius and coworkers have recommended the use of the $[\text{Fe(II)(EDTA)}]^{2-}/\text{H}_2\text{O}_2/\text{ascorbate}$ system.⁵⁴ Here, complex formation between Fe(II) and DNA is minimized by using negatively charged Fe(II) complexes with ethylenediaminetetraacetic acid (EDTA). Hydroxyl radicals produced by the $[\text{Fe(II)(EDTA)}]^{2-}/\text{H}_2\text{O}_2/\text{ascorbate}$ system and by ionizing radiation generate the same 2-deoxyribose damage the chemistry.⁵⁵ However, the damage of

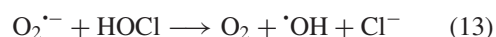
DNA nucleobases by radiolytically generated $\cdot\text{OH}$ radicals is more efficient than damage of the sugar residues because the rates of $\cdot\text{OH}$ addition to nucleobases are higher than the rates of H-atom abstraction from 2-deoxyribose.^{56,57} In turn, addition of ascorbate, which can repair the nucleobase radicals via a reduction mechanism, enhances the relative yields of 2-deoxyribose damage in comparison with base damage.⁵⁸

Hypochlorous acid is a weak acid with $\text{p}K_a = 7.5$.⁵⁹ HOCl is capable of initiating two-electron oxidation reactions with proteins⁶⁰ and thiols. For instance, HOCl oxidizes glutathione at pH 5–9 with a rate constant $\geq 10^7 \text{ M}^{-1} \text{ s}^{-1}$,⁶¹ which is five orders of magnitude greater than the analogous rate constant with ONOOH.³⁸ Another important reaction is the oxidation of amines by HOCl to form chloramines.⁶² The rate constants of these reactions are typically two orders of magnitude smaller than those of thiols. For instance, the rate constant of the reaction of HOCl with taurine (2-aminoethanesulfonic acid) at pH 7 is $4.8 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.⁶¹



In this reaction, taurine is released by isolated neutrophils in large amounts and is transformed to taurine chloramines, which retain their ability to react with thiol groups.⁶³

The reduction of HOCl by superoxide radicals (the analog of the Haber–Weiss reaction) is considered to be an efficient source of $\cdot\text{OH}$ radicals^{42,43}:



The rate constant of $\sim 7.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for this reaction is seven orders of magnitude greater than the constant for H_2O_2 (9).⁶⁴ The formation of $\cdot\text{OH}$ radicals in (13) has been confirmed using benzoate as a trap; the hydroxylation of this compound in the presence of HOCl and $\text{O}_2^{\cdot-}$ generates three isomeric hydroxybenzoates in the same ratio as the radiolytically generated $\cdot\text{OH}$ radicals.⁶⁵

The one-electron reduction of HOCl by metal ions (analog of the Fenton reaction) can potentially generate both hydroxyl and chlorine radicals⁶¹:



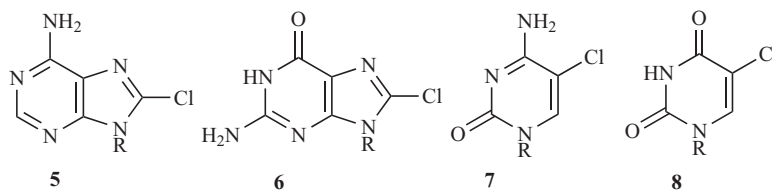


Figure 3 Chlorinated nucleobases generated in DNA by HOCl.

In the case of ferrocyanide, Fe(II)(CN)_6^{4-} , (14) produces $\cdot\text{OH}$ radicals in 27% yield as shown by the hydroxylation of benzoate to give a product distribution identical to that produced by radiolytically generated hydroxyl radicals.⁶⁶ The products of benzoate chlorination were not identified in these experiments.

Products of DNA Damage Produced by HOCl

The latter directly reacts with DNA to form *N*-chloramine derivatives of nucleobases.^{67,68} The heterocyclic NH groups are generally more reactive than the exocyclic NH_2 groups. For instance, the rate constant for reaction of HOCl with N1H of guanosine-5'-monophosphate ($k = 2.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) is four orders of magnitude greater than for the reaction with the NH_2 group ($k = 2.4 \text{ M}^{-1} \text{ s}^{-1}$).⁶⁹ The *N*-chloramines of nucleobases are highly unstable and readily decompose to form a wide spectrum of the chlorinated nucleobases (Figure 3) including 8-chloro-2'-deoxyadenosine (5),^{70–73} 8-chloro-2'-deoxyguanosine (6),^{70,71} 5-chloro-2'-deoxycytidine (7),^{70,71,73,74} and 5-chloro-2'-deoxyuracil (8).^{75,76}

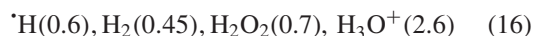
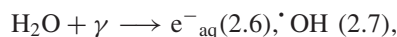
2.2.2 Radical Reactive Species

Persistent oxidative stress associated with chronic inflammation is associated with the overproduction of free oxyl radicals ($\text{O}_2^{\cdot-}$, $\text{CO}_3^{\cdot-}$, $\cdot\text{NO}_2$, $\cdot\text{OH}$).^{1–3,5,6} Among these radicals, $\text{CO}_3^{\cdot-}$, $\cdot\text{NO}_2$, and $\cdot\text{OH}$ are strong oxidizing agents, but only hydroxyl radicals^{56,57} and carbonate radical anions⁷⁷ can directly react with nucleic acid bases in DNA to produce irreversible damage.

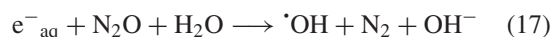
Hydroxyl radicals are powerful oxidants with a standard reduction potential of $E^\circ = 1.9 \text{ V}$ versus NHE.⁷⁸ In alkaline solutions, the $\cdot\text{OH}$ radical ($\text{p}K_a = 11.9$) dissociates to its conjugate base $\cdot\text{O}^-$.⁷⁹

In reactions with organic molecules, $\cdot\text{OH}$ radical reacts as electrophile, whereas $\cdot\text{O}^-$ acts as a nucleophile. For instance, the addition of $\cdot\text{OH}$ to unsaturated bonds is typically fast; in contrast, $\cdot\text{O}^-$ does not add to unsaturated compounds. In the case of aromatic molecules with aliphatic side chains, $\cdot\text{OH}$ adds preferentially to the aromatic ring, whereas $\cdot\text{O}^-$ readily abstracts H atoms from aliphatic C–H bonds.⁷⁹

Some common methods of $\cdot\text{OH}$ -radical generation are (i) radiolysis of water, (ii) photolysis of appropriate compounds, and (iii) Fenton-type reagents.⁷⁹ Radiolysis of water generates a wide spectrum of reactive species:



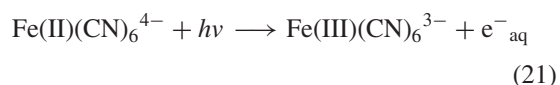
where the numbers in parentheses are the *G* values, which represent the number of molecules formed per 100 eV energy absorbed by pure water.⁷⁹ In order to remove hydrated electrons and H atoms, experiments are typically conducted in solutions saturated with nitrous oxide that produce additional $\cdot\text{OH}$ radicals by reacting with e^-_{aq} ($k = 9.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) and $\cdot\text{H}$ ($2.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).⁷⁹



Photochemical methods of generating $\cdot\text{OH}$ radicals can be illustrated by the following equations⁷⁹:



An alternative method is to photoionize the appropriate compounds in aqueous solutions:



saturated with N₂O, which requires the conversion of e⁻_{aq} to [•]OH radicals (17). Hydroxyl radicals have relatively small molar extinction coefficients in the far UV spectral range ($\lambda_{\text{max}} = 230$ nm, $\epsilon = 530$ M⁻¹ cm⁻¹),⁸⁰ and the kinetics of [•]OH radicals is typically monitored by the appearance of product radicals that have characteristic absorption spectra.⁷⁹

The Carbonate Radical Anion

At pH > 0, the carbonate radicals exist in the form of CO₃^{•-}, because the conjugate HCO₃⁻ is a strong acid ($pK_a < 0$).⁸¹ The carbonate radical is a strong one-electron oxidant with a standard reduction potential⁸² of $E^\circ = 1.59$ V versus NHE, and can rapidly and selectively oxidize biomolecules by one-electron abstraction mechanisms.⁸³ These radicals rapidly abstract electrons from aromatic amino acids (tyrosine and tryptophan). However, reactions of CO₃^{•-} radicals with sulfur-containing methionine and cysteine are less efficient.^{84–86} Hydrogen-atom abstraction by carbonate radicals is generally very slow,⁸³ and their reactivities with amino acids are negligible.^{84–86} One-electron oxidation reactions mediated by CO₃^{•-} radicals can be monitored in real time by spectroscopic transient absorption methods (e.g., laser flash photolysis and pulse radiolysis) because CO₃^{•-} radicals have a characteristic absorption band at 600 nm ($\epsilon = 1970$ M⁻¹ cm⁻¹).⁸¹

Carbonate radical anions are commonly generated by the following methods: (i) oxidation of HCO₃⁻ anions (or CO₃²⁻ in alkaline solutions) either by radiolytically generated [•]OH radicals or by photochemically generated SO₄^{•-} radicals and (ii) photolysis of carbonate transition-metal complexes.⁸³ In typical pulse radiolysis experiments, the oxidation of HCO₃⁻ anions by [•]OH radicals (rate constant 8.5×10^6 M⁻¹ s⁻¹) is described by the following equation⁷⁹:



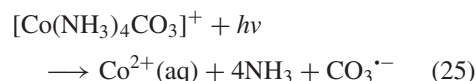
In our experiments, either steady-state^{87–91} or pulsed UV light (e.g., 308 nm XeCl excimer laser pulses)^{77, 92–94} photolysis methods were employed. In buffered solutions containing bicarbonate and persulfate anions, irradiation with UV light induces the dissociation of the S₂O₈²⁻ ions to sulfate radical anions SO₄^{•-}:



The latter is a strong one-electron oxidant with a standard reduction potential⁸² of $E^\circ = 2.43$ V versus NHE, which oxidizes HCO₃⁻ anions with the rate constant of 4.6×10^6 M⁻¹ s⁻¹.⁷⁷

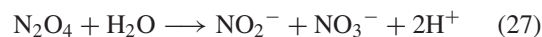


However, these methods cannot be used at pH < 7.5 owing to the transformation of HCO₃⁻ to CO₂, which is not oxidized by [•]OH and SO₄^{•-} radicals. The photolysis of carbonatotetraminecobalt(III) complexes by steady-state or pulsed UV light allows overcoming this unfavorable pH effect and can be used to generate CO₃^{•-} radicals in a wide range of pH values (pH ~3–13)^{95,96}:

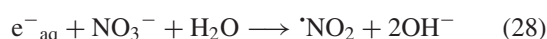


Our experiments have shown that CO₃^{•-} radicals, regardless of the method of generation, exhibit the same reactivities and generate the same oxidation products.⁹⁰

Nitrogen dioxide radicals are mild one-electron oxidants with a standard reduction potential of $E^\circ = 1.04$ V versus NHE.⁷⁸ In aqueous solutions, [•]NO₂ radicals typically react reasonably rapidly in free-radical reactions, but react more slowly by electron transfer mechanisms with appropriate electron donors and by addition to unsaturated bonds.^{83,97} In pure aqueous solutions (without substrates), the lifetimes of [•]NO₂ radicals are limited by dimerization to form nitrogen tetroxide ($k = 4.5 \times 10^8$ M⁻¹ s⁻¹)⁸³ that rapidly hydrolyzes ($k = 1 \times 10^3$ M⁻¹ s⁻¹)⁹⁸ to form nitrite and nitrate anions.



In aqueous solutions, [•]NO₂ radicals are commonly generated by two methods: (i) reduction of nitrate anions by hydrated electrons ($k = 9.7 \times 10^9$ M⁻¹ s⁻¹)⁷⁹



and (ii) oxidation of nitrite anions by [•]OH radicals ($k = 1.0 \times 10^{10}$ M⁻¹ s⁻¹)⁷⁹ or SO₄^{•-} radicals

($k = 8.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$)⁸³:

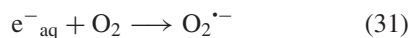


Absorption of $\text{}^{\bullet}\text{NO}_2$ radicals in the spectral range 300–500 nm is weak ($\lambda_{\text{max}} = 400 \text{ nm}$, $\varepsilon = 200 \text{ M}^{-1} \text{ cm}^{-1}$) and reactions of these radicals are typically monitored by the appearance of the absorption bands of the reaction product.⁷⁹

Superoxide Radicals

In neutral aqueous solutions, $\text{O}_2^{\bullet-}$ is the major form because the pK_a of the conjugated acid (i.e., the hydroperoxyl radical $\text{HO}_2^{\bullet}$) has a value of 4.8.⁹⁹ In contrast to organic peroxy radicals $\text{RO}_2^{\bullet}$, which exhibit only oxidizing properties, the $\text{O}_2^{\bullet-}$ radicals have both reducing and oxidizing properties. The standard reduction potential of O_2 is of $E^\circ(\text{O}_2/\text{O}_2^{\bullet-}) = -0.16 \text{ V}$ versus NHE.⁷⁸ In agreement with this potential, $\text{O}_2^{\bullet-}$ radicals rapidly reduce quinones and other appropriate acceptors by one-electron transfer mechanisms.⁹⁹ Combination reactions of $\text{O}_2^{\bullet-}$ radicals with other free radicals play an important role in the chemistry of the superoxide. One of these reactions is the extremely fast combination of $\text{O}_2^{\bullet-}$ and $\text{}^{\bullet}\text{NO}$ radicals to form the highly toxic peroxynitrite (1).

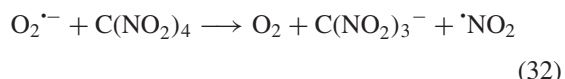
In aqueous solutions, superoxide radicals are commonly produced by the reduction of oxygen by radiolytically or photochemically generated hydrated electrons. These reactions occur with the diffusion-controlled rate constant of $2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ⁹⁹:



In biochemical experiments, continuous fluxes of superoxide radicals are generated by the enzymatic oxidation of xanthine catalyzed by xanthine oxidase.¹⁰⁰ In this process, electrons abstracted from xanthine by xanthine oxidase are transferred to oxygen molecules to form superoxide radicals. In pure aqueous solutions, the lifetimes of $\text{O}_2^{\bullet-}$ radicals are determined by their dismutation to O_2 and H_2O_2 molecules with the rate constant⁹⁹ of $5.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7 and become significantly shorter in the presence of SOD (2).^{18,19}

Superoxide radicals absorb light in the far UV spectral region ($\lambda_{\text{max}} = 243 \text{ nm}$, $\varepsilon = 2.35 \times 10^3$

$\text{M}^{-1} \text{ cm}^{-1}$),⁹⁹ which is a spectroscopically inaccessible region because of the strong absorbance of biomolecules in this range of wavelengths. An effective method for monitoring $\text{O}_2^{\bullet-}$ radicals in laser flash photolysis and pulse radiolysis experiments is the fast reduction of tetranitromethane ($k = 1.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) to the nitroform anion ($\lambda_{\text{max}} = 350 \text{ nm}$, $\varepsilon = 14.6 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$).¹⁰¹



In contrast, other $\text{RO}_2^{\bullet}$ radicals have only oxidizing properties and do not react with tetranitromethane.¹⁰²

3 REACTION KINETICS OF ROS/RNS RADICALS WITH DNA

3.1 Radical Addition/Hydrogen-Atom Abstraction

3.1.1 Kinetics of DNA Damage by $\text{}^{\bullet}\text{OH}$ Radicals

The reactions of highly reactive hydroxyl radicals with DNA occur by two major mechanisms: (i) $\text{}^{\bullet}\text{OH}$ radical addition to nucleobases, which can produce base modifications and (ii) H-atom abstraction from 2-deoxyribose residues, leading to DNA strand breaks.^{54, 56–58, 103} The $\text{}^{\bullet}\text{OH}$ -addition reactions do not show any base-sequence selectivity, because they are extremely fast and occur with close to diffusion-controlled rate constants.⁵⁶ The rate constants of H-atom abstraction from the sugar residues in double-stranded DNA are typically smaller by one order of magnitude than the rate constants for $\text{}^{\bullet}\text{OH}$ -addition reactions.⁵⁷ The H-atom abstractions generate C-centered radicals of 2-deoxyribose. Further fragmentation of these intermediates results in cleavage of 2-deoxyribose and the formation of the “direct” DNA strand breaks. In DNA sequences with 5'- or 3'-ends labeled by a radioactive isotope of phosphorus (^{32}P), these strand breaks can be visualized and quantitated by denaturing polyacrylamide gel electrophoresis with a one-base resolution.⁵⁴ In turn, DNA containing oxidatively modified nucleic acid bases can be cleaved at the sites of modification by hot piperidine or by enzymatic treatment and detected as strand breaks by gel electrophoresis.⁵⁸

Hydroxyl radicals can abstract all seven H atoms of 2-deoxyribose.⁵⁴ The substitution of 2-deoxyribose hydrogen atoms by deuterium affects the yields of strand breaks in double-stranded DNA in a site-specific manner with the following preference of $\cdot\text{OH}$ radical attack: $\text{H}5' > \text{H}4' > \text{H}3' \approx \text{H}2' \approx \text{H}1'$.¹⁰⁴ This trend of reactivity correlates with the solvent accessibility of the different deoxyribose H atoms. Correlation of the solvent-exposed areas of the deoxyribose H atoms with the efficiencies of direct strand cleavage induced by $\cdot\text{OH}$ radicals provides insights into the structures of DNA and DNA–protein complexes.^{103,105} Using this method (footprinting), the binding sites of the proteins are revealed by the nucleotides that are not cleaved by $\cdot\text{OH}$ radicals because these sites are shielded by the bound proteins. Typically, $\cdot\text{OH}$ radicals are generated by the $[\text{Fe}(\text{II})(\text{EDTA})]^{2-}/\text{H}_2\text{O}_2/\text{ascorbate}$ system, which efficiently generates direct strand breaks by the base-sequence-independent cleavage of the 2-deoxyribose moieties.⁵⁵ Another method of hydroxyl radical generation for footprinting purposes involves the spontaneous homolysis of peroxyxynitrite in neutral solutions (3)¹⁰⁶ and the radiolysis of water by synchrotron radiation.¹⁰⁷ These methods generate similar DNA cleavage patterns.

Hydroxyl radical footprinting has also been successfully used to study the structural properties of nucleosome core particles, which are the basic repeating units of chromatin.¹⁰⁸ Nucleosome core particles are assembled from an octamer consisting of two copies of four histone proteins, H2A, H2B, H3, and H4, and a 147-base pair double-stranded DNA molecule. High-resolution X-ray studies of the structures from different organisms have revealed that the 147 base pairs of DNA are wrapped as 1.65 left-handed superhelical turns around the histone octamer.¹⁰⁹ In these structures, the tight interactions between the rigid framework of the histone core at 14 independent DNA binding locations induce a massive distortion of the normal DNA structure. These interactions change the accessibility of the individual DNA bases to hydroxyl radicals in the core region, which results in the appearance of strong periodic patterns of direct DNA strand cleavage patterns.^{110,111} Hydroxyl radical footprinting of the nucleosome core particles in solution has shown that distortions induced by the interactions of DNA with the histone core are not uniform, and that the

region of DNA containing approximately the central 30 base pairs of DNA has a periodicity of 10.7 bases per turn, whereas DNA segments on either side of this region have periodicities of 10.0 bases per turn.¹¹⁰

In biological systems, DNA damage by free $\cdot\text{OH}$ radicals is highly restricted. The electrophilic $\cdot\text{OH}$ radicals rapidly react with the most organic molecules, and $\cdot\text{OH}$ radicals will be efficiently intercepted before they can arrive at the DNA molecule via diffusive processes. The average distance of diffusion of randomly generated $\cdot\text{OH}$ radicals in cells is about 30 Å. Highly reactive species (e.g., $\cdot\text{OH}$ and FeO^{2+}) can be generated by metal ions bound to DNA (e.g., Fe^{2+}) because hydrogen peroxide is a relatively small, reactive, and freely diffusing molecule in biological systems.

3.1.2 Products of DNA Damage Generated by $\cdot\text{OH}$ Radicals

The highly reactive hydroxyl radicals produce oxidative modifications of 2-deoxyribose residues and all four natural DNA bases.^{54,58,112,113} The dominant reactions of $\cdot\text{OH}$ radicals with DNA bases occur via their addition to unsaturated bonds, except in the case of thymine and guanine where hydrogen-atom abstraction from the methyl group of thymine^{112,114} or from the exocyclic amino group of guanine occurs.¹¹⁵

Thymine

The addition of $\cdot\text{OH}$ radicals to the 5,6 double bond of thymine (**9**) generates 5-hydroxy and 6-hydroxy C-centered radicals, which can potentially abstract hydrogen atoms from adjacent 2-deoxyribose residues to produce direct strand breaks.⁵⁸ These C-centered radicals are short-lived because of their rapid reactions with molecular oxygen to form peroxy radicals, which further lead to diverse products that include *cis*- and *trans*-5,6-dihydroxy-5,6-dihydrothymidine (**10**), *N*¹-(2-deoxy- β -D-erythro-pentafuranosyl)-5-hydroxy-5-methylhydantoin (**11**), and *N*-(2-deoxy- β -D-erythro-pentafuranosyl)formamide (**12**) (Figure 4).¹¹² The H-atom abstraction from the methyl group results in the formation of the C-centered 5-(uridiny)methyl radical ($\text{U}\cdot\text{CH}_2$), which can potentially react with guanine bases to form intrastrand cross-links.^{116–119} The C-centered

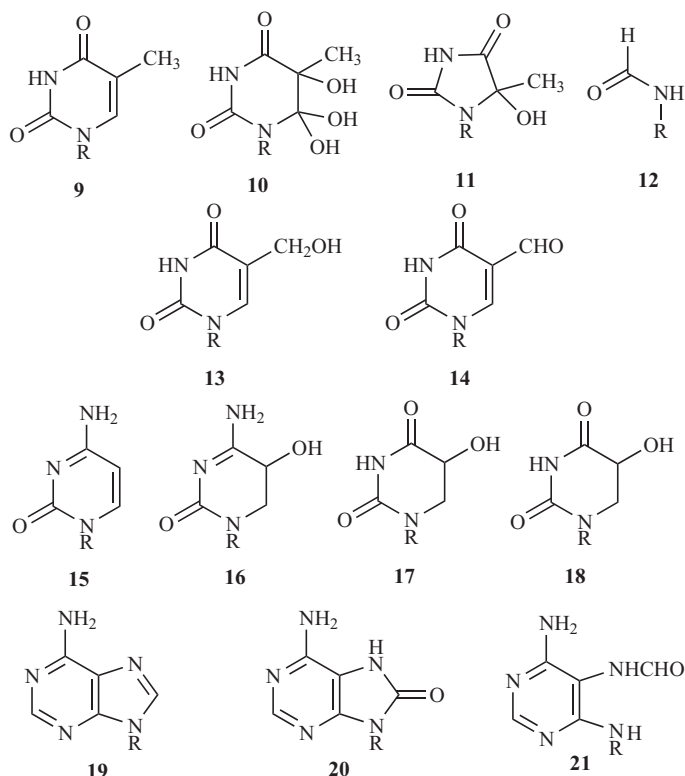


Figure 4 Oxidative products generated by the oxidation of thymine (**9**), cytosine (**15**), and adenine (**19**) by hydroxyl radicals.

U- $\cdot\text{CH}_2$ radicals rapidly react with O_2 to form peroxyl radicals, which further leads to the formation of 5-(hydroxymethyl)-2'-deoxyuridine (**13**) and 5-formyl-2'-deoxyuridine (**14**) (Figure 4).¹¹²

Cytosine

Addition of $\cdot\text{OH}$ radicals to the 5,6 double bond of cytosine (**15**) makes the exocyclic amino group of cytosine more susceptible to hydrolytic deamination.⁵⁸ This leads to a wide spectrum of oxidative modifications, which include both oxidatively modified cytosine and uracil arising from deamination reactions. These products include 5-hydroxy-5,6-dihydrocytosine (**16**), 5-hydroxy-5,6-dihydrouracil (**17**), and 5,6-dihydroxy-5,6-dihydrouracil (**18**) (Figure 4).^{57,58}

Adenine

Hydroxyl radicals generate two well-known products arising from the hydroxyl radical addition to the C8 position of adenine (**19**): 8-oxo-7,

8-dihydro-2'-deoxyadenosine (**20**) and 4,6-diamino-5-formamidopyrimidine (**21**) (Figure 4).^{58,112}

Guanine is the most easily oxidizable natural DNA base.^{120–122} The reactions of guanine bases with ROS/RNS generated at sites of inflammation are particularly important and are discussed in detail in the following sections of this article.

3.1.3 Intrastrand G–T Cross-Links Generated by $\cdot\text{OH}$ Radicals

Intrastrand cross-links, which involve a covalent bond between adjacent guanine and thymine residues on the same strand in oligonucleotides (the so-called tandem lesions), were originally discovered by Box and coworkers (Figure 5).^{116–119} These tandem lesions were generated by radiation-induced $\cdot\text{OH}$ radicals in oxygen-free solutions. The G–T intrastrand cross-links involve covalent bonds between guanine C8 and the C5 methyl group

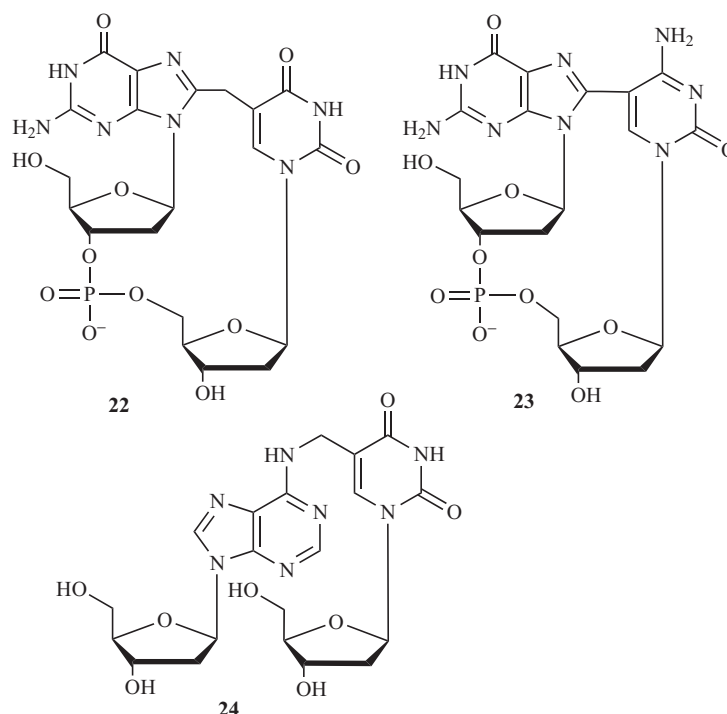


Figure 5 Tandem lesions generated in DNA by hydroxyl radicals.

of thymine or a 5-methyl group at the C5 position of cytosine. These cross-links arise from the formation of C-centered 5-(uracil)methyl radicals ($\text{U}^{\bullet}\text{CH}_2$).^{123,124} The independent generation of $\text{U}^{\bullet}\text{CH}_2$ radicals by photolysis of 5-(phenylthiomethyl)-2'-deoxyuridine also results in the formation of these G–T tandem lesions, which supports this conclusion. The $\text{U}^{\bullet}\text{CH}_2$ radicals rapidly react with O_2 , thereby suppressing the formation of the covalent bond between $\text{U}^{\bullet}\text{CH}_2$ and G–C8.¹²⁵ The formation of GC tandem lesions (**23**) generated by hydroxyl radicals has been reported by Wang and coworkers.^{126–128} The mechanism is similar: the 6-hydroxy-5,6-dihydrocytosyl radical produced by $\bullet\text{OH}$ radical adds to the C8 position of guanine and, after dehydration, the GC lesion is formed. Interestingly, O_2 does not seem to interfere with the formation of interstrand tandem lesions between adjacent A and T bases (**24**) (Figure 5).^{129,130} In order to account for this effect, it was proposed that the reaction of the $\text{U}^{\bullet}\text{CH}_2$ radicals with O_2 is reversible; this is possible since the forward bimolecular rate constant $k(\text{O}_2) = 2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, whereas the

first-order rate constant of the decomposition of the peroxy radical is $k_{-}(\text{O}_2) = 3.4 \text{ s}^{-1}$. Thus, the small transient concentrations of $\text{U}^{\bullet}\text{CH}_2$ radicals can account for the formation of such tandem lesions even in the presence of O_2 .^{124,129,130}

3.2 One-Electron Oxidation

3.2.1 Thermodynamics of DNA Oxidation

Guanine is the most easily oxidizable natural DNA base. Pulse radiolysis experiments have shown that the reduction potential of guanine neutral radicals $\text{dG}(-\text{H})^{\bullet}$ (calculated from equilibria with reference radicals of known potentials) is equal to $E_7[\text{dG}(-\text{H})^{\bullet}, \text{H}^+/\text{dG}] = 1.29 \text{ V}$ versus NHE at pH 7.¹³¹ The values of E_7 for the other three nucleosides (N) increase as follows: $\text{dG} < \text{dA} < \text{dC} \sim \text{dT}$ (Table 2). The values of the standard reduction potentials^{131,132} $E^{\circ}(\text{dN}^{+}/\text{dN})$ calculated from the experimental plots of E_{pH} versus pH are systematically higher than the E_7 values and correlate

Table 2 Reduction potentials (vs NHE) of nucleoside radicals.

Nucleoside	E_7^a (V)	$E^o,^b$ (V)	$E_{CV}^o,^c$ (V)
dG	1.29	1.58	1.49
dA	1.42	2.03	1.96
dT	~1.6	—	2.11
dC	~1.7	—	2.14

^aObtained for pairs dN(-H)[•], H/dN in aqueous solutions (pH 7) by pulse radiolysis methods.^{131,132}

^bCalculated from the dependence of E_{pH} versus pH.^{131,132}

^cObtained from potentials measured by cyclic voltammetry in acetonitrile.¹³³

with the values obtained by cyclic voltammetry in acetonitrile.¹³³ Thus, the thermodynamic characteristics of one-electron oxidation of nucleic acid bases are consistent with the preferential oxidation of guanine bases by one-electron mechanisms.

3.2.2 Effects of Base Sequence on the One-Electron Oxidation of Guanine

In double-stranded DNA, the one-electron oxidation of G-bases depends on the base-sequence context. For example, oxidatively generated guanine damage is more abundant at the 5'-G in 5'-...GG... sequences and the first two 5'-guanines in the 5'-...GGG... sequences than in isolated guanines, that is, at guanines that are not flanked by other guanines. These effects are attributed to the redistribution of guanine radicals among the contiguous guanine bases by the hole hopping mechanism that occurs after the initial electron abstraction steps (hole injection); it is further assumed that the subsequent chemical reactions that lead to product formation at a particular guanine in runs of GG or GGG depend on the probability that the hole is localized at that guanine (see **Charge Transfer in DNA**). These mechanisms can successfully account for the sequence-dependent distributions of guanine damage initiated by one-electron oxidants generated by the photosensitization of metal complexes,^{134,135} anthraquinones,^{136,137} naphthalimides,¹³⁸ riboflavin,^{139,140} 4'-pivaloyl derivatives,^{141,142} cyanobenzoyl- and cyanobenzophenone-substituted 2'-deoxyuridine,^{143,144} and other chemical one-electron oxidants.^{145,146} Saito and coworkers demonstrated that the probability of formation of oxidatively generated guanine damage within runs of contiguous guanines varies according to 5'-G < 5'-GG <

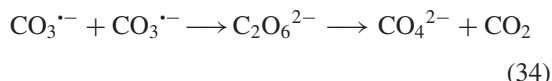
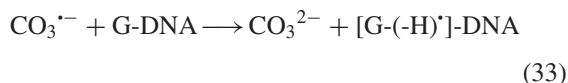
5'-GGG. This trend is consistent with the calculated gas-phase ionization potentials of each guanine in the case of 5'-G (flanked on both sides by bases other than guanine), 5'-GG, and 5'-GGG sequence contexts.^{139,140,147–149}

3.2.3 Reaction Kinetics of the Oxidation of Guanine by Carbonate Radicals

In our laboratory, we have extensively used laser kinetic spectroscopy methods to monitor the kinetics of one-electron oxidation of guanine in DNA by CO₃^{•-} radicals.^{77,90,92,94,150} In typical experiments, we use the transient absorbance properties of radical intermediates. The CO₃^{•-} radical has a characteristic absorption spectrum with a maximum at 600 nm. In the presence of guanine, either in the form of a nucleoside or incorporated in oligonucleotides, the decay of this band is correlated with the rise of another narrow absorption band with a maximum near 315 nm. This band is characteristic of the guanine radical cation G^{•+} or the guanine neutral radical G(-H)[•] species, which have similar absorption spectra¹⁵¹ and which are generated by the oxidation of G by carbonate radical anions. However, in double-stranded DNA, deprotonation of the G^{•+} radical cations occurs on submicrosecond timescales,^{152,153} while the kinetics of oxidation of G in DNA by CO₃^{•-} radicals occurs on millisecond time scales. Thus, the 315-nm absorbing species in the microsecond to millisecond time range can be predominantly assigned to the neutral G(-H)[•] radicals.^{77,90,92,94,150}

The CO₃^{•-}-mediated oxidation of guanines in single-stranded and double-stranded oligonucleotides 20–35 nucleotides in length containing single G (flanked by bases other than G) and guanines grouped as contiguous GG and GGG sequences was monitored by transient absorption laser kinetic spectroscopy.^{77,90,92,94,150,154} In these experiments, the decay of CO₃^{•-} radicals occurs via two competitive reactions: (i) oxidation of G-bases in DNA associated with the growth of the G(-H)[•] absorption band at 315 nm and (ii) the bimolecular recombination of CO₃^{•-} radicals

$$(k_r = 1.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1})^{77}:$$



The rate constants of G-base oxidation (k_g) in (33) were obtained by fitting the integrated forms of the kinetic equation describing the decay of $\text{CO}_3^{\cdot-}$ radicals to the experimental kinetic decay curves of $\text{CO}_3^{\cdot-}$ recorded at different concentrations of double-stranded oligonucleotides and $\text{CO}_3^{\cdot-}$ radicals:

$$-\text{d}[\text{CO}_3^{\cdot-}]/\text{d}t = k_g [\text{G-DNA}] [\text{CO}_3^{\cdot-}] + 2k_r [\text{CO}_3^{\cdot-}]^2 \quad (35)$$

Regardless of the number or distributions of guanines in these double-stranded and single-stranded oligonucleotides, the rate constants of G-oxidation by $\text{CO}_3^{\cdot-}$ radicals thus obtained exhibited only small variations within the narrow range of $k_g = (1.5 - 3.0) \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. These results show that solvent exposure of guanine G-sites, which in duplex **1d** with two G bases near the duplex ends is greater than in duplex **2d** with two internal G's, does not strongly control the initial rates of oxidation of guanine by $\text{CO}_3^{\cdot-}$ radicals (Figure 6). Thus, the one-electron oxidation of G-bases in DNA by $\text{CO}_3^{\cdot-}$ radicals significantly differs from the hydrogen-atom abstraction from 2-deoxyribose residues by $\cdot\text{OH}$ radicals, where solvent exposure controls the reaction yield.¹⁰⁴ The rate constant k_g of guanine oxidation by $\text{CO}_3^{\cdot-}$ radicals exhibits a very weak temperature dependence with activation energies of $7 \pm 3 \text{ kJ mol}^{-1}$. The lack of dependence of the rate constant on sequence context and the small activation energy indicates that the one-electron oxidation of guanine in DNA by $\text{CO}_3^{\cdot-}$ radicals occurs via an inner-sphere mechanism of electron transfer,^{94,150} which was proposed earlier for the one-electron oxidation of diverse organic molecules such as ascorbate, tryptophan, cysteine, and methionine by $\text{CO}_3^{\cdot-}$ radicals.¹⁵⁵ The mechanisms of outer/inner sphere electron transfer reactions in chemistry and biology have been extensively discussed by Marcus and Sutin.¹⁵⁶

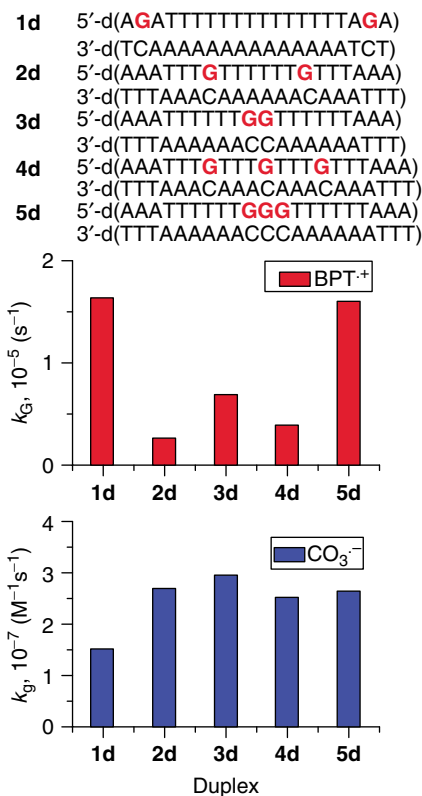


Figure 6 The net rate constants of guanine oxidation in DNA duplexes by B[a]PT⁺ radicals (k_g) and bimolecular rate constants of DNA oxidation by $\text{CO}_3^{\cdot-}$ radicals (k_g). [Reprinted with permission from Ref. 94. Copyright 2008 American Chemical Society.]

3.2.4 Comparison with Aromatic Radical Cations

An outer-sphere electron transfer mechanism is expected in one-electron abstraction reactions from guanine by rigid aromatic radical cations.^{157–159} Indeed, the rate constants of oxidation of guanines in DNA by the pyrene derivative 7,8,9,10-tetrahydroxytetrahydrobenzo[a]pyrene (B[a]PT), a bulky and rigid aromatic molecule, do depend on the base-sequence context,^{94,150} in agreement with the Saito model.^{139,140,147} In these experiments, the selective excitation of the pyrenyl residue of B[a]PT by intense 355-nm nanosecond laser pulses yields free-radical products by a two-photon mechanism¹⁶⁰:





In air-equilibrated solutions, the hydrated electrons are rapidly trapped by molecular oxygen (31), while the BPT^{*+} radicals can oxidize guanine in DNA. Reactions of one-electron oxidation mediated by BPT^{*+} radicals can be monitored in real time by laser flash photolysis because these radicals have a characteristic absorption band at 455 nm.^{160,161}

The $\text{B}[a]\text{PT}$ molecules form noncovalent intercalation complexes with double-stranded DNA¹⁶² and with oligonucleotides.¹⁶³ The photoionization of $\text{B}[a]\text{PT}$ can occur either in solution or within a DNA complex. The fractions of $\text{B}[a]\text{PT}$ molecules in DNA complexes (ϕ) can be determined by examining the fluorescence decay profiles¹⁶⁴ because the fluorescence of BPT is strongly quenched by neighboring bases in DNA complexes.^{162,163} In 100-mM aqueous solutions of double-stranded oligonucleotides, under conditions where the concentrations of $[\text{BPT}] \ll [\text{DNA nucleotides}]$, most of the BPT molecules are bound to the DNA ($\phi = 0.8\text{--}0.9$).⁹⁴ In such solutions, the decay of the $\text{B}[a]\text{PT}^{*+}$ radicals exhibits a non-exponential decay profile and can be described by a sum of two-exponentials with first-order decay rate constants k_1 and k_2 and relative amplitudes a_1 and a_2 . The analysis of these decay profiles can be simplified by using the mean rate constant of $\text{B}[a]\text{PT}^{*+}$ radical decay: $k_a = a_1k_1 + a_2k_2$. A net overall rate constant of oxidation of guanines (k_G) in a given DNA duplex by $\text{B}[a]\text{PT}^{*+}$ radicals has been defined as follows: $k_G = k_a - k_0$, where k_0 is the rate constant of the decay of $\text{B}[a]\text{PT}^{*+}$ in duplex **6d** without any guanine bases.

The difference between the effects of base-sequence context on the rate constants of guanine oxidation by $\text{B}[a]\text{PT}^{*+}$ (k_G) and $\text{CO}_3^{\cdot-}$ (k_g) radicals in duplexes **1d–5d** is of significant interest for understanding the mechanisms of one-electron oxidation of guanine by different oxidants⁹⁴ (Figure 6). The value of k_G strongly depends on base-sequence context. For instance, the value of k_G for duplex **3d** (GG sequence) is larger by a factor of ~ 2.6 than in the case of duplex **2d** which has two nonadjacent guanines. In the duplex **5d**, which has a single contiguous GGG sequence, the value of k_G is larger by a factor of ~ 4.1 than in the case of duplex **4d** with three noncontiguous guanines. The value of k_G for duplex **4d**, which

has three guanines separated from one another, is about 20% greater than for duplex **2d** which has two noncontiguous guanines. These results are consistent with the Saito model,^{139,140,147–149,165} which predicts that guanines in contiguous runs of two or three guanines are more easily oxidized by one-electron oxidation mechanisms than isolated guanines in double-stranded DNA.

These rules, however, are not applicable if the guanines are positioned at or near the ends of oligonucleotide duplexes. For example, the k_G value for the sequence **1d** with isolated guanines near the ends in an AGA sequence contexts is similar to that in the GGG sequence context in the inner region of duplex **5d**. According to Saito *et al.*,¹³⁹ the oxidation of guanine in an AGA sequence context in the inner region of the duplexes is ~ 7 times smaller than that in a GGG sequence context.¹³⁹ The unexpectedly high value of k_G for guanine in the AGA sequence context is attributed to end effects rather than to sequence effects. Similarly, the k_G value for G in an isolated TGT sequences in duplex **4d** is 4 times smaller than that in the GGG sequence of duplex **5d**, which is in agreement with the Saito model. In contrast to the results obtained with $\text{B}[a]\text{PT}^{*+}$ radicals as the one-electron oxidants of guanine (Figure 6), the rate constants of the G-oxidation by $\text{CO}_3^{\cdot-}$ radicals in the same duplexes (**2d–5d**) with single G and contiguous GG and GGG sequences are close to each other (Figure 6).

The different base-sequence dependence of k_g (or k_G) in sequences **2d–5d** when $\text{CO}_3^{\cdot-}$ or $\text{B}[a]\text{PT}^{*+}$ radicals are used as the one-electron oxidants of guanine can be accounted for by considering the Marcus relationship describing the dependence of the rate constant on the free energy (ΔG^0) and reorganization energy (λ) of electron transfer¹⁵⁶:

$$k_{\text{el}} = (\lambda RT)^{-1/2} \exp[-(\Delta G^0 + \lambda)^2 / 4\lambda RT] \quad (38)$$

The $\text{CO}_3^{\cdot-}/\text{CO}_3^{2-}$ redox couple is characterized by a very small self-exchange rate constant ($k \sim 0.4 \text{ M}^{-1} \text{ s}^{-1}$), and the internal reorganization energy λ is therefore relatively high.¹⁶⁶ Whenever $\lambda > -\Delta G^0$, the electron transfer rate constant becomes less sensitive or even insensitive to small differences in ΔG^0 , as is the case for the G, GG, and GGG sequence contexts, thus explaining why the differences in k_g for $\text{CO}_3^{\cdot-}$ radicals is small. In the case of rigid aromatic radical cations, $\lambda < -\Delta G^0$ and k_G is now sensitive to changes in

the ΔG° values (Figure 6). Therefore, the k_G values shown in Figure 6 are consistent with the Saito model.^{139,140,147–149,165}

On the other hand, the high value of k_G (B[a]PT^{•+}) for duplex **1d** (Figure 6) is not consistent with the Saito model. This effect is attributed to the fraying of the ends of the oligonucleotide duplexes that enhances exposure of G near the ends to the aqueous solvent.¹⁶⁷ Increasing the solvent exposure of guanine to water is associated with the enhanced hydration of guanines, which is known to lower the reduction potentials of the guanine radicals.^{168–173} Thus, the lower ionization potential of guanine (or change in ΔG° in (38)) gives rise to a higher rate constant of oxidation at the ends of duplexes than in the inner regions of the duplexes.

In summary, the initial oxidative one-electron transfer reactions between guanine and different oxidants can be either sensitive or insensitive to base-sequence context, and can also depend on the exposure of the guanines in double-stranded DNA to the aqueous solvent environment.

3.2.5 Effects of Oxidant Charge and Solvent Exposure on the Distributions of Guanine Lesions in DNA

In Section 3.2.4, we focused on values of the rate constants of the initial one-electron transfer rates from guanine in DNA to different oxidants and their dependence on base-sequence context. Most of the experimental literature on this subject is based on measurements of the end products of this initial step, mostly hot alkali-labile lesions. However, as discussed elsewhere,^{94,150} the base-sequence dependence of the initial electron transfer step and the sequence dependence of the final product distributions are not necessarily the same. While much more research will be needed to resolve this issue in a satisfactory manner, it is of interest to review the presently available information on this subject.

A series of one-electron oxidants including a negatively charged $\text{CO}_3^{\bullet-}$ radical,¹⁷⁴ a neutral photoexcited riboflavin,¹⁷⁵ and a positively charged B[a]PT^{•+} radical cation¹⁶⁰ were utilized to explore the effects of charge and solvent exposure on the localization of the final oxidatively generated guanine damage at different sites in DNA.^{94,150} The

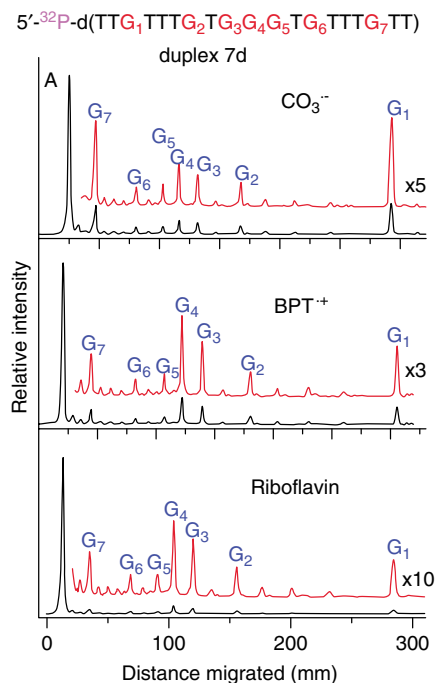


Figure 7 Distributions of alkali-labile lesions generated by $\text{CO}_3^{\bullet-}$ and B[a]PT^{•+} radicals, and by photoexcited riboflavin, in a DNA duplex with noncontiguous guanines (G₁, G₂, G₆, G₇) and a sequence of three contiguous guanines (G₃, G₄, G₅) in the central region of the duplex. The complementary strand is not shown. [Reprinted with permission from Ref. 94. Copyright 2008 American Chemical Society.]

duplex **7d** was designed for this purpose (Figure 7); it contains two single noncontiguous guanines near each of the two ends of the duplexes (G₁, G₇) and two single guanines in the interior of the duplexes (G₂, G₆) separated by single T bases from the central contiguous G₃G₄G₅ sequence (Figure 7). The distribution of oxidatively generated damage in this sequence, determined by the standard hot-alkali high-resolution gel electrophoresis method,⁹⁴ is also depicted in Figure 7. In the case of oxidation by $\text{CO}_3^{\bullet-}$ radicals, the extent of cleavage is significantly higher at the guanines positioned near the ends of the duplexes (G₁ and G₇) than cleavage at the other single guanines in the interior of the duplexes (G₂ and G₆) as well as at the contiguous G₃G₄G₅ guanines. The preponderance of damage at the ends of the duplexes is consistent with the higher rate constant of one-electron oxidation of guanine (Figure 6). The extent of damage at the inner guanines is consistently smaller than the

damage at the ends of the duplexes. In contrast, the oxidation of the contiguous G₃G₄G₅ sequences is most efficient when the B[a]PT^{•+} radicals or riboflavin are employed as the oxidants (Figure 7). The cleavage efficiencies are the highest at G₄ in the 5'...TG₃G₄G₅T... sequence context in both cases. It is noteworthy that, in the case of the initial oxidation by the CO₃^{•-} radicals, the relative distributions of damage among the individual bases in the 5'...TG₃G₄G₅T... sequence and the lower damage at G₂ and G₆ than at G₄ qualitatively resemble the distributions of damage in the case of B[a]PT^{•+} and riboflavin. Thus, while the distribution of the oxidized hot alkali-labile guanines is in agreement with the Saito model,^{139,140,147–149,165} the rate constant of one-electron oxidation by CO₃^{•-} of guanine in duplex **7d** is not consistent with the predictions of this model.

3.2.6 Redistribution and Localization of Holes at Guanine Sites

This apparent discrepancy can be accounted for by considering the distribution of holes among contiguous guanines once holes are injected into the

duplex. These holes can migrate from guanine to guanine within the duplex across bridging T bases as long as the donor and acceptor are close enough to each other.^{176–178} Ultimately, the distributions of holes among the different guanines in a duplex equilibrate at the different sites according to the relative redox potentials at each individual guanine. Thus, in contiguous ...GG... or ...GGG... sequences^{139,140,147–149,165} and the solvent-exposed guanines at the ends of the duplexes, the holes will tend to have higher probabilities of localization at the sites characterized by the lowest values of ΔG° .^{94,150} When some of the guanines are too far apart in the duplex for efficient transfer to occur, hole equilibration occurs according to the same principle in contiguous ...GG... and ...GGG... sequences. This redistribution of the hole density apparently occurs before the subsequent chemical reactions take place, and thus the ultimate product distributions are expected to mirror the distributions of hole densities.^{94,150}

These effects on reactivity and cleavage patterns of contiguous guanines were further evaluated in different duplexes within the inner regions of duplexes **8d**, **9d**, and **10d** (Figure 8). The inner ...GG... or ...GGG... regions were positioned further from the ends than in the case of duplex **7d**

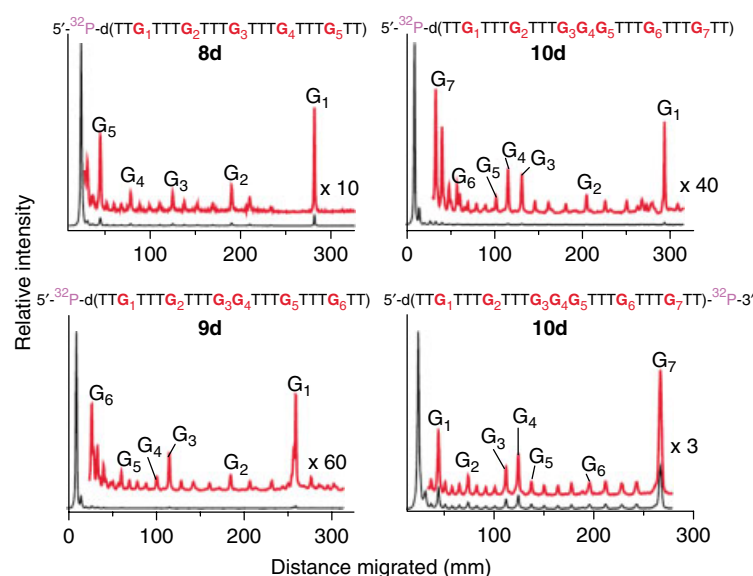


Figure 8 Distributions of alkali-labile lesions generated by CO₃^{•-} radicals in different DNA duplexes (the complementary strands are not shown) with noncontiguous guanines G, and grouped as contiguous GG and GGG sequences. [Reprinted with permission from Ref. 94. Copyright 2008 American Chemical Society.]

(Figure 7) to ensure that end effects would not influence the distributions of damaged guanine bases in these longer duplex sequences. The levels of cleavage at all noncontiguous guanines G₂, G₃, and G₄ in **8d** are similar, thus indicating that end effects can be neglected in the observed product distributions at these guanines (Figure 8). The cleavage efficiencies are higher at the 5'-side guanine G₃ in the 5'...TG₃G₄T... sequence context of **9d** and at the central guanine G₄ in the 5'...TG₃G₄G₅T... sequence context of **10d** (Figure 8). In all cases, the least damage is observed at the 3'-side guanines. In the 5'...TG₃G₄G₅T... sequence context of duplex **10d**, the order of reactivities is G₄ > G₃ > G₅ (Figure 8). Since the oligonucleotide strands were ³²P-end labeled at the 5'-side in these experiments, care was taken to limit the fraction of damaged strands to no more than 20% in any given experiment. Otherwise, the distributions closer to the 3'-ends could be different from the true values whenever there is more than one damaged site per oligonucleotide sequence. Indeed, the cleavage patterns in duplexes **10d**, with the guanine-containing strand ³²P-end-labeled either at its 5'-end or at its 3'-end, were similar, thus ensuring that the cleavage patterns within the inner contiguous sequences shown in Figure 8 were not distorted. In summary, in runs of contiguous guanines, the distribution of holes at the different sites reflects the redox potentials of the individual guanines.^{139,140,147–149,165} These distributions are reflected in the patterns of oxidatively damaged oligonucleotides, revealed by treatments of the oxidatively damaged oligonucleotides with hot alkali solutions. Similar considerations explain the higher levels of damage observed for isolated guanines near the ends of the duplexes, which is explained by their greater exposure to the aqueous solvent and thus the lowering of the redox potential of these hydrated guanines.^{94,150} It follows that a sequence-dependent product distribution will be observed even if the initial electron transfer step from a guanine to a solution-borne oxidant itself is not sequence-dependent. After the initial hole injection, there is a redistribution of the hole among the available guanines in contiguous G sequences.^{94,150} Thus, hole injection and hole distribution events are not necessarily coupled to each other since the distribution of chemical end products primarily reflect the hole distribution (after sufficient time has elapsed for equilibration to occur) rather than hole injection.

However, this conclusion depends on the assumption that the chemical step, after the initial creation of the hole, is itself independent of base-sequence context. This is an assumption that needs to be verified experimentally.

3.2.7 Monitoring Hole Migration

The kinetics of electron transfer reactions in DNA hairpins containing a stilbenedicarboxamide photosensitizer was studied extensively by Lewis and coworkers who determined the rate constants of forward- and back-transfer from single G to a GG doublet and to a GGG triplet.^{178,179} It was found that the free energy values for these reversible hole transfer reactions are approximately -0.052 and -0.077 V, respectively. Using an electrochemical method,¹⁸⁰ Sistare *et al.* determined the rate constants of oxidation of isolated guanines versus 5'-guanines in a GG sequence context. In our own experiments, we have employed hole injection techniques, which are based on laser pulse-induced two-photon photoionization of the DNA base analog 2-aminopurine (2AP) that can be site-specifically inserted into any DNA sequence using automated DNA synthesis methods.^{176,181–185} The 2AP residues have a broad absorption maximum at 305 nm, well outside the DNA absorption band, and can be selectively excited using 308-nm intense nanosecond XeCl excimer laser pulses. These pulses induce efficient and selective photoionization of 2AP residues, thus allowing for the injection of holes into any DNA sequence of interest. The absorption of the first photon results in the formation of the 2AP singlet excited state (¹2AP) and the absorption of the second photon causes photoionization according to the following scheme:



The energy of two 308-nm photons is $E = 7.77$ eV (the sum of the energy of the first singlet excited state of 2AP (¹2AP) is $\Delta E_{00} = 3.74$ eV, and the energy of the 308-nm photon $E = 4.03$ eV), thus providing sufficient energy for the efficient photoionization of 2AP.¹⁸¹ The lifetime of the singlet excited state of 2-aminopurine (¹2AP)

in solution is ~ 10 ns and is sufficiently long for absorption of the second photon to occur within the same excimer laser pulse (halfwidth ~ 12 ns) as long as this pulse is sufficiently intense. In double-stranded DNA, the ^12AP lifetime is severely reduced owing to quenching by neighboring nucleobases.¹⁸⁶ Thus, the efficiency of two-photon photoionization of 2AP is significantly reduced in double-stranded DNA. Nevertheless, the efficiency of the two-photon ionization of 2AP in DNA is sufficient, and we have used this method extensively for injecting holes into double- and single-stranded oligonucleotides.^{176,181–185} Although the photoionization step initially produces the $2\text{AP}^{+\bullet}$ radical cation, it rapidly deprotonates so that the oxidizing species in most of these experiments was the $2\text{AP}(\text{-H})^\bullet$ neutral radical.¹⁸⁷

The kinetics of electron transfer phenomena in DNA when both the donor and acceptor are embedded within the same molecule are entirely different than in the case of solution-borne oxidants. In the latter case, the oxidant and DNA diffuse freely and encounter each other before the electron transfer reaction resulting in hole injection into the DNA molecule can occur. An example of intramolecular hole injection processes is the one-electron oxidation of guanine by $2\text{AP}(\text{-H})^\bullet$ radicals, both site-specifically positioned within a DNA duplex.¹⁷⁶ The kinetics of oxidation of G by $2\text{AP}(\text{-H})^\bullet$ radicals were found to follow first-order kinetics. The magnitudes of the electron transfer rate constant in DNA depend on the number of nucleobases positioned between the electron donor and the acceptor.^{176,188–190} The dependence of the rate constant k_{et} of guanine oxidation by the $2\text{AP}(\text{-H})^\bullet$ radicals on the distance r between the donor and acceptor (which is proportional to the number of intervening bases) is experimentally described by the following equation:

$$k_{\text{et}} = k^0 \exp(-\beta r) \quad (41)$$

where β is an attenuation parameter. Plots of the linearized form of (41) are shown in Figure 9. In the case of intervening thymines, the parameter $\beta = 0.4 \text{ \AA}^{-1}$, while in the case of intervening adenines $\beta = 0.12 \text{ \AA}^{-1}$ in double-stranded DNA.^{176,188–190} The shallow distance dependence of hole transfer rates through the adenine tracts is consistent with the data of Majima and coworkers,^{191,192} also obtained by laser kinetic spectroscopy. The base-sequence

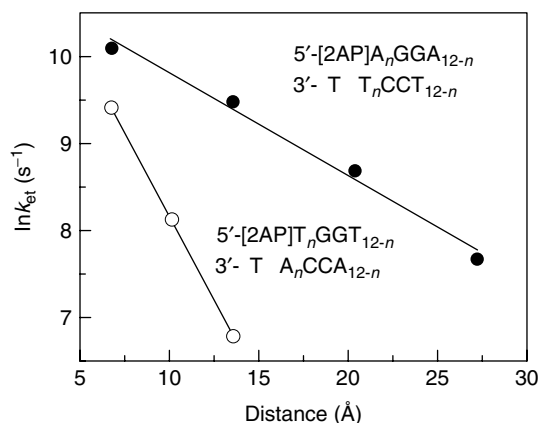


Figure 9 Distance dependence of the one-electron transfer rate constants from guanine bases (G) to neutral $2\text{AP}(\text{-H})^\bullet$ radicals in double-stranded oligonucleotide duplexes separated by different numbers of bridging A or T bases. [Reproduced from Ref. 190. © Wiley-VCH Verlag GmbH & Co. KGaA, 2009.]

effects on the distance dependence of hole transfer in DNA and the effects of intervening bases have been the subject of extensive theoretical investigations and associated with two distinct mechanisms of hole transfer: (i) a two-center unistep superexchange induced hole transfer and (ii) a multistep hole transfer mechanism via hole hopping.^{193–195}

3.3 Reactions of Free Radicals in DNA: End Products of Guanine Reactions Initiated by One-Electron Oxidation

3.3.1 Cation and Neutral Forms of Guanine Radicals

The primary product of one-electron abstraction from guanine (**25**) is the guanine radical cation $\text{G}^{+\bullet}$ (**26**) (Figure 10). The spectrum of $\text{G}^{+\bullet}$ exhibits a sharp absorption band with a maximum at 312 nm and two broad, less intense bands near 385 and 510 nm. The spectrum of the conjugate neutral form $\text{G}(\text{-H})^\bullet$ (**27**) is very similar but differs from the spectrum of $\text{G}^{+\bullet}$ by a weak broad absorption in the spectral range 610–750 nm. Using this spectral difference, Candeias and Steenken have shown that the free nucleoside radical cation $\text{dG}^{+\bullet}$ is a weak acid with $\text{p}K_{\text{a}} = 3.9$.¹⁵¹ The deprotonation

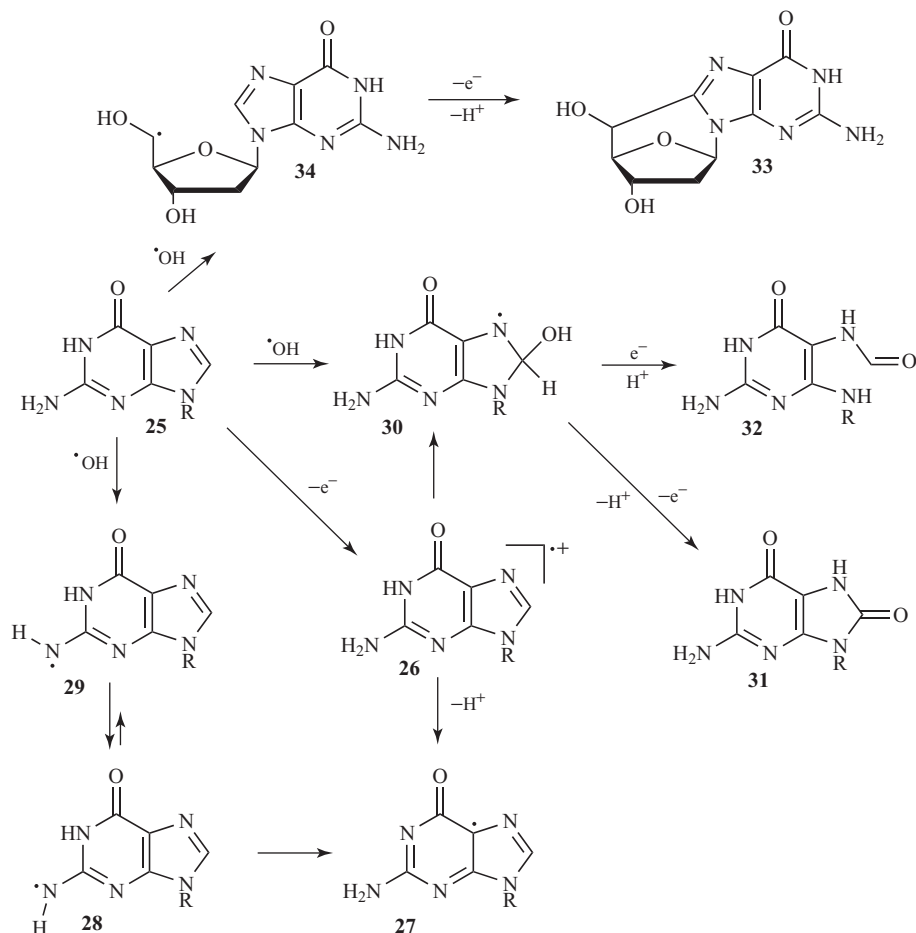


Figure 10 Guanine radicals generated by one-electron oxidation or by the addition of hydroxyl radicals. [Adapted from Refs 151, 205, 206, 265.]

of $\text{G}^{+\bullet}$ is associated with a buildup of the $\text{G}(\text{H})^{\bullet}$ radical which is characterized by an absorption band at 625 nm. The kinetics of this band has been determined by pulse radiolysis experiments of the Kobayashi group: the deprotonation rate constant for the free nucleoside $\text{dG}^{+\bullet}$ was found to be equal to $1.8 \times 10^7 \text{ s}^{-1}$.¹⁵² In double-stranded DNA, depending on the position within a DNA strand, the rate constant of deprotonation ($\geq 3 \times 10^6 \text{ s}^{-1}$) is smaller than that of free $\text{dG}^{+\bullet}$.^{152,153}

The deprotonation of $\text{G}^{+\bullet}$ has been considered in terms of a release of the N1 proton and the formation of the $\text{G}(\text{N1-H})^{\bullet}$ tautomer (27).⁵⁶ On the basis of electron paramagnetic resonance (EPR) studies in aqueous solutions ($\text{pH} \leq 3$) at room temperature, coupled with a theoretical study, it was

concluded that the $\text{G}^{+\bullet}$ radical is protonated at N1 and is indeed deprotonated by the loss of the proton at N1 to form the $\text{G}(\text{N1-H})^{\bullet}$ neutral radical.¹⁹⁹ A similar mechanism probably applies at $\text{pH} > 3$ as well. The radical cation of 1-Me-dG does not have a proton at the N-1 position and has a pK_a of 4.7; in this case, deprotonation occurs via release of a proton from the exocyclic (N^2) amino group, which results in the formation of the $\text{G}(\text{N}^2\text{-H})^{\bullet}$ neutral radical. Thus, both the N1 and N^2 sites may, in principle, be deprotonated in the guanine neutral radical.¹⁵¹ On the basis of UV-visible spectroscopy in combination with EPR studies in frozen D_2O solutions at low temperatures, the $\text{G}(\text{N1-H})^{\bullet}$ (27) neutral radical form is dominant.²⁰⁰ In contrast, EPR/ENDOR (electron nuclear double resonance)

studies at low temperatures have shown that G(-H)[•] radicals generated by ionizing radiation in single crystals of 2'-deoxyguanosine 5'-monophosphate are present mostly in the G(N²-H)[•] form (**28**, **29**).^{201,202} Extensive density functional theory (DFT) calculations based on various tautomeric forms of G(-H)[•] suggest that these two radical forms that are close to one another in energy may coexist.^{200,203,204} In the gas phase, the *syn*-G(N²-H)[•] tautomer (**28**) is more stable than the anti conformer (**29**), and the *syn*-G(N²-H)[•] tautomer is more stable than the G(N1-H)[•] tautomer by ~4.5 kcal mol⁻¹. However, a similar analysis for the aqueous solution case suggests that the hydration of G(-H)[•] may reverse this order, with the G(N1-H)[•] being more stable than *syn*-G(N²-H)[•] by ~3.3 kcal mol⁻¹.²⁰⁰

The addition of [•]OH radicals to guanine generates isomeric radicals (Figure 10) which are not identical to the G^{•+}/G(-H)[•] species produced by typical one-electron oxidants, such as SO₃^{•-}, Br₂^{•-}, and CO₃^{•-}.^{90,92,151,205} The pulse radiolysis studies of the O'Neill^{206,207} and Steenken^{56,196} groups showed that the OH adducts of guanine resemble both reducing and oxidizing radicals. The main adducts formed in 60–70% yields are oxidizing radicals, which undergo a fast dehydration to form G(-H)[•] radicals. The structure of the oxidizing radicals have been assigned as 4-OH-G[•], which are derived from the addition of [•]OH radicals to the C4 position of guanine.¹⁹⁶ Recently, Chatgililoglu and coworkers revisited the addition of [•]OH radicals to guanine and reported that the oxidizing radicals are formed by the abstraction of a hydrogen atom from the exocyclic NH₂ group of guanine to form the G(N²-H)[•] tautomers (**28**, **29**) (Figure 10).¹¹⁵ They found that, at room temperature, these tautomers are unstable and rapidly transform to the G(N1-H)[•] tautomer (**27**) with the rate constant of ~2 × 10⁴ s⁻¹.¹⁹⁷ The reducing radicals, identified as the OH adduct at the C8 position of guanine (**30**), are formed with a yield of 17%.¹⁹⁶ These radicals rapidly react with oxygen (*k* ~ 4 × 10⁹ M⁻¹ s⁻¹) and other oxidants such as methylviologen, Fe(III)(CN)₆³⁻, and 1,4-benzoquinone (BQ) to form 8-oxo-7,8-dihydroguanine (**31**) (Figure 10).^{196,208} In the absence of oxygen, the 8-OH-G[•] radicals undergo a rapid ring-opening reaction. A one-electron reduction of the ring-opened product of the 8-OH-G[•] radicals results in the formation of the well-known guanine lesion

2,6-diamino-4-hydroxy-5-formamidopyrimidine (**32**), known as FapyG, as shown in Figure 10.¹⁹⁶

The alternative pathway of [•]OH radical attack is hydrogen-atom abstraction from the 2-deoxyribose moiety, which leads to the formation of the 5',8-cyclo-2'-deoxyguanosine (**33**) lesions.^{209–213} Abstraction of the H atom from C5'H with the formation of the C5'-hydroxymethyl radical (**34**) is followed by intramolecular cyclization via addition of this radical to the C8 position of guanine. The cyclization product is finally oxidized by O₂, thus yielding the 5',8-cyclo-2'-deoxyguanosine lesions (**33**).

3.3.2 Nucleophilic Addition Reactions with Guanine Radicals

As we have already discussed, the products of the one-electron oxidation of guanine bases in DNA are the G^{•+} radical cation and its deprotonated form the neutral G(-H)[•] radical.¹³¹ Both are oxidizing species that do not react with observable rate constants with molecular oxygen.^{56,77,90,92,151} The decay modes of these radical species involve reactions with nucleophiles and combination reactions with other free radicals.^{121,122,214} The nucleophilic addition of water to the G^{•+} radicals cations generates the reducing 8-OH-G[•] radicals (**30**).^{121,122} This radical is also formed by the direct addition of [•]OH radicals to the C8 position of guanine (Figure 10).¹⁹⁶ The one-electron oxidation of 8-OH-G[•] radicals by weak oxidants (O₂, Fe³⁺) generates the widely used biomarker of oxidative stress, the 8-oxoG lesion (**31**). The nucleophilic addition mechanism has been confirmed by the one-electron oxidation of guanine induced by photoexcited riboflavin in H₂¹⁸O solutions.²¹⁵ In agreement with the nucleophilic addition mechanism of water to G^{•+} radicals, the C8-oxygen atom in 8-oxoG was the ¹⁸O-isotope derived from H₂¹⁸O.

Our own experiments have shown that nucleophilic addition reactions of guanine radicals are base-sequence-dependent. When oligonucleotides with the 5'-...GCT... sequence context are (**35**) exposed to one-electron oxidants, a novel intrastrand cross-linked product (**36**) involving a covalent bond between guanine and thymine (Figure 11) was discovered.⁸⁹ This lesion was excised from the oligonucleotide by enzymatic digestion with

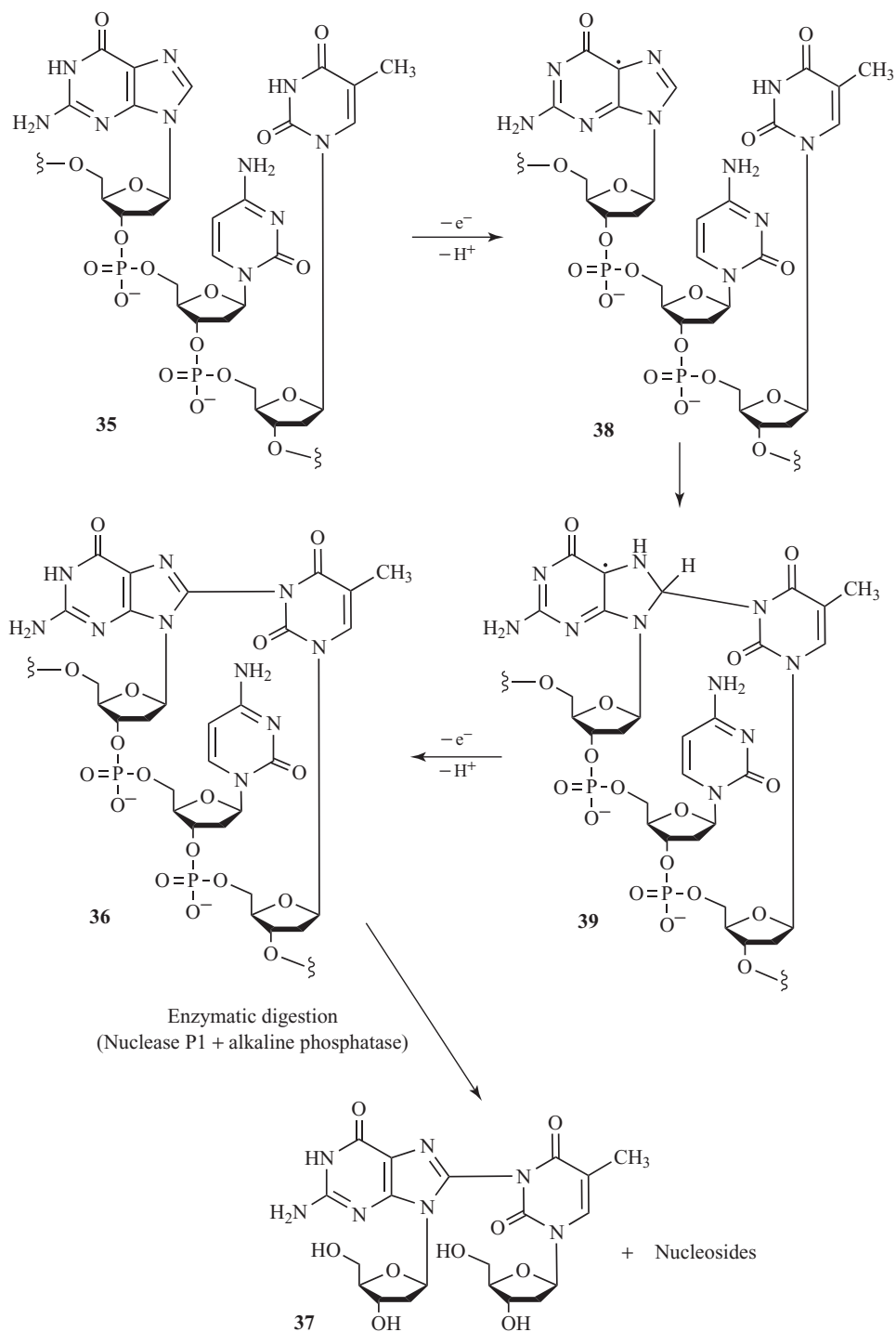


Figure 11 Intrastrand G*(C8)–(N3)T* cross-links generated by the one-electron oxidation of guanine in 5'-GCT sequences. [Adapted from Refs 89 and 91.]

nuclease P1 and alkaline phosphatase. The mass and identity of the lesion were identified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis as the dinucleoside d(G^{*}-T^{*}) (37) in which the G(C8) and T(N3) positions are linked covalently. By exposing the dinucleotide 5'-d(GpT) and trinucleotide 5'-d(GpCpT) to carbonate radicals, the same type of 5'-d(G^{*}pT^{*}) and 5'-d(G^{*}pCpT^{*}) lesions were found, respectively. The structures of these species were identified by LC-MS/MS as well as 1D and 2D NMR methods.⁸⁹ The 5'-d(G^{*}pCpT^{*}) cross-linked structure is unusual because G and T are not adjacent to each other in the parent oligonucleotide.

The efficiency of formation of the G^{*}-T^{*} cross-links is base-sequence-dependent⁸⁹ and the greatest efficiency was observed in the case of the 5'-d(GpCpT) sequence. In the case of 5'-d(GpT), the efficiency of formation of the G^{*}-T^{*} product is ~3 times lower. When there are two C bridging residues as in 5'-d(GCCT), the yield of cross-linked products was lower than in the case of 5'-d(GCT). However, no cross-linked products were detected in the case of the 5'-d(GCCCT) sequence which has three bridging C bases. Furthermore, no intrastrand 5-d(T^{*}pC^{*}) cross-links were detected in the case of the dinucleotide 5'-d(TpG) either, although there was a substantial yield in the case of 5'-d(GpT). This latter result supports the conclusion, further supported by experiments with the sequence isomers 5'-d(GpCpT) and 5'-d(TpCpG), that cross-link formation is more efficient when the T residue is on the 3'-side rather than on the 5'-side of the guanine.

Similar cross-links 5'-d(G^{*}pT^{*}) and 5'-d(G^{*}-T^{*}) were also observed in native double-stranded DNA.^{89,90} Since the d(G^{*}pT^{*}) is completely resistant to nuclease P1, we conclude that the product 5'-d(G^{*}pT^{*}) must entirely originate from *intrastrand* cross-linked lesion. However, the same enzymatic digestion of 5'-d(G^{*}pCpT^{*}) leads to loss of pCp, thus yielding the 5'-d(G^{*}-T^{*}) digestion fragment.⁸⁹ Since such an intrastrand G^{*}-T^{*} lesion can arise from any 5'-d(GpN_npT) sequence with N = C or A, and n = 1, 2, 3,⁸⁹ the possibility cannot be excluded that such across-linked lesion can also arise from an *interstrand* cross-linked product.

Thymine is not the only pyrimidine that can form intrastrand cross-links with guanine radicals derived from one-electron transfer reactions. We found that similar cross-links can also be generated

by analogous one-electron oxidation of 5'-r(GpCpU) and 5'-d(GpCpU) trinucleotides containing uracil that lack the C5-methyl group of thymine.⁹¹ Like thymine, uracil contains the N3(H) group that is available for cross-link formation with the C8 site of guanine. The positive ion MS/MS spectra as well as the 1D and 2D NMR spectra of the 5'-r(G^{*}pCpU^{*}) and 5'-d(G^{*}pCpU^{*}) products are completely consistent with G^{*}(C8)-(N3)U^{*} structure, which is entirely analogous to the G^{*}(C8)-(N3)T^{*} cross-links discussed above.

Mechanistically, the formation of G^{*}(C8)-(N3)T^{*} (or G^{*}(C8)-(N3)U^{*}) cross-links includes the loss of two electrons and two protons. While in much of our work CO₃^{•-} radicals were utilized to abstract the first electron from guanine,^{77,90,92,94,150} other one-electron oxidants that have appropriate reduction potentials are equally suitable. Identical cross-linked G^{*}-T^{*} cross-links are formed when SO₄^{•-} radicals and photoexcited riboflavin (a typical type I photosensitizer that reacts with guanine via an electron transfer mechanism) also generate the 5'-G^{*}CT^{*} cross-linked products.^{89,91} Insights into the second electron abstraction step were obtained from our observation that the yields of G^{*}-T^{*} (or G^{*}-U^{*}) cross-linked products are negligible in the absence of molecular oxygen.^{89,91} We rationalized that the second electron is abstracted by O₂, thus forming the superoxide anion O₂^{•-}. This second electron can also be removed by other mild oxidants such as 1,4-benzoquinone in deoxygenated aqueous solutions.⁹¹ Benzoquinone has a redox potential E°(BQ/BQ^{•-}) = 0.078 V versus NHE,²¹⁶ and is a weaker oxidant than O₂ with E°(O₂/O₂^{•-}) = -0.16 V versus NHE.⁷⁸

This mechanism is supported by a strong increase of the yields of the cross-linked product (36) when the pH is increased from neutral to basic values (pH ≥ 10). In a strongly basic solution, T-N3(H) is deprotonated since its pK_a = 9.67,²¹⁷ thus greatly enhancing the nucleophilicity of T-N3. At pH 10, the yield of the G^{*}-T^{*} cross-linked product is ~5 times greater than at pH 7.5, which is fully consistent with the nucleophilic addition of T(N3) to the G(C8) radical. Similar enhancements in cross-linked product yields are also observed in the case of 5'-GCU sequences⁹¹ because T-N3(H) and U-N3(H) have the same pK_a values.²¹⁷ A similar nucleophilic mechanism was proposed by Perrier *et al.* for the formation of cross-linked products between guanine in d(TpGpT) and lysine mediated

by the photoexcited riboflavin in aerated solutions containing the KKK tripeptide.²¹⁸ These authors suggested that an *N* ϵ -(guanine-8-yl)-lysine cross-link is formed via the nucleophilic addition of the ϵ -amino group of the lysine residue to the C8 atom of G^{•+} or G(-H)[•] radicals, followed by the oxidation of the radical adduct formed.

3.3.3 Radical–Guanine Radical Reactions

Guanine radical cations that do not react with any nucleophiles undergo deprotonation to form the guanine radicals G(-H)[•], as already discussed in this article and elsewhere.^{122,219} The combination of guanine neutral radicals with other radicals is one of the most important pathways of the formation of oxidatively generated and stable modifications of guanine. Here, we focus on the combination of G(-H)[•] radicals with oxyl radicals ([•]NO₂, O₂^{•-}, and CO₃^{•-}). These radicals are overproduced at sites of inflammation and are thus of biological significance.^{1–6}

Nitrogen Dioxide Radicals

On the basis of thermodynamic considerations, the direct oxidation of guanine by [•]NO₂ radicals is unfavorable and this was demonstrated experimentally.²¹⁹ Furthermore, G(-H)[•] oxidize NO₂⁻ anions with the rate constant of $\sim 1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, which is consistent with the low reactivity of [•]NO₂ with guanine in aqueous solutions.¹⁸⁴ In contrast, [•]NO₂ radicals rapidly combine in bimolecular reactions with G(-H)[•] radicals resulting in the formation of diverse nitration products. We devised two photochemical methods for generating controlled fluxes of G(-H)[•] and [•]NO₂ radicals for studying such radical–radical reactions in detail. The competitive oxidation of NO₂⁻ and HCO₃⁻ anions by photochemically generated SO₄^{•-} radicals (23) to form [•]NO₂ (29) and CO₃^{•-} (24) radicals constitutes the first method.^{87,93} The G(-H)[•] radicals in DNA (derived by the one-electron oxidation of guanines by CO₃^{•-}) rapidly combine with [•]NO₂ radicals to form guanine nitration products. In the second method, the [•]NO₂ radicals are generated by the one-electron reduction of NO₃⁻ anions by hydrated electrons (28) that are produced by the two-photon ionization of 2-aminopurine (39 and 40); in this method, both 2AP and the target

guanine are site-specifically positioned in single- or double-stranded oligonucleotides as described elsewhere in this article.¹⁸⁴ Once the guanine radical G(-H)[•] is formed, it combines with [•]NO₂ radicals on millisecond timescales. This reaction can be directly monitored by transient absorption laser kinetic spectroscopy techniques. The decay of the G(-H)[•] radical absorption band at 315 nm is correlated with the growth of the characteristic absorption band of the nitration products at 385 nm. The combination of the G(-H)[•] and [•]NO₂ radicals is not significantly dependent on the secondary structure of oligonucleotides since the rate constants ($\sim 4.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) are similar in both single- and double-stranded DNA.¹⁸⁴

The same nitrated products are formed regardless of the mode of generation of [•]NO₂.^{87,93,184} These products were isolated by reversed-phase HPLC techniques and unambiguously identified by MS methods. The combination of G(-H)[•] and [•]NO₂ radicals occurs via the addition of [•]NO₂ radicals to either the C8 or the C5 positions of G(-H)[•] radicals (Figure 12). The unpaired electron in [•]NO₂ is delocalized on the N and the O atoms.²²⁰ Therefore, in principle, both the N and the O atoms can participate in reactions with another radical species. In reactions between [•]NO₂ and G(-H)[•] radicals, the covalent bond formed involves the nitrogen atom in the [•]NO₂ precursor molecule. The addition of [•]NO₂ to the C8 position of the G(-H)[•] radical (27) yields the well-known 8-nitroguanine (8-nitroG, 40) adducts, whereas attack at the C5 position generates unstable adducts which rapidly decompose to 5-guanidino-4-nitroimidazole (NIm, 41) (Figure 12).^{87,93} The combined yields of the nitration products NIm and 8-nitroG in aqueous solutions are typically in the range 20–40%. The ratio of the 5-guanidino-4-nitroimidazole and 8-nitroG lesions gradually decreases from 3.4 in the model compound 2',3',5'-tri-*O*-acetylguanosine, to 2.1–2.6 in single-stranded oligonucleotides, and to 0.8–1.1 in oligonucleotide duplexes.

Superoxide radicals are potentially mild three-electron oxidants with the reduction potential $E_7(\text{O}_2^{\bullet-}, 2\text{H}_2\text{O}/4\text{OH}^-) = 1.2 \text{ V}$ versus NHE.²²¹ Owing to their oxidative properties, O₂^{•-} radicals can also contribute to the formation of oxidation end products via radical–radical addition reactions.¹⁰² In order to further explore these radical combination pathways, a photochemical method was developed to simultaneously generate G(-H)[•] radicals in model oligonucleotides and O₂^{•-}.¹⁸³ The

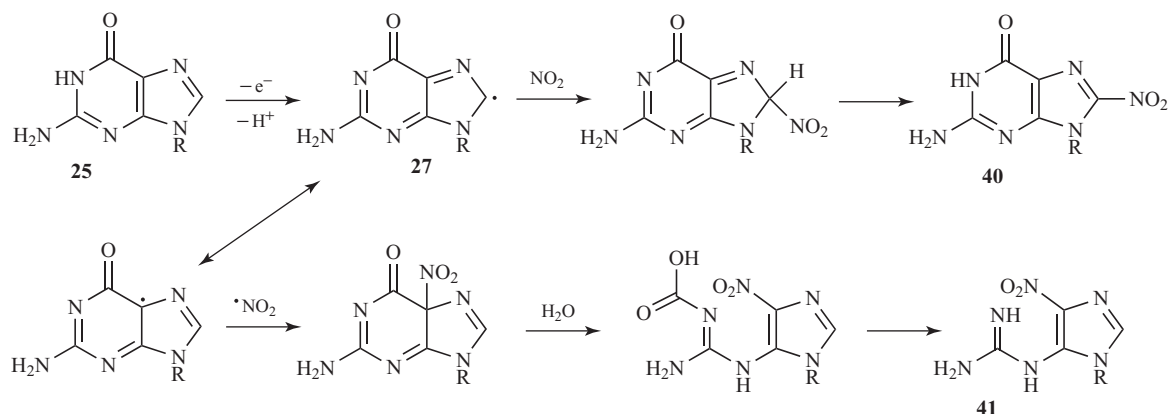


Figure 12 Formation of nitration products via the combination of $\text{G}(-\text{H})^\bullet$ with $\cdot\text{NO}_2$ radicals. [Adapted from Ref. 184.]

hydrated electrons were obtained by the two-photon ionization of 2AP embedded in oligonucleotides as already described (39). The hydrated electrons are quantitatively scavenged by dissolved O_2 to form $\text{O}_2^{\bullet-}$ radicals (31).⁹⁹ The combination of $\text{G}(-\text{H})^\bullet$ and $\text{O}_2^{\bullet-}$ radicals occurs with the identical rate constant $\sim 4.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ in single- and double-stranded oligonucleotides.¹⁸³ In the presence of $\sim 5 \mu\text{M}$ Cu,Zn-superoxide dismutase (Cu,Zn-SOD, an enzyme that reacts with $\text{O}_2^{\bullet-}$ radicals with nearly diffusion-controlled rates^{18,19}), the lifetimes of the DNA-bound $\text{G}(-\text{H})^\bullet$ radicals are dramatically enhanced from 4–7 ms to 0.2–0.6 s.¹⁸³ This remarkable increase in the lifetimes of $\text{G}(-\text{H})^\bullet$ lifetimes in the presence of Cu,Zn-SOD strongly suggests that the primary partner of reaction of $\text{G}(-\text{H})^\bullet$ radicals in aqueous solutions is indeed the superoxide anion under the conditions described.

The reaction of $\text{G}(-\text{H})^\bullet$ with $\text{O}_2^{\bullet-}$ radicals can produce two different outcomes: (i) electron transfer from $\text{O}_2^{\bullet-}$ to $\text{G}(-\text{H})^\bullet$, which regenerates the guanine and is therefore a “repair” reaction and (ii) formation of oxidatively generated end products.¹⁸³ A detailed analysis by combined HPLC and MS methods showed that these products, in both single- and double-stranded DNA, include mostly 2,5-diamino-4*H*-imidazolone (Iz) lesions and minor amounts of 8-oxoG (Figure 13). The addition of $\text{O}_2^{\bullet-}$ to the C5 position of $\text{G}(-\text{H})^\bullet$ is followed by a rapid protonation of the adduct and the generation of the 5-HOO-G(-H) hydroperoxide (42). This intermediate is unstable and cleaves via the opening of the pyrimidine ring at the C5–C6 bond,

thus generating another unstable intermediate (43) which is readily hydrated at the 7,8-C=N double bond. Ring-chain tautomerization of the carbino-lamine (44) results in the opening of the imidazole ring and a subsequent intramolecular cyclization of the guanidine residue, finally yielding the Iz lesions (45). The latter slowly hydrolyzes to form 2,2-diamino-4-amino-2,5-dihydrooxazol-5-one, Oz (46). Heavy molecular oxygen ^{18}O -labeling experiments showed that the oxygen atom in the Iz lesion originates from $^{18}\text{O}_2$.²²² In the presence of even small quantities of 1,4-benzoquinone ($\sim 100 \mu\text{M}$), the yields of Iz lesions are negligible because BQ reacts with $\text{O}_2^{\bullet-}$ and $\text{G}(-\text{H})^\bullet$ radicals. BQ rapidly reacts with $\text{O}_2^{\bullet-}$ (rate constant $9 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$),⁹⁹ and then the $\text{BQ}^{\bullet-}$ radical thus produced ($E^\circ = 0.078 \text{ V}$ vs NHE²¹⁶) rapidly reduces the $\text{G}(-\text{H})^\bullet$ radical ($E_7 = 1.29 \text{ V}$ vs NHE¹³¹). The addition of $\text{O}_2^{\bullet-}$ to the C5 position of $\text{G}(-\text{H})^\bullet$, followed by the rapid protonation of the adduct, gives rise to the 5-HOO-G(-H) hydroperoxide.^{183,215} The analogous addition of $\text{O}_2^{\bullet-}$ to the C8 position of $\text{G}(-\text{H})^\bullet$, followed by the two-electron reduction of the 8-HOO-G(-H) hydroperoxide formed, leads to the formation of 8-oxoG. The latter is detected in minor quantities, together with the Iz/Oz lesions. This mechanism of 8-oxoG formation has been confirmed by experiments conducted in isotopically substituted water, H_2^{18}O . These experiments reveal that the additional O-atom in 8-oxoG originates from $^{16}\text{O}_2$, which is reduced to $\text{O}_2^{\bullet-}$ by hydrated electrons.¹⁸³

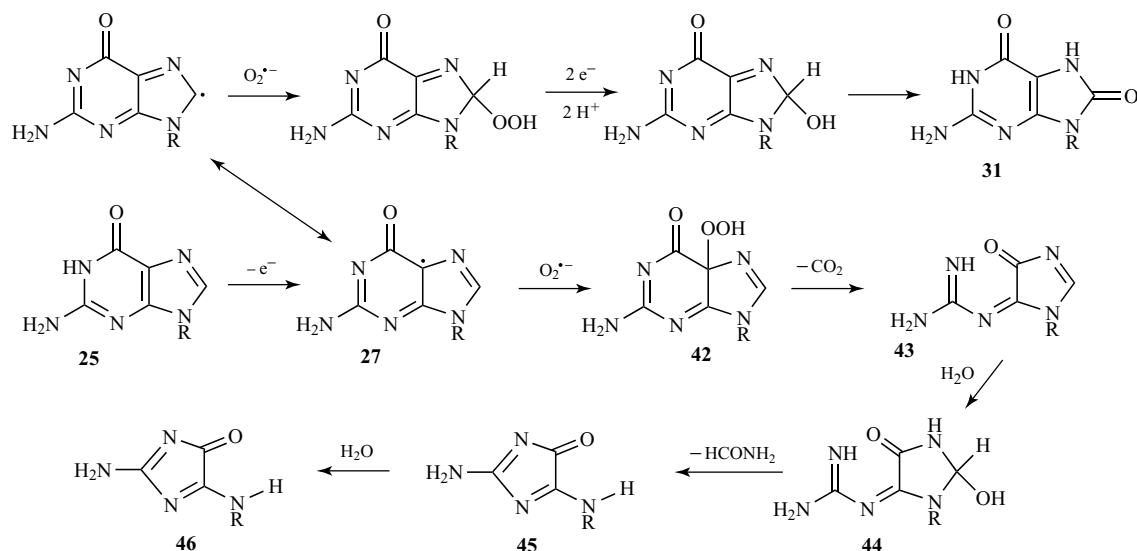


Figure 13 Formation of 8-oxoG and Iz lesions via the combination of G(-H)[•] radicals with O₂^{•-} in DNA. [Adapted from Ref. 183.]

Peroxyl Radicals

In contrast to HO₂[•]/O₂^{•-} radicals, the ROO[•] radicals ($E_7 = 1.0 - 1.1$ V vs NHE) derived from lipid peroxidation exhibit only oxidizing properties.¹⁰² The reduction potential of these radicals^{223,224} is lower than the reduction potential of G(-H)[•] radicals,¹³¹ $E_7 = 1.29$ V versus NHE. Therefore, the thermodynamics of oxidation of guanine by ROO[•] radicals is unfavorable. It is also unlikely that H-atom abstraction from G residues by ROO[•] radicals can occur with observable rates because the bond dissociation energy (BDE) of the C-H bonds in guanine (94.3 ± 0.5 kcal mol⁻¹)²²⁵ is higher than that of the ROO-H bond (~ 88 kcal mol⁻¹, regardless of the exact structure of R²²⁶). However, we have shown that the major pathway of reaction of ROO[•] radicals are their combination reactions with G(-H)[•] radicals.²²⁷ The peroxy radicals were generated by the addition of O₂ to C-centered radicals of polyunsaturated fatty acids, such as arachidonic acid (ArAc),²²⁷ or photolysis of the water-soluble radical generator 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH).²²⁸ Transient absorbance spectroscopy experiments showed that the alkyl peroxy radicals generated by both methods are unstable and spontaneously decompose to form O₂^{•-} radicals. The formation of O₂^{•-} radicals was directly monitored by the reduction of tetranitromethane.^{99,102} The major products detected in these experiments were

imidazolone formed by the combination reactions of G(-H)[•] radicals with O₂^{•-} and ROO[•] radicals.^{227,228}

The relative contributions of these pathways to the observed formation of the end products were estimated using selective traps of O₂^{•-} radicals, such as 1,4-benzoquinone and Cu,Zn SOD. According to our previous results, BQ and Cu,Zn-SOD completely suppress the formation of the Iz lesions arising from the combination the O₂^{•-} and G(-H)[•] radicals.¹⁸³ The results of these experiments indicate that the formation of Iz occurs by the both pathways (combination of G(-H)[•] radicals with O₂^{•-} and with ROO[•] radicals).^{227,228}

Carbonate Radical Anions

The expected product of bimolecular reaction of the G(-H)[•] radical with strong one-electron oxidants such as the CO₃^{•-} radical is 8-oxoG, the product of a two-electron oxidation of guanine.⁵⁶ However, 8-oxoG is more easily oxidizable by one-electron oxidants than the parent guanine.¹³² The major products of 8-oxoG oxidation are the diastereomeric spiroiminodihydantoin Sp (**50**) and guanidinohydantoin Gh (**51**) products (Figure 14).^{88,90,92,229-234} Our experiments have indeed demonstrated that oxidation of guanine in oligonucleotides to Sp/Gh involves 8-oxoG as an intermediate.⁹² However, when CO₃^{•-} radicals are used as oxidants, the maximum observed yield of 8-oxoG in oligonucleotides does not exceed $\sim 2\%$.

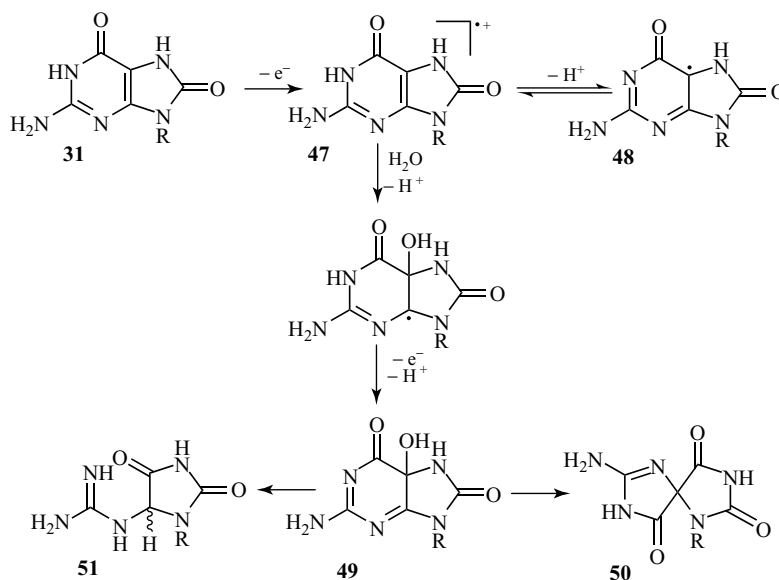


Figure 14 8-Oxoguanine radicals generated by one-electron oxidation or by the addition of hydroxyl radicals. [Adapted from Refs 132 and 236.]

The low yield of 8-oxoG indicates that the rate of oxidation of 8-oxoG is much faster than that of parent guanine embedded in the oligonucleotide. The rate constant of oxidation of 8-oxoG by $\text{CO}_3^{\cdot-}$ radicals is ~ 13 times greater than the analogous rate constant for the one-electron oxidation of guanine in oligonucleotides.⁹² Another factor that decreases the transient yields of 8-oxoG lesions in aqueous solutions of oligonucleotides is that they are rapidly oxidized by $\text{G}(-\text{H})^\bullet$ radicals even though the latter are also embedded in oligonucleotides. Steenken has shown that, at the nucleoside level, $\text{dG}(-\text{H})^\bullet$ radicals oxidize 8-oxodG with the relatively large rate constant of $4.6 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.¹³² This reaction leads to the recovery of the parent dG and constitutes a very efficient protection of dG against oxidation in nucleoside solutions²³⁵; this accounts for the low levels of 8-oxodG (less than 0.1% of the dG degraded) in oxidation reactions of dG photosensitized by the photexcitation of riboflavin.²³⁵ In double-stranded DNA, on the other hand, the repair of $\text{G}(-\text{H})^\bullet$ radicals by this bimolecular pathway is much less efficient. We have shown that the bimolecular rate constant of oxidation ($2.7 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) of 8-oxoG in a particular oligonucleotide duplex by a $\text{G}(-\text{H})^\bullet$ radical in another duplex is two orders of magnitude smaller than in the case of free nucleosides.¹⁸³ The

8-oxoG lesion in oligonucleotides is also likely to be an intermediate in the oxidation of the parent guanine bases by $\text{CO}_3^{\cdot-}$ radicals to either Sp or Gh lesions.

3.3.4 Radical Forms of 8-Oxo-7,8-dihydroguanine

The primary product of the one-electron oxidation of 8-oxoG is the radical cation 8-oxoG^{•+} (47) (Figure 14), which can be detected by direct spectroscopic methods by the appearance of the sharp absorption band at 325 nm and a broad, less intense band near 380 nm.^{132,237} In neutral aqueous solutions, the radical cation ($\text{p}K_a = 6.6$) is in equilibrium with its neutral form 8-oxoG(-H)[•] (48), which has very similar spectroscopic characteristics. Recently, O'Neill and coworkers reported that $\cdot\text{OH}$ radicals react with 8-oxodG via the addition to the C4 position and H-atom abstraction from the exocyclic NH_2 group to form highly unstable radicals.²³⁶ The latter rapidly transform to neutral 8-oxoG(-H)[•] radicals within $\leq 1.6 \mu\text{s}$. Our laser flash photolysis experiments^{184,185,237} and the pulse radiolysis experiments of the O'Neill group²³⁶ have shown that 8-oxoG^{•+}/8-oxoG(-H)[•] radicals do

not react with observable rates with molecular oxygen O_2 , and their lifetimes are controlled by other radicals and nucleophiles that may be present,^{184,185,237} as discussed below.

3.3.5 Nucleophilic Addition Reactions with 8-oxoG Radicals

The hydration of the 8-oxoG^{•+} radicals (**47**), followed by a one-electron oxidation of the hydration product, gives rise to the 5-HO-8-oxoG intermediate (**49**). The latter is a precursor of Sp (**50**) and Gh (**51**) that are formed by subsequent oxidation reactions (Figure 14).^{229,238} This mechanism was established by detailed investigations of the oxidation of guanine by the irridium complex $IrCl_6^{2-}$ in $H_2^{18}O$ solutions.²²⁹ Consistent with the nucleophilic addition mechanism, the additional oxygen atom in Sp was found to be the ^{18}O isotope. The transformation of 5-HO-8-oxoG (**49**) to form either Sp (**50**) or Gh (**51**) is pH-dependent. Tannenbaum *et al.* proposed that the partitioning of the two 5-HO-8-oxoG(-H) reaction pathways that lead to the formation of either Sp or Gh is governed by the different reactivities of the deprotonated and protonated forms of this hydrated intermediate ($pK_a \sim 5.8$).²³³ At pH below 5.8 it favors pyrimidine ring-opening, followed by the formation of the Gh lesions, while the acyl shift leading to the Sp lesions dominates at pH > 5.8. This conclusion is in accordance with the higher yields of Gh products at low pH which has been reported for the oxidation of 8-oxoG by peroxynitrite,²³³ by photosensitized riboflavin, and by $IrCl_6^{2-}$ ^{232,239} or Cr(VI) complexes.²⁴⁰

3.3.6 Radical Addition to 8-oxoG Radicals

The neutral 8-oxoG(-H)[•] radical is a key intermediate in the subsequent oxidative cascade of reactions which leads to a variety of stable end products, and its reactions with other radical species defines the nature of the end products formed. In this section, we focus on the combination of 8-oxoG(-H)[•] radicals with oxyl radicals ($\cdot NO_2$, $O_2^{\cdot-}$, and $CO_3^{\cdot-}$), all of which are overproduced at sites of inflammation by macrophages.^{1-3,5,6}

Nitrogen Dioxide

The oxidation of 8-oxodG ($E_7 = 0.74 - 0.79$ V vs NHE)^{132,236} by $\cdot NO_2$ radicals ($E^0 = 1.04$ V vs NHE)⁷⁸ is thermodynamically feasible and occurs with a rate constant of $5.3 \times 10^6 M^{-1} s^{-1}$.²⁴¹ The combination of the 8-oxoG(-H)[•] and $\cdot NO_2$ radicals occurs with similar rate constants ($\sim 4.3 \times 10^8 M^{-1} s^{-1}$) in both single- and double-stranded DNA as shown in our laser flash photolysis experiments.¹⁸⁴ The dominant reaction products are the diastereomeric Sp lesions (Figure 15). The reaction of 8-oxoG(-H)[•] radicals with $\cdot NO_2$ radicals can yield the unstable C5 nitro (**52**) or nitrosooxy adducts. The hydrolysis of these adducts can occur via a nucleophilic addition of a water molecule to C5, followed by the release of the NO_2^- anion and the formation of the 5-HO-8-oxoG(-H) intermediate (**49**), a precursor of the Sp lesions (Figure 15). The 5-HO-8-oxoG(-H) adduct, and hence the Sp end products, contain an oxygen atom derived from $H_2^{18}O$ rather than from $N^{16}O_2$. As described above, the subsequent transformation of 5-HO-8-oxoG(-H) to either Sp or Gh depends on the pH.^{90,229,233,239,240} The mechanism proposed in Figure 15 is consistent with the two basic observations: (i) the combination

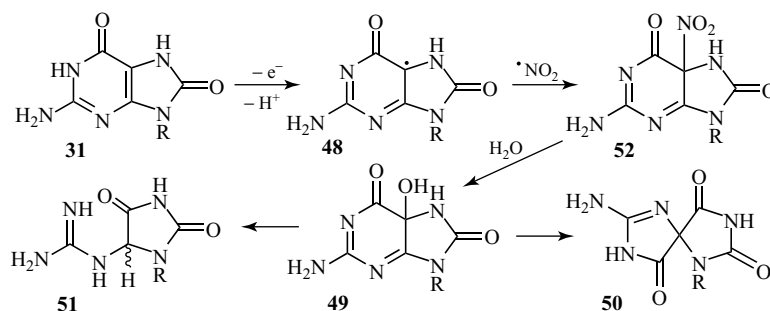


Figure 15 Formation of oxidation products via the combination of 8-oxoG(-H)[•] with $\cdot NO_2$ radicals. [Adapted from Ref. 184.]

of $\cdot\text{NO}_2$ and 8-oxoG(-H) $\cdot$ radicals occurs with a rate characteristic of bimolecular radical–radical addition reactions and (ii) the additional O atom in the final oxidation product is derived from H_2O . An alternative proposed reaction mechanism is the one-electron transfer reaction from 8-oxoG(-H) $\cdot$ to $\cdot\text{NO}_2$ which yields the 8-oxoG(-H) $^+$ cation and the NO_2^- anion. In this pathway, proposed by Burrows *et al.* based on their studies of the oxidation of 8-oxoG by IrCl_6^{4-} , the addition of H_2^{18}O to 8-oxoG(-H) $^+$ leads to the 5-HO-8-oxoG(-H) precursor of the Gh and Sp lesions that contain the ^{18}O -isotope which originates from water molecules, as expected.^{229,242} However, the electron transfer mechanism cannot explain the high rate constants for the combination reaction measured by us experimentally for both the 8-oxoG(-H) $\cdot$ radicals and the G(-H) $\cdot$ radicals ($\sim 4.3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$).¹⁸⁴ This conclusion is based on the typically slow electron transfer reactions of $\cdot\text{NO}_2$ radicals which are the result of the small self-exchange rate constant and high internal reorganization energy in the $\cdot\text{NO}_2/\text{NO}_2^-$ system.²⁴³

Superoxide Anion

The combination of $\text{O}_2^{\cdot-}$ with 8-oxoG(-H) $\cdot$ radicals in double- and single-stranded DNA occurs with the rate constant of $(1.0 - 1.3) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.¹⁸⁵ The major end products of this reaction are the dehydroguanidinohydantoin (Gh_{ox}) lesions (**53**) derived from the addition of $\text{O}_2^{\cdot-}$ to the C5 position of 8-oxoG(-H) $\cdot$ (**48**) followed by the decomposition of the 5-HOO-8-oxoG(-H) hydroperoxide (**54**) (Figure 16). According to this mechanism, the cleavage of 5-HOO-8-oxoG(-H) occurs via the opening of the pyrimidine ring at the C5–C6 bond

in 5-HOO-8-oxoG(-H), thus leading to an unstable intermediate (**55**), which decomposes readily with the release of CO_2 and the formation of Gh_{ox} (**53**).¹⁸⁵ The Gh_{ox} lesions are unstable and slowly hydrolyze to oxaluric acid (Oa). In the presence of Cu,Zn-SOD, the yields of the Gh_{ox} lesions are negligible. Under these conditions, the 8-oxoG radicals do not exhibit any observable reactivities with O_2 ($k < 10^2 \text{ M}^{-1} \text{ s}^{-1}$) since they have a decay time of several seconds in air-saturated aqueous solutions at ambient temperatures. The major reaction products are the diastereomeric Sp lesions which are derived via the hydration of 8-oxoG(-H) $\cdot$.¹⁸⁵

Carbonate Radical Anion

The mechanistic aspects of the consecutive oxidation of G(-H) $\cdot$ and 8-oxoG(-H) $\cdot$ radicals by $\text{CO}_3^{\cdot-}$ radicals which result in the formation of Sp lesions from the free nucleoside were investigated in detail in H_2^{18}O buffer solutions.^{88,90} In these experiments, we used 2',3',5'-tri-*O*-acetylguanosine and 2',3',5'-tri-*O*-acetyl-8-oxo-7,8-dihydroguanosine as model compounds⁸⁸ and DNA duplexes derived from the self-complementary sequence⁹⁰ 5'-d(AA-CGCGAATTCGCGTT). In the latter experiments, the Sp lesions were enzymatically excised from the oxidized DNA in the form of 5'-d(C[Sp]) dinucleosides. We found that the oxygen atoms in the tri-*O*-acetyl-Sp and 5'-d(C[Sp]) dinucleosides added to either the C5 or C8 positions of the oxidized guanine intermediates originate from the $\text{C}^{16}\text{O}_3^{\cdot-}$ radicals. The oxidation of the 8-oxoG moieties by $\text{CO}_3^{\cdot-}$ radicals generates Sp products that contain a single O atom which originates from the $\text{C}^{16}\text{O}_3^{\cdot-}$ radicals. In contrast, when the reactions are carried out in buffer solutions containing carbonic anhydrase,²⁴⁴ which enhances the isotope exchange

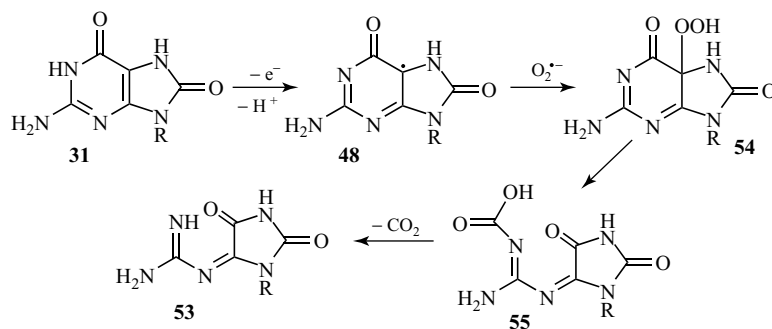


Figure 16 Formation of oxidation products via the combination of 8-oxoG(-H) $\cdot$ with $\text{O}_2^{\cdot-}$ radicals. [Adapted from Ref. 185.]

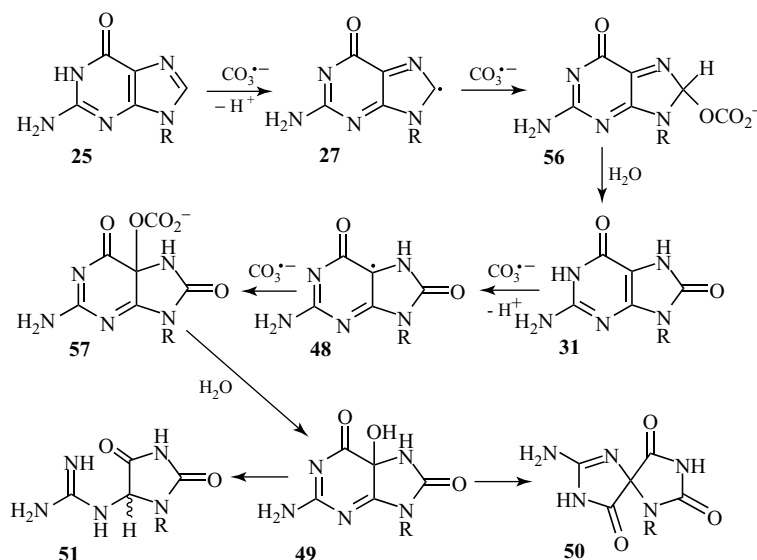


Figure 17 The O^- transfer mechanism of the combination of $\text{CO}_3^{\bullet-}$ radicals with $\text{G}(-\text{H})^{\bullet}$ and 8-oxo $\text{G}(-\text{H})^{\bullet}$ radicals to form the Sp and Gh lesions. [Adapted from Refs 88 and 90.]

between $\text{HC}^{16}\text{O}_3^-$ and H_2^{18}O , the Sp nucleoside products contain ^{18}O -atoms. It was concluded that the formation of Sp oxidation products involves the consecutive bimolecular combination reactions of $\text{CO}_3^{\bullet-}$ radicals with $\text{G}(-\text{H})^{\bullet}$ and 8-oxo $\text{G}(-\text{H})^{\bullet}$ radicals (Figure 17) involving monoesters (**56** and **57**, respectively) of the carbonic acid (H_2CO_3) as intermediates. Previous classic experiments of Polanyi and Szabo,²⁴⁵ Ingold,²⁴⁶ and their coworkers demonstrated that in the acid–base hydrolysis of esters, the ^{18}O atoms from water are transferred to the acid component and not to the alcohol product. Since the O atoms in Sp originate from the $\text{CO}_3^{\bullet-}$ radicals and not from H_2O (Figure 17), these findings are consistent with the proposed mechanism of ester hydrolysis. The combination reactions of $\text{CO}_3^{\bullet-}$ with $\text{G}(-\text{H})^{\bullet}$ or 8-oxo $\text{G}(-\text{H})^{\bullet}$ radicals can therefore be formally considered as the transfer of O^- from $\text{CO}_3^{\bullet-}$ to these radicals. The O^- transfer mechanism has been proposed earlier for the reactions of $\text{CO}_3^{\bullet-}$ radicals with inorganic radicals such as $\cdot\text{NO}_2$, $\text{SO}_3^{\bullet-}$, and $\cdot\text{NO}$, which results in the formation of CO_2 , NO_3^- , SO_4^{2-} , and NO_2^- anions.^{247,248} In contrast, metal complexes such as IrCl_6^{2-} involve the consecutive abstraction of two electrons from 8-oxoG, followed by the addition of water molecules to the carbocation intermediates;

thus the oxygen atoms in the Sp products originate from water.²²⁹

4 BIOLOGICAL IMPLICATIONS

Among the many guanine lesions described in this article, 8-oxoG is the best known and most widely studied and is also widely used as a biomarker of oxidative stress in cellular and tissue environments. While all the guanine lesions described in this article have been identified and studied *in vitro*, only 8-oxoG and 8-nitroG have been detected in humans till now.¹²⁰ Detailed studies by several groups have shown that the levels of 8-oxoG in normal human cells are in the range 0.3–4.2 per 10^6 molecules of intact G bases.^{249,250} However, because 8-oxoG is efficiently removed by base excision repair enzymes, it is difficult to accurately measure the levels of 8-oxoG in tissues under inflammatory conditions.^{121,122,251} Furthermore, 8-oxoG is easily oxidized to other products, and it is widely suspected that such deeper oxidation products of guanine are also formed in cells. Significant efforts have been made to identify such adducts in biological systems. Sugden *et al.* found that the spiroiminodihydantoin is indeed formed in *Escherichia coli* cells after treatment

with Cr(VI).²⁵² However, in mammalian cells or tissues, the Sp and other deeper oxidation products were not observable and it was concluded that their levels are likely to be less than 1 in 10⁷ DNA bases.²⁵³ Nevertheless, the four-electron oxidation product of guanine, Oz, has been found at a level of 2–6 Oz lesions per 10⁷ molecules of intact G in liver DNA of diabetic and control rats maintained on a diet of high animal fat.²⁵⁴ In the case of 8-nitroG, there is abundant proof that such lesions exist in tissues although they are unstable because they readily depurinate and dissociate from the DNA. The 8-nitroG adducts have been found in biological fluids of patients with various diseases including chronic hepatitis C,^{255,256} intrahepatic cholangiocarcinoma,^{257,258} nasopharyngeal carcinoma,²⁵⁹ malignant fibrous histiocytoma,^{260,261} *Helicobacter pylori* infection,^{262,263} and inflammatory bowel disease.^{264,265} More research should be conducted to determine whether 5-guanidino-4-nitroimidazole lesions exist *in vivo*; *in vitro*, these Nim lesions are formed with nearly the same proportions as 8-nitroG lesions but, unlike 8-nitroG, do not undergo depurination. Formally, 8-oxoG and 8-nitroG are both products of a two-electron oxidation of guanine. The formation of 8-nitroG occurs in two steps: (i) electron abstraction from guanine (the “first hit”), and (ii) combination of [•]NO₂ radicals (the “second hit”). In contrast, the formation of 8-oxoG requires only one electron abstraction step from guanine (a “single hit”) which is followed by hydration and the abstraction of a second electron from the hydrated guanine radical by molecular oxygen. The formation of the intrastrand G[•]–T[•] cross-links involves a similar sequence of events: first, the one-electron oxidation of guanine (“single hit”) is followed by the nucleophilic addition of T-N3 to G-C8 and the abstraction of an electron by O₂ or another electron acceptor. Such a reaction mechanism may also occur *in vivo*, since molecular oxygen is abundant. Since such G[•]–T[•] cross-linked lesions are also formed in native DNA, further research should be directed toward determining whether these lesions are also formed in cellular DNA.

The Sp and Iz lesions, as well as Oz, the product of hydrolysis of Iz, are, overall, products of the four-electron oxidation of guanine. The Iz lesion is formed by only “two hits,” which are the initial one-electron oxidation of guanine, followed by the

combination reaction of guanine radicals with the superoxide radical anion, a three-electron oxidant. The formation of the Sp lesions *in vitro* can occur via the oxidation of 8-oxoG. Since the levels of 8-oxoG in cells are quite low,^{249,250} the further oxidation of 8-oxoG to Sp by oxidants that can also oxidize guanine seems to be unlikely because guanine is more abundant than 8-oxoG by a factor of ~10⁶. However, oxidants that can oxidize only 8-oxoG but not guanine convert the existing 8-oxoG to deeper oxidation products. Under inflammatory conditions, the best candidates for such reactions are the ubiquitous [•]NO₂ and ROO[•] radicals. The search for Sp and guanidinohydantoin lesions *in vivo*, especially in tissues under inflammatory conditions, is a critically important task that might further clarify the pathways of oxidatively generated guanine damage in DNA associated with reactive intermediates that are products of the inflammatory response.

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Charge Transfer in DNA

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1 INTRODUCTION

The principal role of DNA is the long-term storage and replication of genetic information of living organisms. In DNA, π -aromatic compounds, that is, purine and pyrimidine bases, form well-ordered stacking structure, by means of π -stacking between the bases and hydrogen bonding with the bases of the complementary DNA strand to form a double helix structure. For the one-dimensional π -stacked aromatic arrays, charge conduction is also expected.¹ Recently, the charge transfer in DNA has attracted substantial attention of scientists, especially in the field of bioscience and nanotechnology.

In the body, DNA is always attacked by various oxidizing and reducing agents that are generated naturally (see **Reactions of Small Reactive Species with DNA**). The oxidative DNA damage may cause mutation, apoptosis, and cancer.^{2,3} The charge transfer in DNA is a key issue to explain the oxidative damage at remote sites in the DNA. On the other hand, the repair of the damaged DNA also takes place in living cells. For example, DNA photolyase enzymes repair T–T cyclobutane dimer lesions in the DNA duplex, which is generated by UV irradiation, by negative electron (excess electron) transfer in DNA from reduced and deprotonated FADH[–].^{4–6} Thus, understanding of the charge transfer in DNA is essential for the study of photoinduced damage or repair of DNA. Charge transfer in DNA is important for biomedical application, including photodynamic

therapy. For these reasons, great achievements in this subject have been realized by various research groups in the field of biochemistry and radiation chemistry.

From the viewpoint of nanotechnology, DNA is expected to take an important role as a nanowire based on the charge transfer in DNA.^{7,8} DNA can be regarded as an artificial copolymer, whose sequence and chain length can be controlled precisely by means of polynucleotide synthesizer and so on. In addition to natural nucleobases, that is, adenine, cytosine, guanine, and thymine (A, C, G, and T, respectively), various artificial nucleobases can be employed as constituents of DNA with the desired functionality. Although the unit length of one nucleotide of DNA is 3.4 Å and width is ~2 nm, polymerization degree reaches several millions, indicating that well-defined tailor-made properties can be obtained using DNA even in the micro- and millimeter domain. These flexibilities in controlling copolymer sequence and polymerization degree are quite rare in other artificial copolymers. Thus, these quite unique characteristics of DNA which are useful for electric wire in nanoscale appeals to various scientists in fields far removed from biology. Furthermore, DNA is quite useful in forming artificial structures in addition to duplex or quadruplex structures.^{9,10} The nanosheet based on the programmed sequences is one example of such artificial structures.^{11–17} This means that DNA can be employed as a scaffold of various chromophore arrays for various functions.^{18–22} These studies are

also attracting various researchers in a wide range of fields.

Charge transfer in DNA is also an important subject for the scientists in the field of physical and theoretical chemistries. Especially it attracts the attention of scientists who are engaged in the study of electron transfer phenomena in various molecular systems. Can the electron transfer mechanism in DNA be described by the theory developed for conventional molecular systems? Is the rate constant of the charge transfer through DNA faster than that through other materials? How about the sequence and structure dependence of the electron transfer rate? Is the charge in the DNA localized or not? These are very basic issues that have been discussed for various materials such as polymers, supramolecules, and so on for years. In this sense, DNA, whose sequence and polymerization degree are fully controllable, is an ideal system to assess the electron transfer theory (see **Electron Transfer in Peptides and Proteins**).

From these points, the electron transfer in DNA attracts wide attention of various researchers. Our research group has also investigated the charge transfer in DNA by means of laser flash photolysis and pulse radiolysis techniques for years. Here, we summarize our understandings of the charge transfer in DNA.

2 OXIDATION AND REDUCTION POTENTIALS OF THE DNA NUCLEOBASES

In order to discuss the oxidation and reduction processes of DNA, information on the oxidation and reduction potentials is essential. In Table 1, these potentials estimated by the electrochemical method are listed.²³ According to the values listed in Table 1, oxidation potentials of purine bases, that is, G and A, are lower than that of pyrimidine bases. On the other hand, the reduction potentials of the pyrimidine bases, T and C, are higher than those of others. Thus, G and A are considered the target of the oxidation process, while T and C are the target of the reduction process.

The oxidation potentials of nucleobases are also affected by the surrounding conditions. One of the most important surrounding conditions is the neighboring nucleobases in the DNA duplex. For example, it was revealed by Saito *et al.*²⁴ that oxidation cleavage at G shows the sequence

Table 1 The oxidation (E_{ox}) and reduction (E_{red}) potentials of nucleobase.

	E_{ox}/V versus NHE	E_{red}/V versus NHE
G	1.47	< -2.74
A	1.94	-2.43
C	2.12	-2.21
T	2.09	-2.12

Source: Reproduced from Ref. 23. © American Chemical Society, 1996.

selectivity, that is, G adjacent to purine bases is more reactive than that next to pyrimidine bases. GG and GGG sequences are more reactive than GA. This effect can be explained by the lower oxidation potentials of GG or GGG than GA, as revealed by computational study, which estimated that formation of GG or GGG lowers the ionization potential by 0.23 or 0.47 eV, respectively.²⁵ Actual oxidation potential difference between G and GG or GGG was evaluated to be 0.052 or 0.077 eV, respectively, from the evaluation of equilibrium of the hole as discussed in the following section.

In addition to the base stacking, the nucleobase for base pairing has also been revealed to have an effect on the oxidation potentials of the nucleobase. Our research group revealed experimentally that the oxidation potential of 8-oxo-7,8-dihydroguanine (8-oxo-G) is changed by the partner of base pairing.^{26,27} For example, the oxidation potential of 8-oxo-G : 5-methylcytosine is lower than that of 8-oxo-G : C pair by 0.09 V, while 8-oxo-G : 5-bromocytosine is higher by 0.034 V. We confirmed that the difference in the oxidation potentials affected the rate constant of the photoinduced electron transfer with solute in solution.

As summarized in this section, G and A are the targets of the oxidation process, while T and C are targets of the reduction process. That is, the radical cation of G and A or radical anion of T and C will act as the positive or negative charge carrier, respectively. Other important information is that the oxidation and reduction potentials of nucleobases are affected by various factors. The charge transfer in DNA should reflect the difference in the oxidation and reduction potentials, which is affected by surrounding conditions such as neighboring and pairing nucleobases. These factors should become important for fine-tuning of the charge conductivity in DNA. In addition, these issues are quite interesting from the viewpoint of the charge delocalization or localization in DNA. It

should be noted that the stability of the oxidized or reduced nucleobases is also an important factor. For example, it was revealed that reduced C forms the protonated form very rapidly, which decreases its mobility in DNA, as discussed in the following section. Actual hole and excess electron transfers are summarized in the following sections.

3 HOLE TRANSFER IN DNA

Whether DNA is an electric conductor has been an interesting scientific subject from the 1960s.¹ On the basis of the analogy to various organic conductors, in which π -conjugated aromatics form the stacked structure, DNA has been expected to be a good electric conductor owing to its base-stacking structure in the duplex form. The earliest studies on this subject measuring electric current flow in bulk DNA films led to confusing results ranging from conductive to insulating trends.¹ Recent single molecular-level measurements of current flow in the DNA still remain confusing.^{7,8,28}

For the charge transfer in DNA, two kinds of charged species have to be considered in the transport mechanisms. One is the hole transfer in DNA, which is the consecutive oxidation of nucleobase by the neighboring radical cation of the nucleobase that is generated by the hole injection to DNA. The other is the excess electron transfer, in which the radical anion of the nucleobase causes reduction in the neighboring nucleobase. Among them, the hole conduction in DNA has been investigated in detail in advance because many organic crystallines show good hole conductivity.²⁹ Other important motivation for investigation of the hole transfer in DNA is the oxidation of G, which has the lowest oxidation potential among the four natural nucleobases and has close relation to DNA damage.^{2,3} In this section, mechanistic investigations of the hole injection, that is, the electron transfer from the nucleobase to the photosensitizing electron acceptor, are summarized first. Then, the hole migration in the DNA is summarized.

3.1 Hole Tunneling in DNA

During the initial stage of investigation of the electron transfer in DNA, studies were conducted

using electron donors and acceptors, which can be intercalated to DNA in a random manner. Using such systems, Barton and coworkers indicated the fast electron transfer between Ru and Co complexes in the presence of DNA.^{30,31}

In 1992, Harriman and Brun have reported the results of fluorescence lifetime measurements of calf thymus DNA intercalated with ethidium bromide (EB^+) and *N,N'*-dimethyl-2,7-diazapyrenium dichloride (DAP^{2+} ; Figure 1).³² They found the short fluorescence lifetime components due to the electron transfer between EB^+ and DAP^{2+} . The formation of the products of electron transfer was confirmed by transient absorption spectroscopy. They analyzed the fluorescence decay profiles by three components based on the assumption that they came from the electron transfer between EB^+ and DAP^{2+} separated by 3–5 base pairs. According to the Fermi golden rule for the electron transfer, the electron transfer rate is proportional to the square of the electron interaction between the orbitals of the donor and acceptor. Thus, the electron transfer rate (k_{et}) can be expressed as follows using the distance for the electron transfer (r):

$$k_{\text{et}} \propto \exp[-\beta(r - r_0)] \quad (1)$$

where β and r_0 are the dumping factor and contact distance, respectively. The β value has been employed as a characteristic parameter of various conduction media. $\beta = 0$ indicates super conductivity. They evaluated the β value to be $0.88 \text{ \AA}^{-1}$, close to that estimated for proteins.

For a detailed analysis of the distance dependence of the electron transfer, site-selective intercalation of the donor and acceptor is essential. In 1993, Barton and coworkers investigated the electron transfer in DNA by means of the fluorescence quenching experiments. In their system, bis(phenanthroline)(dipyridophenazine)ruthenium(II) ($\text{Ru}(\text{phen}')_2\text{dppz}^{2+}$) and bis(9,10-phenanthrene diimine)(phenanthroline)rhodium(III) ($\text{Rh}(\text{phi})_2\text{phen}^{3+}$), which were tethered to 5' termini of the complementary 15 base pairs, were used as the donor and acceptor, respectively (Figure 2).³³ These metal complexes were intercalated either one or two base steps from the termini of 15 base pair DNA due to high affinity for intercalation, $\geq 10^6 \text{ M}^{-1}$, and intercalation was confirmed by the NMR measurements as well as modeling and product analysis of the photoirradiation. The driving force for the electron transfer was

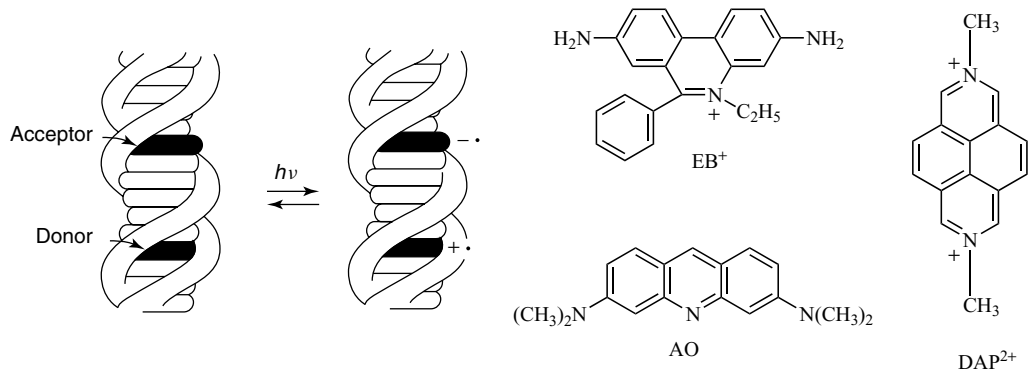


Figure 1 Electron transfer between intercalators through DNA. [Reproduced from Ref. 32. © American Chemical Society, 1992.]

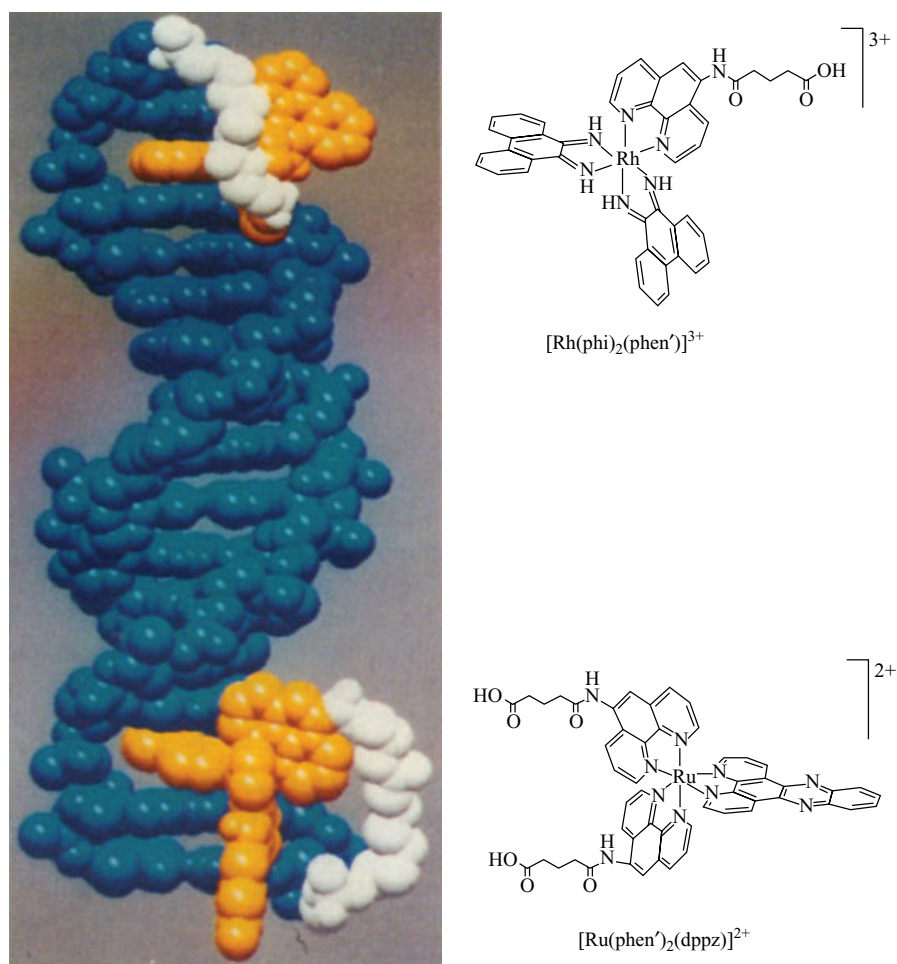


Figure 2 DNA with Ru and Rh complexes as the donor and acceptor, respectively, investigated by Barton and coworkers. [Reproduced with permission from Ref. 33. © American Association for the Advancement of Science, 1993.]

estimated to be 0.75 eV. Complete fluorescence quenching was observed in the DNA containing both donor and acceptor. The fluorescence lifetime was shorter than their instrumental limitation (300 ps). From these findings, they concluded that the photoinduced electron transfer between intercalated donor and acceptor occurred very rapidly over 40 Å through the DNA helix over pathway consisting of π -stacked base pairs. They confirmed the importance of the intercalation of donor and acceptor in the electron transfer using DNA octamer tethered with $\text{Ru}(\text{phen})_3^{2+}$ and $\text{Rh}(\text{phen})_3^{3+}$, which have lower ability of intercalation, from the no fluorescence quenching. From the estimated lower limit of k_{et} value, they indicated that the β value of DNA as the electron transfer media is lower than 0.2 Å^{-1} . These results attract quite large attentions of the researchers in wide fields.

The long-range hole transfer has attracted attention in relation to DNA damage at a site remote from the hole injections. In 1996, Barton and coworkers reported the oxidative DNA damage caused by hole transfer from the photoexcited Rh complex intercalated to DNA.^{34,35} In the DNA, two GG doublet sites were included at a distance of 17 and 34 Å from the Rh complex as hole acceptor. DNA damage was observed at both sites. The intensity of the oxidative damage at the site distal to the Rh complex is comparable to (or even higher than) that of proximal GG doublet, suggesting that the yield of the damage is not strongly distance dependent.

The electron transfer between the intercalated donor and G was also investigated by Tanaka and coworkers by means of the fluorescence quenching and lifetime measurement.^{36,37} They used methoxy acridine connected covalently to DNA helix as the donor. From the distance dependence, they estimated the β value to be 1.49 Å^{-1} .

The property of DNA as the media for the electron transfer was further investigated by the research groups of Lewis and Wasielewski using the transient absorption spectroscopy. They employed DNA hairpins, in which stilbene dicarboxamide (SA), the electron acceptor, forms a bridge connecting two oligonucleotide arms (Figure 3).³⁸ By selective excitation of SA with the femtosecond laser pulse, they observed the transient absorption band of the SA radical anion with the decay of the singlet excited state, when the G and SA were separated by small number of A (<3). These findings indicate the electron transfer from G to

singlet excited SA, that is, the hole injection. In this system, A separating G and SA did not act as the electron donor for the photoexcited SA. These can be rationalized by the fact that the driving force for the charge separation between G and SA was estimated to be -0.20 eV , while that for A and SA is $+0.25 \text{ eV}$. From the estimated rate constant and the distance for the electron transfer, they evaluated the β value to be 0.64 Å^{-1} , which is larger than the value estimated by Barton and coworkers indicated earlier. For the charge recombination process generating the ground state, they reported a β value of $\sim 0.9 \text{ Å}^{-1}$. The estimated β values of DNA are larger than that of π -conjugated oligomers such as phenylene vinylene in donor-spacer-acceptor system ($\beta < 0.1 \text{ Å}^{-1}$), but smaller than those of proteins (see **Electron Transfer in Peptides and Proteins**) with the rigid hydrocarbon framework ($\beta = 1.0\text{--}1.4 \text{ Å}^{-1}$). Thus, the β value of DNA indicates relative weak electronic interaction between the stacked π -conjugated molecules.

According to the Marcus theory, the k_{et} can be described as a function of the driving force for the electron transfer (ΔG) as follows:^{39–41}

$$k_{\text{et}} = \frac{2\pi}{\hbar} \frac{H_{\text{DA}}^2}{\sqrt{4\pi\lambda_S k_B T}} e^{-S_C} \sum_{n=0}^{\infty} \frac{S_C^n}{n!} \times \exp\left(-\frac{(\lambda_S + \Delta G + n\hbar\langle\omega\rangle)^2}{4\lambda_S k_B T}\right) \quad (2)$$

$$S_C = \frac{\lambda_v}{\hbar\langle\omega\rangle} \quad (3)$$

In (2), λ_S is the solvent reorganization energy, H_{DA} is the electronic coupling, S_C is the electron-vibration coupling constant given by (3), and $\langle\omega\rangle$ is the averaged angular frequency. In (3), λ_v is the internal reorganization energy. The driving force for charge separation from the excited state (ΔG_{CS}) and recombination to the ground state (ΔG_{CR}) can be given by the following Weller's equations⁴²:

$$\Delta G_{\text{CS}} = E_{\text{ox}} - E_{\text{red}} - E_S + C \quad (4)$$

$$\Delta G_{\text{CR}} = E_{\text{red}} - E_{\text{ox}} - C \quad (5)$$

where E_{ox} , E_{red} , E_S , and C are the oxidation potential of the donor, reduction potential of the acceptor, singlet-excited state energy, and Coulombic

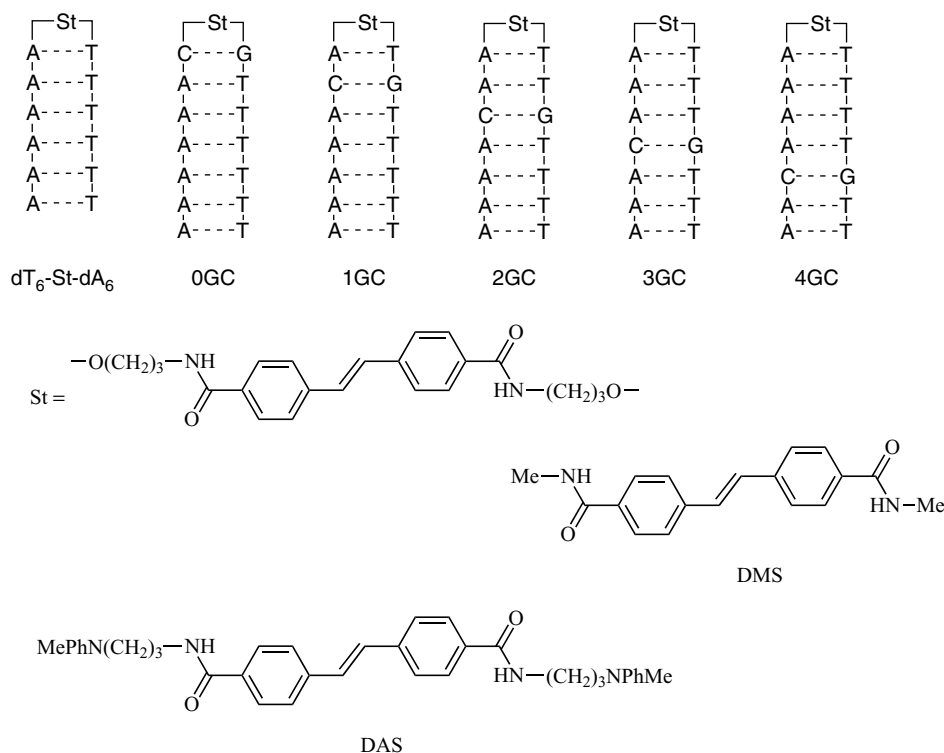


Figure 3 DNA hairpins with stilbene dicarboxamide at the loop position as the photosensitizing electron acceptor. [Reproduced with permission from Ref. 38. © American Association for the Advancement of Science, 1997.]

term, respectively. The C term is negligibly small for a polar solvent. The research groups of Lewis and Wasielewski estimated the rate constant of the charge separation (k_{CS}) and recombination (k_{CR}) between the nucleobase, which acts as the electron donor, and electron acceptor at the loop position of the DNA hairpins, and investigated free energy dependence of the electron transfer rate (Figure 4).⁴³ They confirmed that the electron transfer rate can be described in accordance with (2). When the nucleobase, which acts as the electron donor, contacts the electron acceptor, the ΔG dependence of k_{CS} values can be fitted using (2) with λ_S , λ_V , and H_{AD} values being 0.31 eV, 0.61 eV, and 230 cm^{-1} , respectively. They pointed out that these values are similar to those reported for the cyclophane-bridged donor–acceptor molecules and that the relative small H_{DA} value supported the electron transfer in the nonadiabatic region, which is a prerequisite of the treatment with (2). They also estimated the k_{CS} and k_{CR} values of DNA hairpins, in which the electron acceptor and the nucleobase, which acts as

the electron donor, are separated by two A-T pairs. The λ_S , λ_V , and H_{DA} values were estimated to be 0.41 eV, 0.60 eV, and 17 cm^{-1} , respectively. The λ_S and λ_V values did not show substantial distance dependence. The smaller H_{DA} value of the latter system reflects exponential dependence on the donor–acceptor distance as follows:

$$H_{DA} = H_{DA}^0 \exp[-\beta(r - r_0)/2] \quad (6)$$

From this relation, they estimated the H_{DA}^0 value to be 400 cm^{-1} . These findings indicate that the single-step electron transfer in DNA mediated by nucleobases can be described by Marcus theory developed for nonadiabatic electron transfer systems.^{39–41}

In this section, the hole injection process in DNA is summarized. In the electron injection process to DNA, G, which possesses the lowest oxidation potential among the four natural nucleobases, acts as the electron donor against the photosensitizing electron acceptor. The hole injection process has

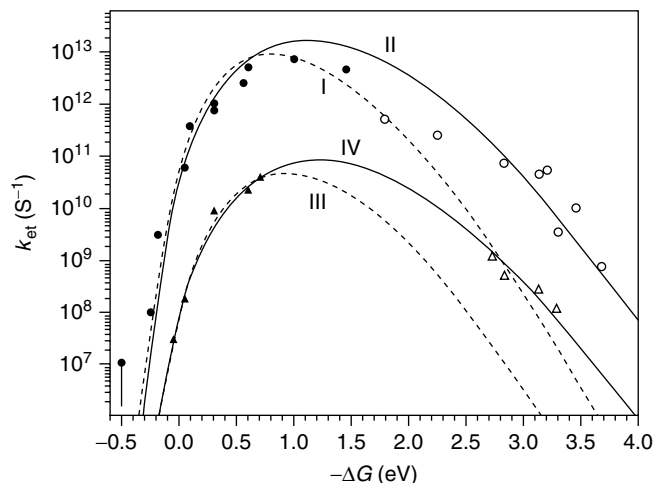


Figure 4 Free energy dependence of the charge separation and recombination rates. I and II are the electron transfers between the photosensitizing electron acceptor and neighboring nucleobase. III and IV are electron transfer between the electron acceptor and nucleobase separated by two A–T pairs. I and III are determined for the charge separation processes. II and IV are for both charge separation and recombination. [Reproduced from Ref. 43. © American Chemical Society, 2000.]

been successfully described by the Marcus theory (2), the electron transfer theory for the nonadiabatic region, in which the electronic interaction between the donor and acceptor is small or moderate. The forward and backward electron transfer rates showed clear parabola-like dependence against the driving force for the electron transfer. Furthermore, the electron transfer rates decreased exponentially with the distance as expected from (1) and (2), supporting that this is the electron tunneling process, governed by the superexchange interaction. As the β value of the DNA, $\beta = \sim 0.7 \text{ \AA}^{-1}$ seems to be accepted widely, although the reported values showed some scattering at the initial stage of this study. This value is located between the conjugated polymer and hydrocarbons including proteins. In this sense, this value is reasonable for the stacked aromatic compounds.

3.2 Hole Hopping in DNA

In the process of hole injection to DNA, which was described in the previous section, the driving force for the electron transfer is exothermicity. Thus, the hole injection rate is on the order of picoseconds in some cases. Once a hole is injected, it can migrate in DNA by successive oxidation of the neighboring nucleobase by nucleobase radical

cation. This process can be categorized as a multistep hole hopping process. In the hole hopping, the driving force for electron transfer between the same kind of nucleobases is zero. Thus, a nanosecond to microsecond timescale is expected for the hopping rate.

In the case of the hole hopping process, G radical cation is expected to act as an important charge mediator, because G has the lowest oxidation potential among the four natural nucleobases, as indicated in the earlier section. That is, oxidation of nucleobases by G radical cation is an endothermic process. Giese and coworkers have investigated the oxidation of GGG by hole transfer from G radical cation separated by A:T pairs by product analysis using gel electrophoresis.⁴⁴ When the number of A:T pairs is less than 5, they confirmed that the formation of GGG radical cation decreased as an exponential function of distance. From the product yield, they have estimated the β value to be $0.7 \text{ \AA}^{-1}$, which is the same as that summarized in the earlier section. In addition, they observed quite high yield of GGG radical cation even when the GGG was separated from G radical cation by 15 base pairs (54 Å), in which several Gs were included acting as relay stations or stepping stones for the hole on the way to the GGG unit (Figure 5). Thus, the hole transfer from the initially formed G radical cation to GGG does not occur in one step but in a multistep

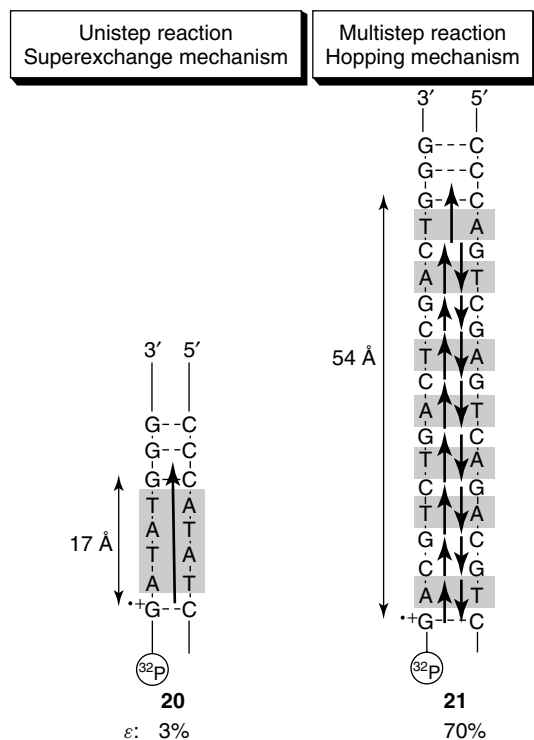


Figure 5 Single-step electron transfer and multistep electron transfer. [Reproduced from Ref. 44. © American Chemical Society, 2000.]

manner, that is, G hopping. In this case, charge migrates by a random work because there is no driving force. The efficiency of the charge transport (E) can be expressed as a function of number of steps (N), as follows:

$$\ln E \propto -\ln N. \quad (7)$$

One of the important characteristics of (7) is the smaller distance dependence when compared to (1), supporting the long-range hole migration.

In 2001, Giese and coworkers investigated the hole transfer from G radical cation to GGG unit separated by only A:T pairs without G, which acts as a stepping stone between initially formed G radical cation and GGG.⁴⁵ When the number of A:T pair is less than 3, the yield of the product due to oxidation of GGG decreases by a factor of 8 for each additional A:T pair. Further elongation of the A:T sequence did not change the yield of GGG radical cation (Figure 6). They explained the smaller distance dependence for DNA with longer

A:T sequence as the contribution of hopping of A radical cation formed by oxidation by G radical cation, that is, A hopping.

For the determination of the rate constant for A hopping, our research group investigated the charge separation and recombination processes in DNA hairpin conjugated with naphthaldiimide (NDI) and phenothiazine (PTZ) as the photosensitizing electron acceptor at loop position and hole trap at 5' end, respectively.⁴⁶ The selective excitation of the NDI generated NDI radical anion and PTZ radical cation within the nanosecond laser duration even when the NDI and PTZ were separated by eight A:T pairs, indicating rapid hole migration by A hopping mechanism. By applying (8) to the dependence of the yield of the radical ion pairs (Φ), that is, NDI radical cation and PTZ radical anion, on the number of A:T base pairs, the rate constant for the single hopping rate (k_A in Figure 7) was estimated to be $2 \times 10^{10} \text{ s}^{-1}$:

$$\Phi = (k_2/k_1)/[1 + (N - 1)(k_2/k_1)] \quad (8)$$

where k_1 and k_2 are the rate constants for the charge recombination and hole shift from A to PTZ, respectively. The estimated rate is quite rapid compared to the estimated value for the G to GG or GGG separated by one A.

This fast hopping rate among consecutive A sequences is considered to enable the efficient charge migration even if the photosensitizing donor and hole acceptor are separated by long distance. This was confirmed in 2006.⁴⁷ When naphthalimide (NI) and PTZ were connected by DNA sequence including consecutive 30 A:T pairs, it was observed that the generation of PTZ radical cation due to the hole migration by A hopping completed within the nanosecond laser duration, indicating long-distance hole migration over 100 Å within several tens of nanoseconds. Furthermore, we confirmed that the very weak distance dependence of the yield of PTZ radical cation is in accordance with the fast A hopping rate.

In 2010, the research groups of Lewis and Wasielewski examined the hole migration process in DNA hairpins conjugated with SA and stilbene diether (SD) by means of the femtosecond and nanosecond laser flash photolysis (Figure 8).⁴⁸ They applied (9) for the unbiased first passage random walk in one dimension to generation kinetics of SD

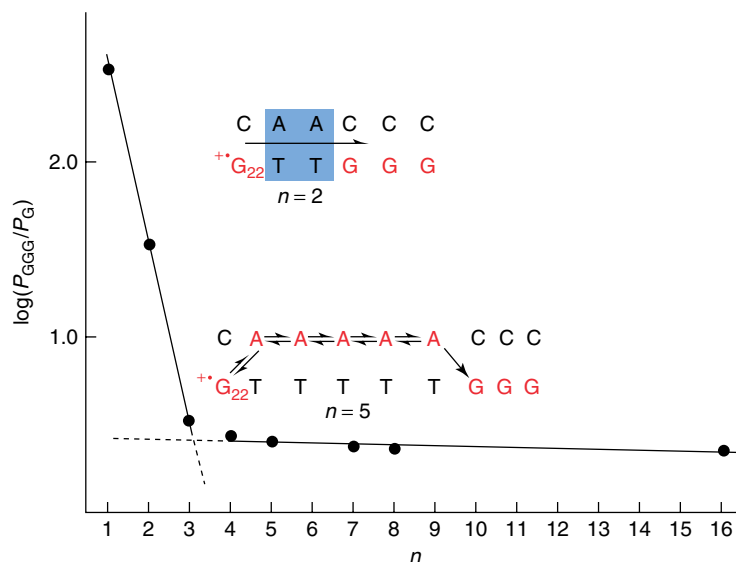


Figure 6 Yield of oxidation product of GGG depending on the number of A–T pairs located between G radical cation and GGG. [Reproduced from Ref. 45. © Nature Publishing Group, 2001.]

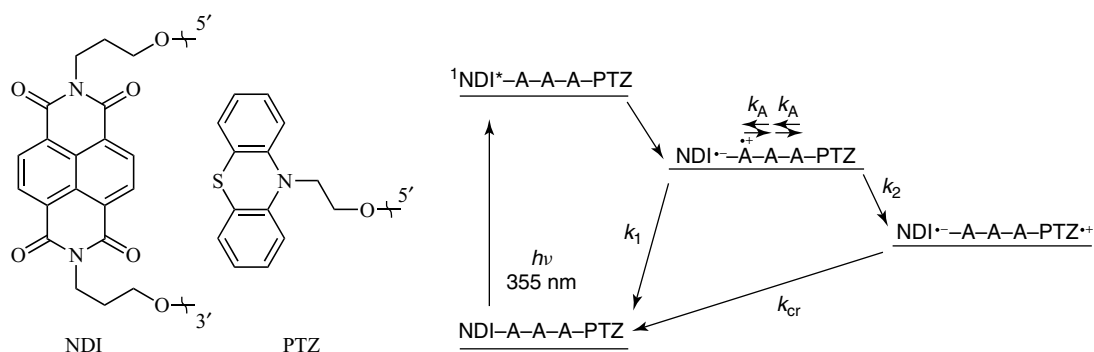


Figure 7 Molecular structures of NDI and PTZ conjugated to DNA hairpins at loop and 5' end. Schematic energy diagram of A hopping in DNA hairpins. [Reproduced from Ref. 46. © American Chemical Society, 2004.]

radical cation:

$$\tau(N) = (1/2k_{\text{hop}})N^2 \quad (9)$$

where $\tau(N)$ is the time required for N hopping and k_{hop} is the rate constant for the single hopping step. They evaluated 4.3×10^9 and $1.2 \times 10^9 \text{ s}^{-1}$ for the k_{hop} values of G-to-G and A-to-A hopping rate, respectively. Furthermore, from the temperature dependence, they evaluated the activation energy for the hopping in the diblock DNA hairpin to be $2.8 \text{ kcal mol}^{-1}$ with an A factor of $7 \times 10^9 \text{ s}^{-1}$, consistent with weakly activated, conformational gated process.

Although there is discrepancy in the reported A hopping rates, it is reasonable to say that the consecutive A–A or G–G hopping rates is of smaller than nanosecond order. The several ten or hundred picosecond-order hole hopping rate along the consecutive sequence can be attributed to the shorter distance between the sites to be hopped (i.e., $3.4 \text{ \AA}$ for B-type DNA). But in the case of G hopping through one or more intervening A, C, or T, the hopping rate should be slowed down because the A, C, or T should work as the barrier for the hole hopping.

The actual hole transfer rate from G radical cation to GG or GGG separated by A was obtained

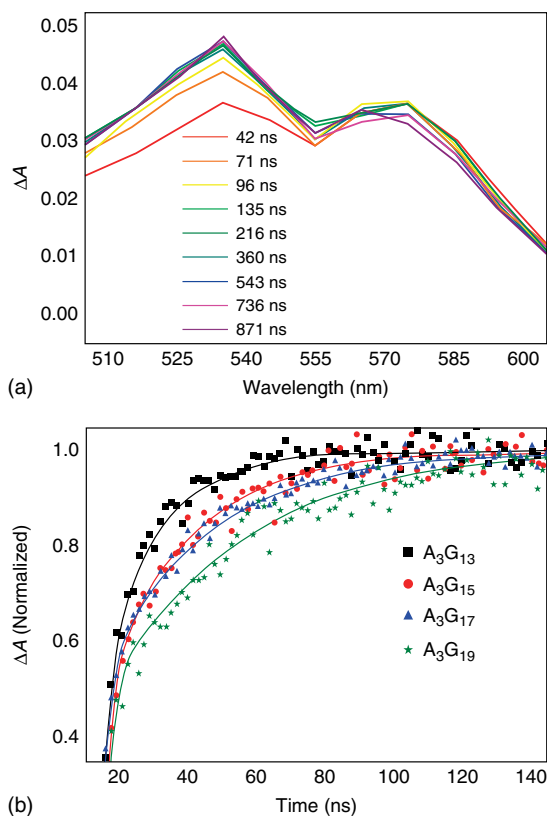


Figure 8 (a) Transient absorption spectra of diblock DNA hairpin conjugated with SD and SA at loop and end cap position. (b) The kinetic trace of SD radical cation during the nanosecond laser flash photolysis. [Reproduced from Ref. 48. © American Chemical Society, 2010.]

from the DNA hairpins, which have SA at the loop position, by the research groups of Lewis and Wasielewski.^{49–51} From the analysis of the kinetic trace of the SA radical anion of the DNA, in which G and GG were separated by single A:T pair, the forward and backward hole transfer rates were estimated to be 5×10^7 and $6 \times 10^6 \text{ s}^{-1}$, respectively. The difference in the forward and backward hole transfer rates reflects the relative energy of the G and GG radical cation. From these values, they estimated that GG radical cation is more stable than G radical cation by 0.052 eV. Thus, it was revealed that the timescale of the single-step hole transfer in DNA is in the order of several ten to hundred nanoseconds order, which is in accordance with the smaller driving force for the electron transfer. Furthermore, they estimated the hole

transfer rate from G to GGG to be 8.7×10^7 and $4.3 \times 10^6 \text{ s}^{-1}$ for forward and backward hole transfers, respectively. In this case, GGG radical cation is lower in energy than that of G by 0.077 eV. These values support the theory that the oxidation potential of G is affected by the surrounding nucleobases as suggested by theoretical calculations and formation of stable radical cation in the consecutive G sequences.

Our research group estimated the hole transfer rates between two Gs separated by A or T by nanosecond laser flash on the DNA conjugated with NI and PTZ (Figure 9).⁵² In this DNA, the hole generated by the photosensitizing electron acceptor, NI, was once trapped by the G by fast hole migration along A consecutive sequence, and then migrated to the PTZ by repeated G-A-G hopping. It was confirmed that the generation rate of PTZ radical cation depends on the number of G-A-G in accordance with one-dimensional random walk model. From the analysis of the kinetic trace of PTZ radical cation, the rate constant for the single hopping was estimated to be $4.8 \times 10^7 \text{ s}^{-1}$. In a similar manner, the single-step G-T-G hopping rate was estimated to be $4.6 \times 10^5 \text{ s}^{-1}$. The two-order smaller hopping rate of G-T-G than that of G-A-G can be attributed to the higher oxidation potential of T, which decreases electronic coupling between two Gs in accordance with the tunneling theory. In addition, the effect of the number of intervening A or T was also examined (Table 2). It was revealed that the insertion of the additional A or T dramatically decreased the hopping rate in an exponential manner, as pointed out by Giese *et al.*

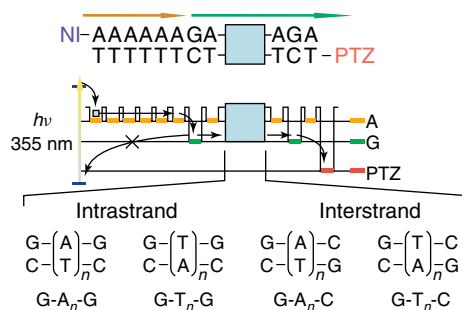


Figure 9 (a) DNA investigated for the estimation of the intra- and interstrand G hopping rate. (b) The schematic energy diagram for the hole migration. [Reproduced with permission from Ref. 52. © Wiley-VCH Verlag GmbH & Co. KGaA, 2005.]

Table 2 The intra- and interstrand hole hopping rates between two Gs separated by A, T, or C and activation energy.

Sequence	<i>n</i>	<i>k</i> _{ht} (s ⁻¹)	<i>E</i> _a (eV)
G-A _{<i>n</i>} -G	1	4.8 × 10 ⁷	0.18
	2	9.7 × 10 ⁴	0.43
	3	1.4 × 10 ⁴	—
G-T _{<i>n</i>} -G	1	4.6 × 10 ⁵	0.35
	2	3.6 × 10 ⁴	0.50
	3	9.1 × 10 ³	—
G-A _{<i>n</i>} -C ^a	1	1.4 × 10 ⁶	0.30
	2	4.5 × 10 ⁴	0.53
G-T _{<i>n</i>} -C ^a	1	1.6 × 10 ⁶	0.25
	2	3.1 × 10 ⁴	0.50
G-C _{<i>n</i>} -G ^a	1	(3.6–4.0) × 10 ⁴	0.22–0.25

Source: Reproduced with permission from Ref. 52. © Wiley-VCH Verlag GmbH & Co. KGaA, 2005.

^aInterstrand hole hopping rate.

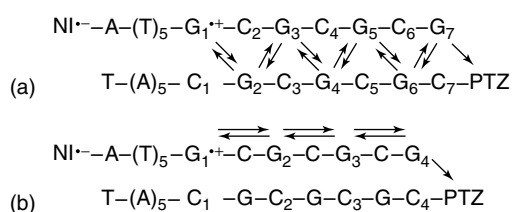
We also estimated the interstrand G hopping rates using DNA sequences including G-A-C or G-T-C. The estimated rates were almost identical (Table 2) and were slower than that of intrastrand G-A-G due to the longer distance to be hopped.

In the case of hopping between two Gs separated by C, inter- and intrastrand G hopping processes have to be considered, as indicated in Figure 10.⁵³ By applying the model of Figure 10 to kinetic trace of the generation profile of PTZ radical cation, rate constant for the G hopping was estimated to be (3.6–4.0) × 10⁸ and (1.0–1.2) × 10⁸ s⁻¹ for the inter- and intrastrand mechanisms, respectively. The estimated values were faster than that for G-A-G hopping rate, which should be faster than that for G-C-G intrastrand G hopping because of the lower barrier to be hopped. From this reasoning, the observed hole hopping can be attributed to the interstrand G hopping with the rate of (3.6–4.0) × 10⁸ s⁻¹. The estimated value, which is smaller than that reported for consecutive G sequence,

seems to be reasonable, because the distance to be hopped should be larger than that for the consecutive G.

As indicated in this section, the hopping rate between two Gs separated by A, C, or T was lowered because these nucleobases with higher oxidation potential than G act as a barrier for the electronic hopping. Thus, inclusion of barrier decreases the hole migration rate. For the realization of the fast hole migration, one of the possible strategies is the inclusion of the artificial nucleobases that possess a highest occupied molecular orbital (HOMO) level similar to that of G.⁵⁴ To test this idea, our research group employed 7-deazaadenine (Z), in which N7 nitrogen of adenine was substituted with C–H group to have an oxidation potential (1.39 V vs NHE) similar to that of G (1.31 V). It was confirmed that by substituting A:T with Z:T, a three-order enhancement of the charge transfer rate was achieved.

In this section, the hole hopping along G and A, of which oxidation potentials are lower than those of the other two, are summarized. Although the electron tunneling mechanism limits the distance for the hole transfer to 3 or 4 nucleobases, successive hopping, that is, repeated electron tunneling, allows long-distance hole migration. The distance of the hopping can reach up to hundreds of angstroms. The single-step hopping rate is on the order of several ten to hundred picoseconds, when A or G is not separated by other nucleobases. When single A or T is inserted between the two Gs, the hopping rate decreases to 10⁵–10⁷ s⁻¹, that is, several ten to hundred nanoseconds. Further decrease in the rate was observed when the number of the intervening A or T was increased. On the other hand, when single C is inserted between the two Gs, interstrand hole hopping becomes operative. This decrease in the hole hopping rate can be rationalized by the increase in the barrier height for the hole tunneling. In this sense, this phenomenon can also be described by the conventional electron transfer theory.

**Figure 10** Inter- and intrastrand G hopping. [Reproduced from Ref. 53. Copyright (2006) National Academy of Sciences, U.S.A.]

3.3 Hole Transfer in Various Structures

One of the important and unique characteristics of DNA is the variety of higher order structures depending on the DNA sequence and/or conditions. One such structure is the T:A·T triplex, in which T:A forms normal Watson–Crick duplex and a

third T is associated by Hoogsteen hydrogen bonding. T:A·T triplex has a structure similar to B-DNA duplex with a 3.3-Å stacking distance and 28° helical pitch. The research groups of Lewis and Wasielewski prepared T:A·T triplex with SA- and SD-linked DNA hairpin, in which SA linked T:A, while SD formed a linkage with the third T (Figure 11).⁵⁵ In these DNA hairpins, T:A·T triplex acts as a spacer of electron transfer

to the photoexcited SA from SD. The electron transfer to photoexcited SA was confirmed by formation of SA radical anion with the decay of the singlet-excited SA in the femtosecond transient absorption spectroscopy. From the distance dependence of the electron transfer rate, the authors determined the β value for charge separation to be 0.39 Å^{-1} , which is smaller than that for the duplex (0.64 Å^{-1}), while the β value for the

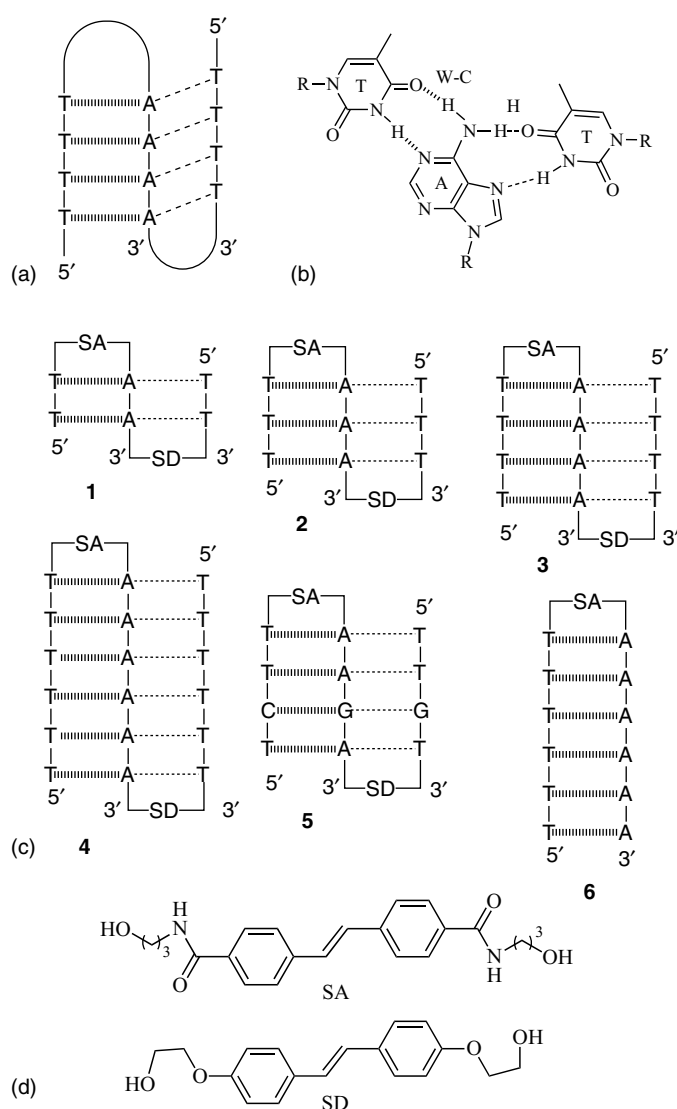


Figure 11 (a) Structure of an intramolecular antiparallel DNA triplex with Watson-Crick (W-C, |||) and Hoogsteen (H, - - -) hydrogen bonding. (b) Structure of the T:A·T canonical triplex. (c) Structure of intramolecular triplexes and hairpin. (d) Structures of the SA and SD linkers. [Reproduced with permission from Ref. 55. © Wiley-VCH Verlag GmbH & Co. KGaA, 2002.]

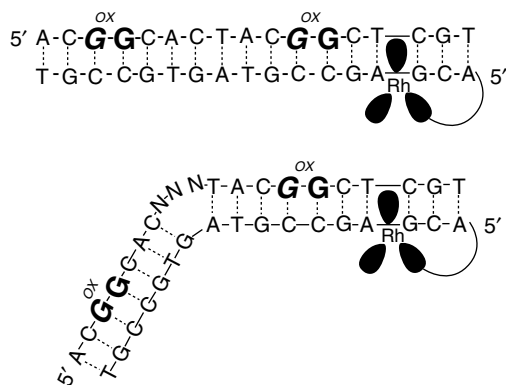


Figure 12 Hole transfer in DNA with a bulge. [Reproduced from Ref. 56. © American Chemical Society, 1997.]

charge recombination ($1.0 \text{ \AA}^{-1}$) is similar to that of the duplex ($0.94 \text{ \AA}^{-1}$). The authors indicated that the shorter base pair stacking distance of triplex and lower oxidation potential of A in the triplex than that in the duplex lowered the energy gap between electron donor and bridge state. This finding also supported the electron transfer by electron tunneling, mediated by the super exchange interaction.

In the case of the above-mentioned triplex structure, the base pairing is maintained. But in the case of DNA structures such as bulge and loop, base pairing is disrupted, forming a bent structure. In 1997, Barton and coworkers reported the effect of the insertion of three kinds of bulge, that is, A_n , T_n ($n = 1 - 3$), and ATA, between the photosensitizing hole donor and GG hole acceptor (Figure 12).⁵⁶ They found that the insertion of the ATA bulge between the proximal and distal GG doublets diminished the oxidation of distal GG doublet by a factor of 4. They also found that insertion of a single A or T bulge effectively diminishes the oxidation of the distal GG doublet, although the effect increases with the n of A_n or T_n . These results indicate the importance of base pairing in DNA long range hole transfer.

The mismatch of the base pairing is another source of the disruption of the base stacking, which has been shown to affect the charge transfer in DNA. There are several reports that show that the mismatch inhibits the DNA charge transfer.^{57–59} Giese and Wessely demonstrated that a G-containing mismatch decreases the efficiency of the charge transfer.⁵⁷ Barton and coworker demonstrated that

the yield of the long-range oxidative DNA damage through intervening mismatches correlates with the imino proton exchange rates of the mismatch in a millisecond.⁵⁸ Schuster and coworker reported a larger effect of T:T mismatch than A:A.⁵⁹ For the quantitative analysis of the effect of the mismatch on the charge transfer efficiency, the estimation of the rate constant for the charge transfer through the mismatch is essential. From this point of view, we have investigated the charge transfer process through the mismatch.⁶⁰ In Figure 13, DNA sequences investigated in the study are summarized. The 14 assemblies, which possess NI and PTZ as the photosensitizing hole donor and hole acceptor, respectively, can be classified into three groups, that is, assembly 1 (bridge parts; A:T), assembly 2 (T:A), and assembly 3 (AA:TT). The mismatches were introduced into the bridge parts of the complementary base of G or several intervening bases between the two Gs (A:A, T:T, or A:C mismatch). In Table 3, the rate constant for the GG hopping with mismatch sequences are shown. From the rate constants in Table 3, it was indicated that the charge transfer from fully matched G to the G-containing mismatch is slower than that for fully matched assembly, while the charge transfer from the G-containing mismatch to the fully matched G is faster than that for the fully matched one. In addition, the charge transfer across the T:T or A:C mismatches are slower than that for the fully matched assembly, while the charge transfer across A:A mismatch is faster than that for the fully matched one. Since the decrease in the hole transfer rate can be associated with the decrease in the base stacking, we also estimated the melting temperature of the assemblies (Table 3). It was clear that the inclusion of the mismatches decreased melting temperature and one-to-one correlation was not observed. From the estimated rate constants for the charge transfer through the mismatch, we have shown that the kinetic discrimination of mismatch sequence is possible.

As the building block of the nanostructure, DNA has been widely employed. In the construction of the nanostructure by DNA, the sequence called *sticky end*, which ensures the selective base pair formation with other DNA chain, is often employed. We have also examined the effect on the charge transfer of the existence of the sticky ends between the photosensitizing hole donor and acceptor.⁶¹ From the comparison, we have confirmed that the effect



Table 3 The melting temperature, rate constants of the charge transfer in fully matched and mismatched DNA, and activation energies.

Assembly	T_m (°C)	k_{ht} (s ⁻¹)	E_a (eV)
GC-1	55.4	1.2×10^6 (k_{GAC})	0.30
GT-1	41.2	7.1×10^4 (k_{GT1})	0.37
GA-1	39.2	9.2×10^4 (k_{GA1})	0.33
AA-1	44.2	9.7×10^5 (k_{AA1})	0.30
TT-1	42.0	1.6×10^5 (k_{TT1})	0.44
AC-1	44.6	1.3×10^5 (k_{AC1})	0.28
GC-2	54.1	1.5×10^6 (k_{GTC})	0.25
GT-2	44.7	1.9×10^5 (k_{GT2})	0.33
GA-2	40.7	1.6×10^5 (k_{GA2})	0.34
GC-3	52.4	6.2×10^4 (k_{GAAG})	0.38
GT-3	41.4	1.0×10^4 (k_{GT3})	0.47
GA-3	45.3	9.5×10^3 (k_{GA3})	0.54
AA-3	36.9	1.3×10^5 (k_{AA3})	0.37
TT-3	38.4	2.7×10^4 (k_{TT3})	0.56
GT-4	45.7	5.2×10^6 (k_x)	0.30
GT-5	46.5	6.9×10^6 (k_y)	0.28

Source: Reproduced from Ref. 60. © Oxford University Press, 2008.

of the sticky end is rather small, in accordance with the electrochemical study carried out by Liu and Barton.⁶²

In addition to the structures indicated in this section, various DNA structures have been reported. For these structures, factors governing the electron transfer, such as base pair distance and flexibility, should be altered. As a result, the charge transfer in these structured materials should be sensitive to the structures. These issues will be important subjects to be clarified.

3.4 Application of Hole Transfer

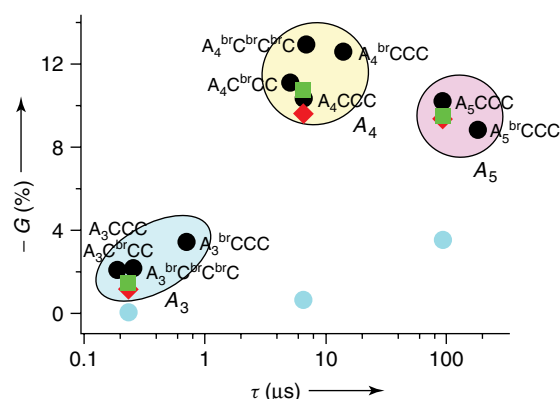
One of the important motivations for the research on the hole transfer in DNA is the clarification of the relation with the oxidative damage of DNA. The mechanism of the damage of DNA by the photoinduced process has been categorized into two types. One is the oxidation of DNA by the photosensitizer (type I) and the other is the oxidation of DNA mediated by singlet oxygen (type II). Since the reaction rate of G radical cation and water, which causes the DNA damage, is quite slower ($\sim 5 \text{ s}^{-1}$ or slower)^{63,64} compared to the charge recombination rate between the photosensitizer and initially generated radical cation, the long-lived radical cation of DNA, which can be generated by

the long-range hole hopping, should be essential in type I DNA damage. In order to confirm this hypothesis, we compared the DNA damage, which can be quantified by the loss of G after the photolysis, the charge separation yield, and the charge recombination rate.⁶⁵ As a simplified model, in which the reaction of the oxygen and G radical cation determines the amount of DNA damage, the following equation can be derived

$$[\text{DNA damage}] = (\text{constant}) \times \phi \times k_{\text{O}_2}[\text{O}_2]/(k_{\text{O}_2}[\text{O}_2] + 1/\tau) \quad (10)$$

where ϕ and τ are the yield of long-lived charge-separated state and lifetime, respectively. In Figure 14, the loss of G was plotted against the lifetime of the generated radical cation. The values estimated by (10) are indicated by cube and diamond in Figure 14, which are in good accordance with the experimental values. These results indicate that the generated long-lived holes, especially generated by fast hole hopping to have longer lifetimes of ten to hundred microsecond regions, cause DNA damages. In this sense, consecutive A or G sequence, which realizes fast charge transfer after the initial hole injection, will enhance DNA damage.

As indicated in the above section, the rate of hole hopping, which has a close relation with the yield of the final oxidized species, is largely affected by the DNA sequence. Another important application of the estimation of hole hopping in DNA will be the

**Figure 14** The relation between the loss of G and the lifetime of the generated radical cation. [Reproduced from Ref. 65. © Elsevier Inc, 2005.]

read out or detection of the single-base mismatch. In order to realize this issue by optical method, we examined detection with the single molecular fluorescence spectroscopy.⁶⁶ In this system, DNA was conjugated with the photosensitizing electron acceptor and reporter fluorescence molecules at both the ends (Figure 15). The hole migration to the reporter fluorescent molecule quenches the fluorescence, while mismatch in DNA decreases the amount of fluorescence quenching by diminishing the hole transfer to the reporter fluorescent molecule (Figure 15). As indicated in the bottom graph of Figure 15, the photobleaching efficiency decreased when the DNA included the mismatch sequences. Furthermore, the efficiency was also sensitive to the position of mismatch. This will be one of the simple applications of the hole migration in mismatch detection. In addition to the conventional organic dye, we also indicated that titanium dioxide can also be used as the photosensitizing electron acceptor for the detection of the mismatch sequence by employing the single molecule fluorescence spectroscopy system.⁶⁷

In addition to the biomedical application, application to nanoscale electronic wiring is another interesting field. In the construction of the nanostructure by DNA, the sequence called *sticky end*, which ensures the selective base pair formation with other DNA chain, is useful. The employment of such sticky ends seems to be useful in biomedical application also. From this viewpoint, we have examined the hole transfer in DNA composed of several blocks, which were connected by sticky ends (Figure 16).⁵³ In this system, the DNA includes three blocks, that is, charge injection block (red), conductive block (green), and charge detection block (yellow). Three blocks form one duplex by means of the connection at the sticky ends. When the conductive block is the full match sequence, fast generation of PTZ radical cation was confirmed, while the inclusion of the mismatch lowered generation rate drastically. Thus, these block structures will be useful in the construction of nanostructured materials with the conductive functions.

In addition to the higher structure of DNA, which can be generated depending on the sequence and/or

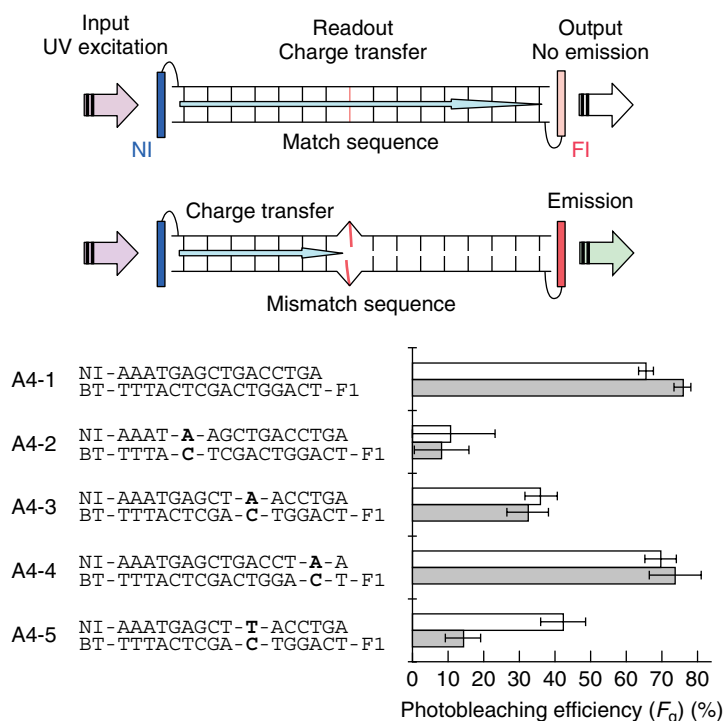


Figure 15 Bleaching of the fluorescence from the reporter molecule due to the hole migration and the inhibition by mismatch sequence. [Reproduced from Ref. 66. Copyright (2007) National Academy of Sciences, U.S.A.]

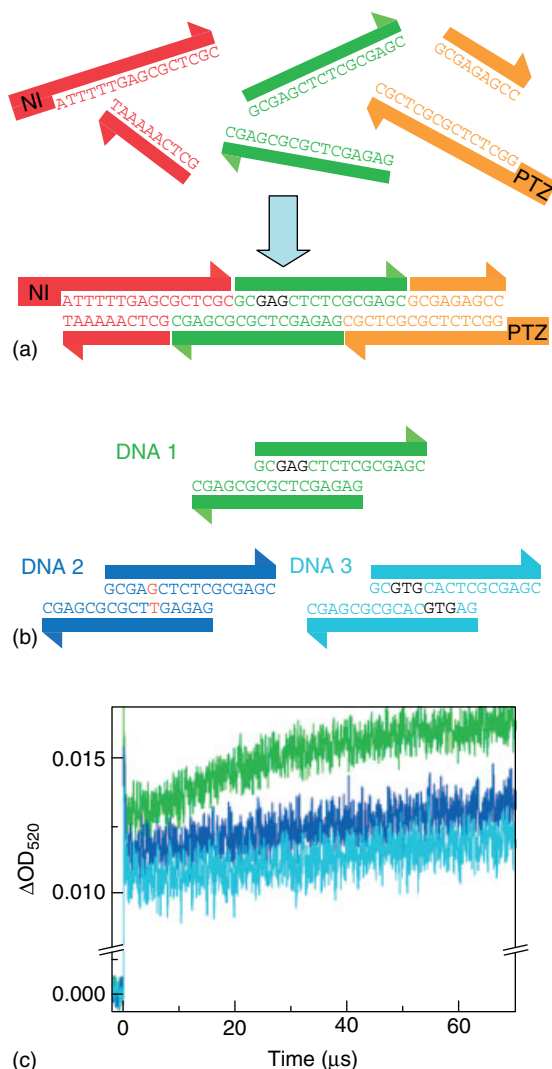


Figure 16 (a) DNA duplex bearing sticky end and constructed DNA containing three blocks: charge injection block (red), conductive block (green), and charge detection block (yellow). (b) DNA block for the conductive block. (c) The time profiles of transient absorption of PTZ radical cation. [Reproduced from Ref. 53. Copyright (2006) National Academy of Sciences, U.S.A.]

surrounding condition, several artificial structures can be realized by the introduction of functional molecules. The DNA conjugated with perylene bisimides (PDI), as investigated by the research groups of Lewis and Wasielewski, is one of the examples of these artificial DNA.⁶⁸ In this case, because of its hydrophobic interaction, PDI tends

to form a dimer. They have investigated electron transfer process and structural relaxation in the formed aggregates.

In this section, some examples for the application of hole migration in DNA are indicated. Applications in the biomedical field are oriented to the detection of mismatch sequence and photodynamic therapy by the photoinduced reactions. From the viewpoint of nanotechnology, nanoscale wiring using DNA attracts wide attention. These studies will be continued by various research groups.

3.5 Summary for Hole Transfer in DNA

In this section, research on the process of hole transfer in DNA is summarized. The mechanism of hole transfer has been established in detail. When the distance for the single-step electron transfer is shorter, typically shorter than 3 or 4 nucleobases, the electron tunneling mediated by the super exchange interaction is the main mechanism. The electron transfer rate can be reproduced by means of the Marcus theory developed for the nonadiabatic conditions. The electron transfer rates are of subpicosecond levels for the short-range and largely exothermic hole injection process. For the long-distance hole transfer, hopping mechanism, in which each step is governed by the tunneling electron transfer theory, is operative. The hopping mechanism can be analyzed by random walk model and ranged to the longer distance even more than hundreds of angstroms. The rate of each hole transfer has also been estimated. The sub-nanosecond rate constants are estimated for A–A and G–G hopping, while it decreases to microsecond to millisecond region when other nucleobases, which act as barrier for hopping, are inserted between A–A or G–G. This long-range hole transfer has close relation to the DNA damage, which is the result of the reaction of the oxidized G and water or molecular oxygen. Thus, the hole transfer is important to develop new photodynamic therapy. In addition, application to nanotechnology as the molecular wire, whose conduction is sensitive to its sequence, is also promising.

4 EXCESS ELECTRON TRANSFER IN DNA

Compared to the hole transfer in DNA, our understanding of the excess electron transfer in DNA,

in which electron acts as a charge carrier, is not sufficient. In this section, research relating to the excess electron injection and migration will be summarized.

4.1 Excess Electron Tunneling in DNA in Low-Temperature Glass

Sevilla and coworkers reported the ESR study on the excess electron transfer in DNA caused by γ -ray radiolysis.⁶⁹ In their system, DNA including intercalator randomly was irradiated with γ -ray in 77 K glassy matrix. The excess electron generated on DNA nucleobases transfers to the intercalator, such as mitoxantrone (MX), EB⁺, 1,10-phenanthroline, and 5-nitro-1,10-phenanthroline, with the timescale of minutes to weeks, which can be monitored by the ESR signal of the radical anion of the nucleobases. In this system, both excess electron and intercalator are distributed randomly in DNA. The excess electron captured by the intercalator increased logarithmically with time as expected for the single-step electron tunneling from the nucleobase radical anion to the intercalator. The distance for the electron tunneling was estimated to be 4–10 base pairs after 1 min at 77 K. The estimated rate was on the order of 10^0 – 10^1 s⁻¹, from which they estimated the β value of (1) to be 0.85–1.2 Å⁻¹ depending on the intercalator.

In 2000, they reported the effect of temperature on the excess electron transfer in DNA with MX intercalator in D₂O, which was employed to distinguish T radical anion and protonated reduced C.⁷⁰ They found that the excess electron tunneling from DNA to MX is the dominant process at less than or equal to 77 K. The β value was the same at 4 and 77 K. The lack of temperature dependence indicates the absence of the vibronic states in this temperature range. Deuteration of T radical anion at C6 position takes place irreversibly above 130 K, which competes with the electron tunneling and acts as an irreversible sink for the electron. Hybridization of G and C results in the protonation of C radical anion at N3 position in a reversible manner, which stabilizes substantially. They indicated that the hole and electron hopping resulting in the recombination of G radical cation and protonated reduced C becomes substantial over 195 K, while the electron transfer from C radical

anion is too slow to be observed under 170 K, at which hopping is activated.

Furthermore, in 2002, from the ESR measurements on polydAdT·pdAdT and pdIdC·pdIdC intercalated with MX, they estimated the β and ET distance depending on the base sequence.⁷¹ The estimated β and ET distance were 0.75 Å⁻¹ and 9.4 base pairs for polydAdT·pdAdT, respectively, while they were 0.92 Å⁻¹ and 9.5 base pairs for pdIdC·pdIdC. They attributed these results to slow deuteron transfer from I to C radical anion forming CD radical.

From the series of the ESR study on the γ -ray-irradiated DNA with intercalator, Sevilla *et al.* successfully revealed the tunneling behavior of the excess electron in DNA. Especially, the contribution of the protonated radical anion to the excess electron transfer is an important finding, which is obtained by ESR measurement. In addition, application of the radiation chemical method is another advantage in excess electron transfer study because of the high ability of the radiation chemical method in the generation of the reduced form of organic materials. By employing the pulse radiolysis technique, which is another important radiation chemical technique, Kobayashi *et al.* reported the transient absorption spectrum of the reduced nucleobases, which showed the delocalization of the excess electron over several nucleobases.⁷² On the other hand, oxidation and reduction by radiation chemical method occurs in a random manner. In addition, oxidation or reduction of the target molecules occurs by a reaction with initially generated oxidized or reduced solvent species. This reaction mechanism limits the time resolution of the kinetic research. The difficulty in the site-selective oxidation or reduction and time resolution limits the detailed investigation of the charge transfer in DNA by radiation chemical method. Although our research group also applied pulse radiolysis for determination of the rate constant of the excess electron transfer in DNA, the actual rate was not obtained because of these limitations.⁷³

4.2 Excess Electron Hopping in DNA

In 2002, Carell and coworkers investigated the distance dependence of the excess electron transfer in a DNA conjugated with the reduced flavin

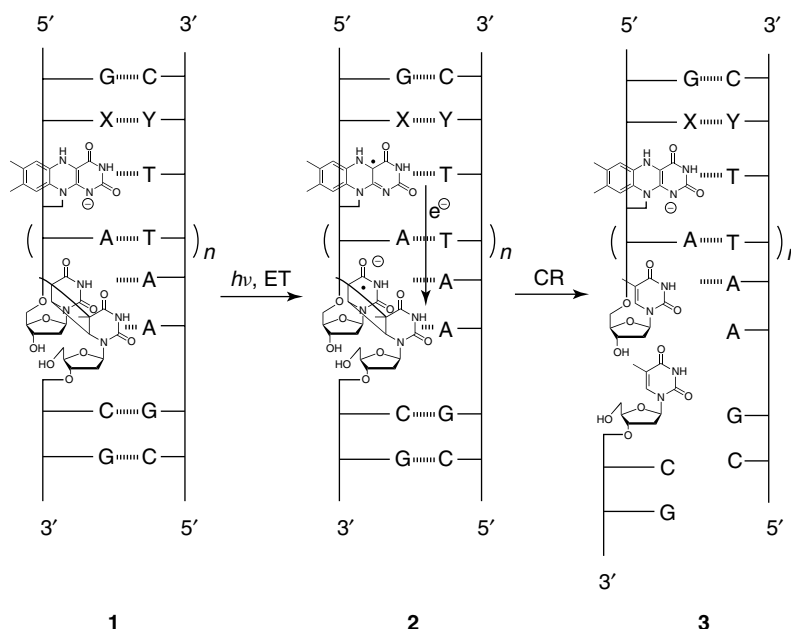


Figure 17 DNA conjugated with the reduced flavin and thymine dimer as the electron donor to DNA and acceptor, respectively. [Reproduced with permission from Ref. 74. © Wiley-VCH Verlag GmbH & Co. KGaA, 2002.]

and T dimer as the electron donor and acceptor, respectively (Figure 17).⁷⁴ It was indicated that the UV irradiation to consecutive T sequence generates cyclobutane pyrimidine dimer lesions in DNA, which can be repaired by DNA photolyase enzymes by the electron transfer from reduced and deprotonated FADH^- cofactor to cyclobutane dimer. In this sense, this system mimics such DNA repair systems. In their system, T dimer and flavin were separated by A:T base pairs (Figure 17). Photoirradiation to reduced and deprotonated flavin causes the excess electron injection to T in the vicinity of flavin. The excess electron transfer to T dimer causes the cycloreversion of a T dimer, which can be detected by HPLC. From the yield of the cycloreversion of T dimer depending on the number of the intervening A:T pairs, they estimated the distance dependence of the electron transfer yield. By employing (1), they estimated the β value to be $0.11 \text{ \AA}^{-1}$. They attributed this small β value to hopping mechanism. Actually from a plot according to (7), the slope was estimated to be ~ 2 , which is in accordance with the one-dimensional random walk model. Using this system, they confirmed that the excess electron induced to DNA can migrate to over $24 \text{ \AA}$. They also fabricated DNA hairpins with flavin

and T dimer as the donor and acceptor, respectively, and found a similar distance dependence of the excess electron transfer.^{75–77}

In addition, using this flavin donor and T dimer acceptor, they investigated the excess electron transfer in PNA:DNA hybrid.⁷⁸ In this hybrid system, flavin donor and T dimer acceptor were included in PNA and DNA chains, respectively. They found that the yield and distance dependence were similar to those of the DNA duplex system, indicating efficient interstrand excess electron transfer. Furthermore, their PNA:DNA hybrids did not show the directional preference of the excess electron migration (i.e., $5' \rightarrow 3'$ or $3' \rightarrow 5'$).⁷⁹ Since the split rate of the T dimer is in the order of 10^6 s^{-1} , they suggested that the rate-determining step of this dimer cleavage may be the splitting rather than the excess electron transfer in DNA, indicating the fast electron transfer in DNA. This issue was examined by them in 2006. They employed BrU, BrA, and BrG as the electron acceptor of the excess electron transfer in DNA, while flavin donor was also employed in this system.⁸⁰ They investigated the effect of G:C pair insertion in A:T pairs on the excess electron transfer yield. It was revealed that the DNA with the electron acceptor with higher electron accepting ability

(BrU) is sensitive to the insertion of G:C pair, because the higher electron accepting ability of BrU makes the electron trapping faster than the excess electron migration in DNA. From these results, they indicated the importance of the electron acceptor, to which the electron trapping is fast enough, in the investigation of the electron migration process. Very recently, from the comparison of the excess electron migration rate through DNA with the debromination rate of BrU or cleavage rate of T dimer, they suggested that the hopping rate through (A:T)₄ pair is faster than $1.8 \times 10^7 \text{ s}^{-1}$ (T dimer cleavage) and slower than $1.4 \times 10^8 \text{ s}^{-1}$ (BrU debromination).⁸¹

In the series of their study on the excess electron transfer using flavin donor, they have also revealed that the formation of the duplex structure is essential for the excess electron transfer. In addition, the absence of any effect of N₂O gas saturation on the excess electron transfer rate eliminates the possibility of the contribution of the solvated electron, which can be generated by electron ejection from the photoexcited donor to solvent to mediate negative charge to the acceptor, on excess electron transfer.⁸² Thus, the excess electron transfer is mediated by nucleobases in DNA. This is another important information obtained from their studies.

Ito and Rokita have investigated the excess electron transfer using DNA conjugated with *N,N,N',N'*-tetramethyl-1,5-diaminonaphthalene (TMDN) and BrU, as the photosensitizing electron donor and acceptor, respectively (Figure 18).^{83,84} Selective excitation of TMDN causes the excess electron injection to DNA and its reach to BrU to generate radical anion, which results in decomposition of the 5' neighbor by generation of U radical, H abstraction, and hydrolysis, as indicated in Figure 18. The yield of the electron transfer to BrU was evaluated by electrophoresis. In 2003, they found the smaller distance dependence of the yield of reduced BrU, which is in accordance with the results of Carell *et al.*, indicating the excess electron migration by hopping mechanism. Furthermore, in 2004, using the DNA described in Figure 19, they clarified the following points: (i) The excess electron transfer becomes efficient when the donor and acceptor are separated by T rather than C (Figure 19), especially when the distance is the same. The contribution of the C radical anion to the excess charge transfer is limited by the preferential protonation of the C

radical anion. This issue was confirmed by the isotope effect using D₂O solvent, which affects DNA with C but not T. From this, they suggested that the T is a primary carrier of the excess electron. (ii) The interstrand excess electron transfer is slower than intrastrand transfer. The electron transfer from 3' to 5' is faster than that in the reverse direction. This trend is opposite to that for the hole migration in DNA. They pointed out the difference in the MO contributing to each carrier migration, that is, HOMO for the hole migration and lowest unoccupied molecular orbital (LUMO) for the excess electron migration. These findings were not observed by Carell *et al.* as indicated above because the slower splitting rate of the T dimer on reduction acted as the rate-determining step.

As summarized in this section, important information on the excess electron transfer in DNA has been obtained from studies based on biochemical assay. According to these results, DNA, especially T, acts as the major mediator of the excess electron transfer, while C has a minor contribution because of the protonation by G, which forms a pair with C, and surrounding water. The distance dependence of the excess electron transfer yield gives a β value of 0.1–0.3 Å⁻¹, which is in accordance with the multi-step hopping conduction of the excess transfer as in the case of the hopping mechanism of the hole transfer. This was confirmed as the excess electron transfer yield obeys the single-step random walk model, as indicated by Carell *et al.* The absence of any contribution from the hydrated electron to the excess electron transfer is another important information obtained from their research results. The tendencies observed by Ito and Rokita are quite interesting to be clarified by more detailed studies. Compared to the hole transfer, on the other hand, the rate constant of the single excess electron transfer has not been determined. For determination of the rate constant, kinetic information based on the time-resolved study is essential. In the next section, time-resolved spectroscopic studies on the excess electron transfer are summarized.

4.3 Excess Electron Injection to DNA

In 1999, the research groups of Lewis and Wasielewski investigated the electron injection from the photoexcited SD, which was introduced at

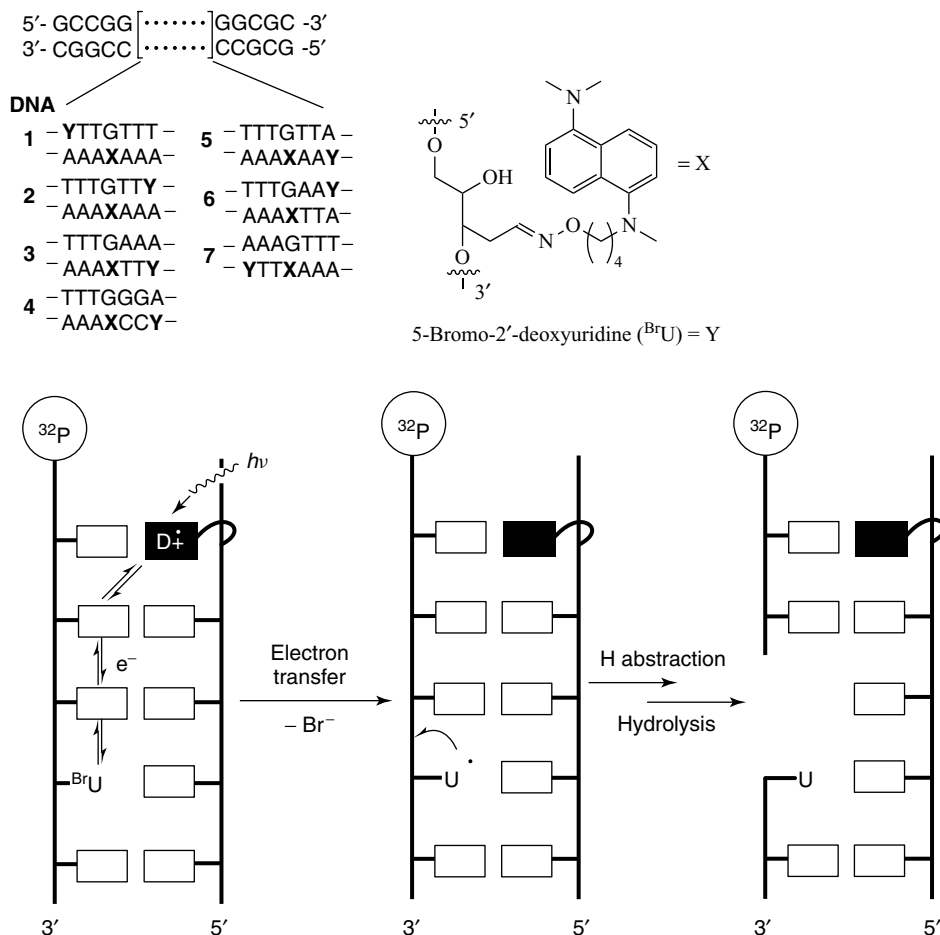


Figure 18 DNA conjugated with the TMDN and BrU as the electron donor to DNA and acceptor, respectively. [Reproduced with permission from Ref. 84. © Wiley-VCH Verlag GmbH & Co. KGaA, 2004.]

the loop position of the DNA hairpin, by the femtosecond transient absorption spectroscopy.⁸⁵ They found the formation of the SD radical cation within ~ 0.2 ps, when T is located next to SD, indicating the excess electron injection to T. Using the hairpin DNA with SD at the loop position, they have also investigated the distance dependence of the excess electron injection, in the subsequent study.⁸⁶ In the study, they inserted a noncanonical G : G base pair between SD and A : T pairs (Figure 20), in order to ensure that G acts as a barrier for the excess electron injection process without the contribution of C, which is also a possible candidate for the electron acceptor from the photoexcited SD. Actually, they confirmed that the electron injection to C occurred with a rate constant of $3.3 \times 10^{11} \text{ s}^{-1}$,

which is slower than that for T ($> 2 \times 10^{12} \text{ s}^{-1}$) due to smaller driving force of the excess electron injection. In addition, they evaluated the electron transfer rate from excited SD to I : C pair to be $1.4 \times 10^{12} \text{ s}^{-1}$, which is much faster than that of G : C pair due to the enhancement of the electron accepting ability of C as a result of base pairing. The electron injection rate was decreased to 5.7×10^9 and $4.4 \times 10^8 \text{ s}^{-1}$ when one and two G : G pairs, respectively, were inserted between SD and T. They pointed out that these rates are circa 25 times slower than those of the hole injection from the singlet-excited SA, in spite of similar driving force for the charge separation. They attributed this difference in the charge injection rate to the longer D–A distance or weak D-bridge-A electronic coupling probably due

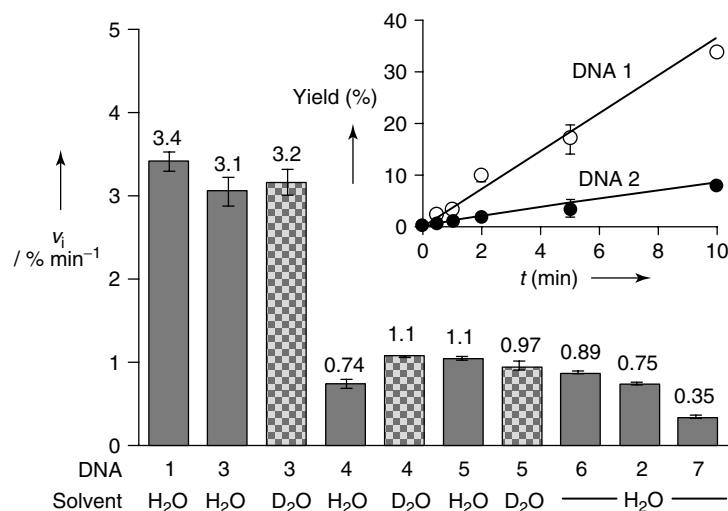


Figure 19 Strand scission rates of DNA conjugated with TMDN and BrU (Figure 18) after UV irradiation and piperidine treatment. [Reproduced with permission from Ref. 84. © Wiley-VCH Verlag GmbH & Co. KGaA, 2004.]

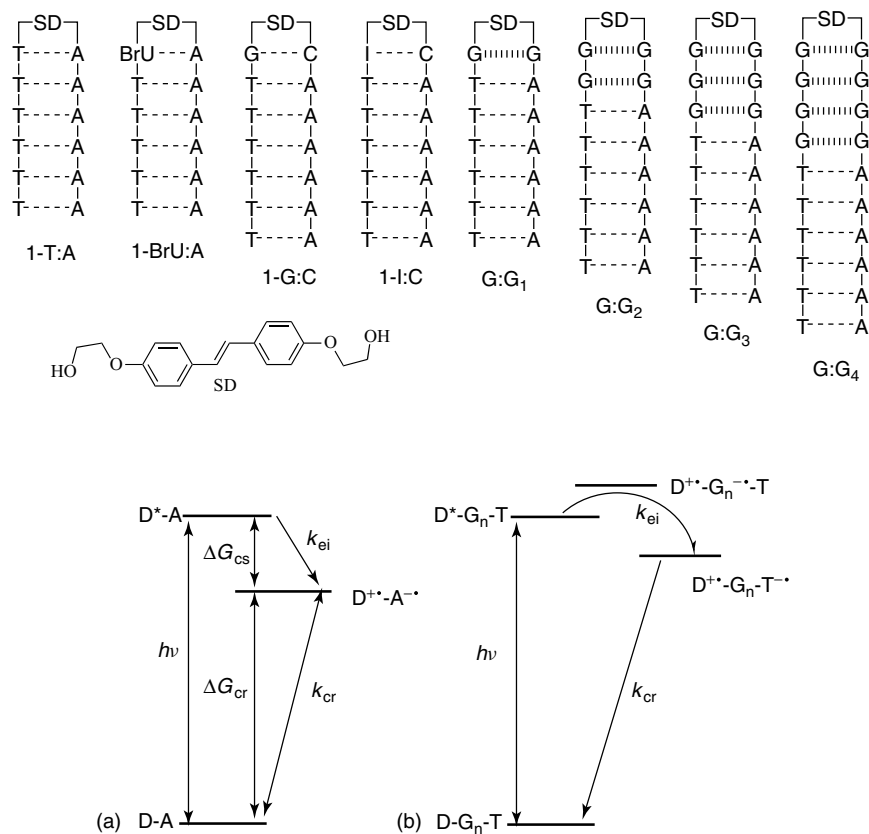


Figure 20 (Upper panel) Structures of DNA hairpins conjugated with SD at the loop position. (lower panel) Schematic energy diagrams for electron injection. D is SD. (a) A is the acceptor nucleobase for nearest neighbour quenching. (b) T is the acceptor for G:G-mediated electron injection. [Reproduced from Ref. 86. © American Chemical Society, 2002.]

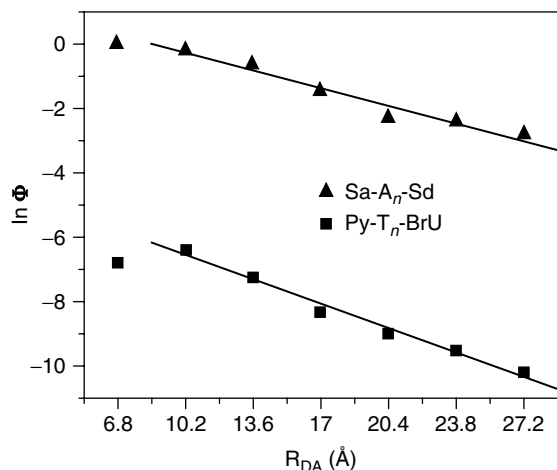


Figure 21 The distance dependence of the yield of the reduced product as well as hole transport yield in SA-An-SD has also been plotted. [Reproduced from Ref. 87. © American Chemical Society, 2009.]

to G : G base pair as evident from the lower melting temperature of multiple G : G inserted samples.

In 2009, the research groups of Lewis and Fiebig investigated the charge injection process of the DNA with aminopyrene (APy) as an end-capping group.⁸⁷ They found a charge separation time of 0.55 ps from the photoexcited APy to T, while the charge separation time decreased to 0.27 ps when BrU was located as the first or second neighbor of APy. The reduction of BrU was evaluated by HPLC or MALDI-TOF mass spectroscopy. The distance dependence of the yield of the reduced product has been indicated in Figure 21, in which the hole transport yield in SA-An-SD is also plotted. The slope of the plot is almost parallel to each other, supporting the hopping transport of excess electron along the DNA. These results are in accordance with those Carell *et al.* and Ito and Rokita described in the former section.

Wagenknecht and coworkers also investigated the process of injection of excess electron to DNA.⁸⁸ In 2004, they investigated the photoinduced process of pyrene-conjugated U and C (PydU and PydC, Figure 22).^{89,90} In their case, PydC showed weak pH dependence (pH 5 or 11), while the electron transfer in PydU was completely inhibited at higher pH. The observation with PydC can be explained on the basis that the C radical anion is protonated even under basic aqueous condition on a picosecond

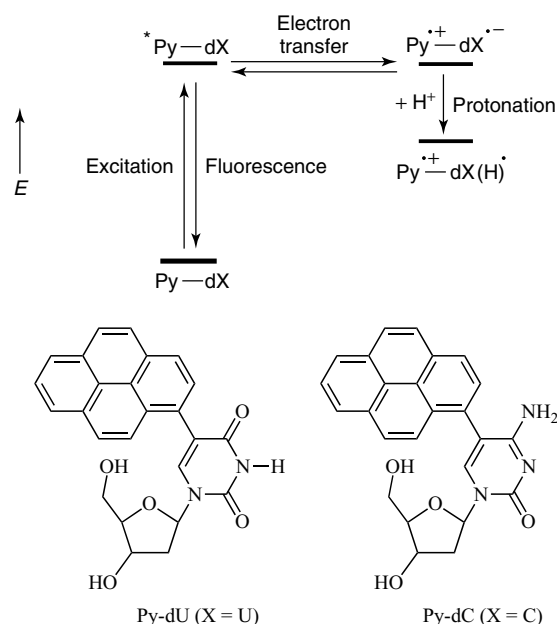


Figure 22 PydU and PydC and schematic energy diagram for the charge separation and protonation. [Reproduced with permission from Ref. 88. © Wiley-VCH Verlag GmbH & Co. KGaA, 2003.]

timescale. The difference in the degree of the proton association to C radical anion varies with the charge recombination rate. In the case of PydU, on the other hand, relative high energy of unprotonated U radical cation inhibited the formation of the radical ion pair. They pointed out that the observed pH dependence is also important for the electron transfer in DNA, that is, protonated C radical anion, which should be generated by complement base G or surrounding water, will limit or terminate the electron migration in DNA. Thus, they suggested that C radical anion cannot act as charge carrier.

In a subsequent study in 2005, Wagenknecht and coworkers investigated the excess electron transfer in DNA using PTZ as the electron donor and BrU as the acceptor.⁹¹ The efficiency of the excess electron migration was confirmed by yield of the strand cleavage. In the article, they confirmed that the A : T base pairs transport electron more efficiently than G : C pair owing to proton transfer of C radical anion from the pairing G. This result is consistent with those of Ito and Rokita.

As summarized in the sections on the excess electron transfer in DNA, the electron injection process

has been investigated by both biochemical assay and transient absorption spectroscopy. On the other hand, the migration process in DNA was revealed mainly by biochemical assay. As seen in the investigations of the hole migration process in DNA, the donor–DNA–acceptor system, of which the acceptor radical anion is detectable with transient absorption spectroscopy, should be quite useful for the detailed

analysis of the excess electron transfer processes. From this point, our research group has investigated the excess electron transfer in DNA hairpin conjugated with APy and diphenylacetylene (DPA), as the photosensitizing electron donor and electron acceptor at loop position, since the DPA radical anion is known to show a sharp absorption band around 490 nm (Figure 23).⁹² In order to enhance

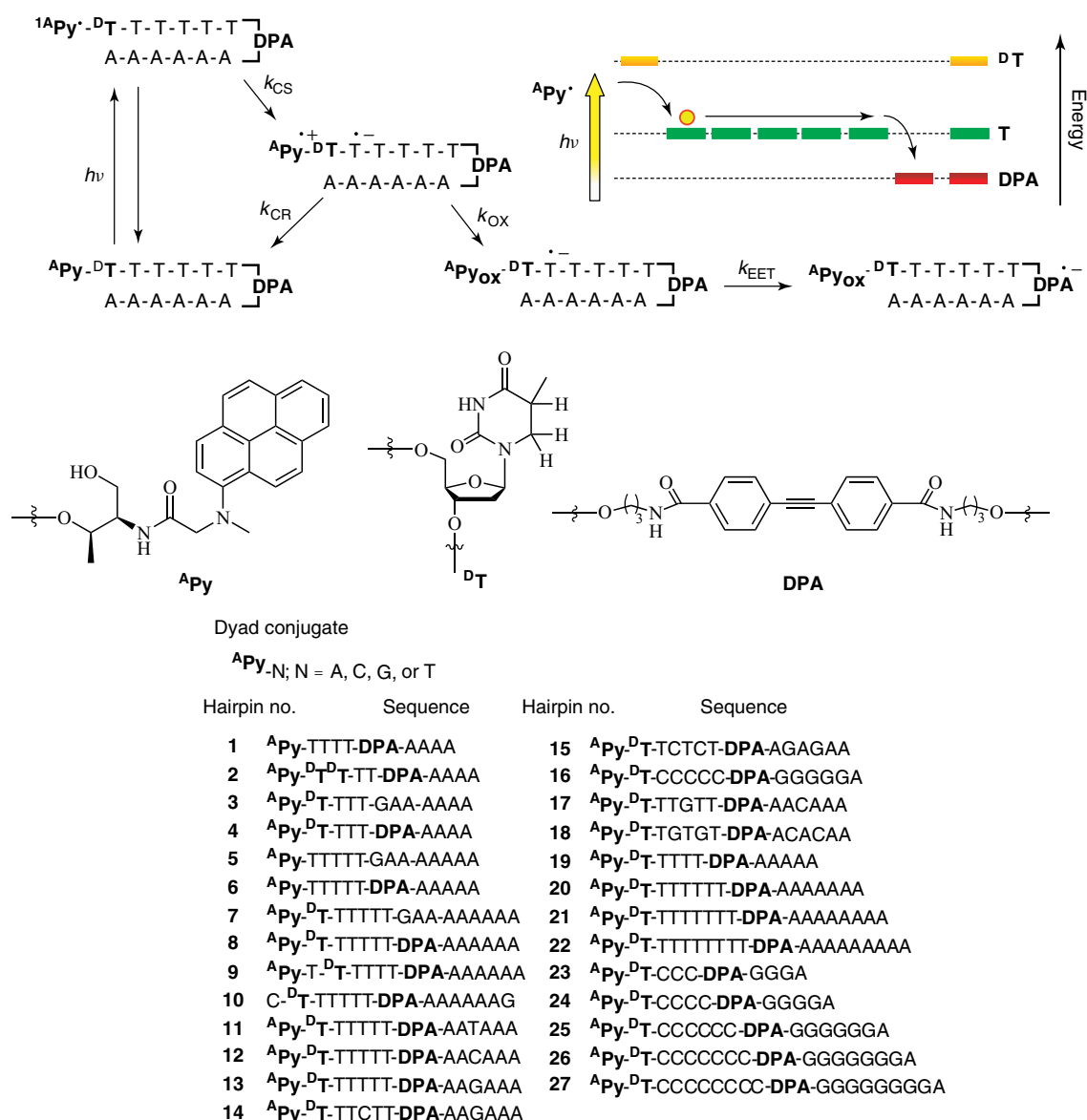


Figure 23 DNA hairpin conjugated with APy and DPA as the electron donor and acceptor, respectively. [Reproduced from Ref. 92. © American Chemical Society, 2010.]

the yield of the DPA radical anion as a result of the excess electron migration to DPA, dihydrothymine (^DT), which acts as a barrier for the rapid charge recombination,⁹³ was inserted between APy and T. From the femtosecond transient absorption spectroscopy, it was revealed that the excess electron injection to T was completed within 10 ps even in the presence of ^DT between APy and T. The generated APy radical cation was deactivated by the charge recombination to form ground state APy with a time constant of 51 ps. Thus, a major part of the injected charge recombined with the APy radical cation. The formation of the DPA radical anion was not observed within our time window of the pump-probe apparatus. On the other hand, DPA radical anion was clearly observed immediately after the nanosecond laser excitation (Figure 24a), indicating that the time for the hole migration should be shorter than 10 ns. Thus, the time constant for the excess electron migration cannot be determined from our experiment. On the other hand, absorbance of the generated DPA radical anion should reflect the efficiency of the excess electron migration. In Figure 24b, large ΔA of hairpin **8** indicates successful retardation of the charge recombination in ^DT -inserted DNA hairpin. From a comparison of **8**, **11**, **12**, and **13**, it was revealed that the mismatch sequence decreased the yield of the DPA radical anion, as in the case of the hole migration (Figure 24c). Furthermore, insertion of C also decreased the yield as seen by the comparison of **14**–**18**. These findings indicated that the discussion based on the biochemical assay can also be discussed on the basis of the yield of DPA radical anion. Furthermore, it was revealed that the electron can migrate even when the APy and DPA were separated by 10 base pairs, that is, 34 Å.

In this section, investigations on the electron injection process by time-resolved spectroscopic method were summarized. Compared to hole injection process, our understanding of the electron injection process is fragmented. In each case, the rate constant for the charge injection process is clarified. But detailed insights into excess electron injection, such as driving force dependence, reorganization energy, electronic coupling, distance dependence, structural fluctuation effect, and so on, have not been obtained. For these issues, further investigations using donor–DNA–acceptor systems have to be carried out. On the other hand, protonation

effect on the excess charge transfer is an interesting phenomenon because DNA always forms its structure via hydrogen bonding and is always surrounded by water. The crucial role perhaps will be included.

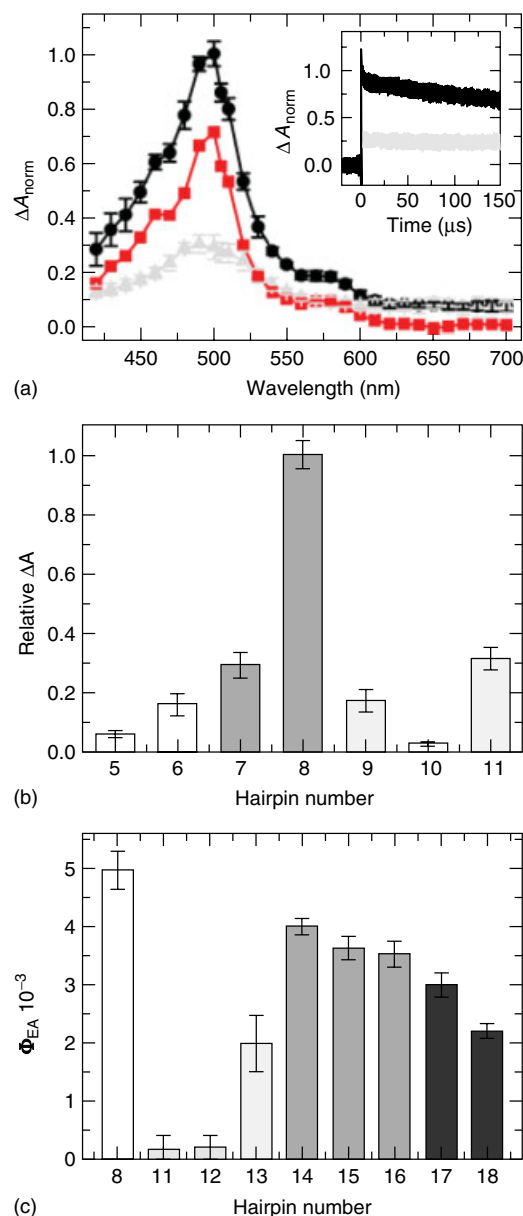


Figure 24 (a) Transient absorption spectra of **7** (gray) and **8** (black) at 1 μs after the 355 nm laser flash during the laser flash photolysis. (b) The relative intensity of ΔA at 490 nm. (c) The yield of DPA radical anion formation. [Reproduced from Ref. 92. © American Chemical Society, 2010.]

4.4 Summary for Excess Electron Transfer in DNA

As summarized in this article, several information on the excess electron transfer have been obtained from the investigation of several researchers. For an electron injection process, excess electron transfer proceeds on the timescale of the picoseconds when the driving force of the charge separation is enough exothermic. The nucleobases that accept electron from the donor are the pyrimidine bases, while C radical anion is easily protonated because of G, which forms a pair with C, or surrounding water, to diminish its role as a charge carrier. Once the electron is injected into the DNA, it can migrate in DNA by a hopping mechanism as evidenced by the random walk model. Except for the protonation process, the electron injection and migration processes have similarity to those of the hole migration. On the other hand, as revealed by Ito and Rokita, preference direction of the excess electron migration was different from that of the hole transfer. Furthermore, as pointed out at the end of the former section, details of the mechanism are not cleared in the case of the excess electron transfer. For the systematic understanding of the excess electron transfer, sequence dependent electron transfer rates have to be determined. These issues will be realized in near future.

5 SUMMARY

In this article, we have summarized charge transfer in DNA. Owing to the efforts of the scientists in the past two decades, detailed mechanisms for the charge transfer, especially the hole transfer, became clearer. It was revealed that the basic mechanisms for the charge injection and single-step charge transfer can be described by the Marcus theory, indicating that the interaction between the donor and acceptor for the charge transfer is not very strong. By one-dimensional random walk mechanism, hole and excess electron can migrate rather longer distance such as hundreds of angstroms. These points seem to be widely accepted, although the information on the excess electron transfer is not sufficient at the present stage. But these information on the excess electron transfer as well as the properties specific to excess electron transfer, such

as protonation effect in the electron transfer rate, will be cleared in future.

In addition to these information on the charge transfer in DNA duplex, charge transfer in other higher order structure is another interesting subject, because such study will enlarge the possibility of application of DNA to the nano-constructed materials and biomedical purpose. In spite of some reported studies, clarification of the charge transport in them is still not satisfactory. In addition, relation with proteins is another interesting point when the importance of the charge conduction in the biomedical sense is considered. These studies will give important information in both biochemistry and nanotechnology in future.

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Understanding DNA Radicals Employing Theory and Electron Spin Resonance Spectroscopy

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1 INTRODUCTION

Genetic information in living systems is stored in DNA molecules in a four letter code of DNA bases, A, T, G, and C, with specific pairing of DNA bases—A with T and G with C. Perturbations of the DNA structure can profoundly affect the performance and survival of organisms. Experimental evidence indicates that damage to DNA is a cause of cell death, mutation, and neoplastic transformation.^{1–3} Among the various types of DNA damage, strand breaks are known to be among the most biologically significant lesions as they disrupt the structural continuity and integrity of the double helix, with the double-strand break a potentially lethal lesion.^{4–6} It has been well established that free radicals on the deoxyribose moiety of DNA are immediate precursors to DNA strand breaks.^{4,7–9} Damage to the DNA bases is usually repairable but can lead to point mutations and subsequent dysfunction. Both sugar and base damage in DNA are chiefly caused by free radical processes. It has been well established that various types of free radicals on DNA (DNA radicals, see Section 1.1)—cation, anion, and neutral—can be stabilized at low temperature and, hence, be studied by employing electron spin resonance (ESR) spectroscopy.^{10–16} Moreover, owing to the tremendous technological development

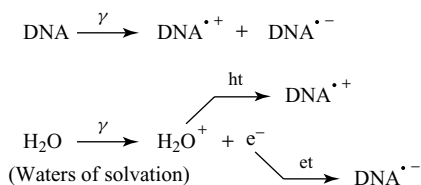
in computational chemistry in both computer hardware and software,¹⁷ theoretical molecular orbital (MO) calculations have provided substantial aid in the understanding of the mechanisms of formation of radiation-induced DNA radicals and their subsequent reactions to strand breaks.^{18–20} The focus of this article is to illustrate how ESR, along with theoretical *ab initio* MO studies have contributed to an understanding of the properties of various DNA radicals and to elucidate the mechanisms of formation of DNA damage products via these DNA radicals.

1.1 Radicals Formed in DNA (DNA Radicals)

1.1.1 Pathways of Formation

DNA radicals are produced via various pathways, viz.,

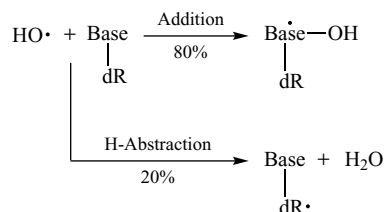
- (i) *Ionizing radiation*: Radiation damage to DNA occurs via two principal processes: the direct and the indirect effects.⁷ The direct effect corresponds to the direct deposition of energy in the DNA molecule itself resulting in the formation of cation ($\text{DNA}^{+\bullet}$) and anion radicals ($\text{DNA}^{\bullet-}$). A consideration of the interface between DNA and its surroundings led



Scheme 1 Formation of DNA cation and anion radical via direct-type effects. ht, hole transfer; et, electron transfer.

to the recognition of the quasi-direct effect in which ionization in the first solvation shell of water leads to transfer of holes and electrons to nearby DNA leading to additional DNA cation and anion radical production.^{10–16} Several experiments have shown that DNA's first 8–10 waters of hydration act in this manner.^{10,12–14} The direct and quasi-direct effects are collectively known as *direct-type effects* as shown in Scheme 1.

For the indirect effect, the energy is deposited into the surroundings, for example, bulk water, proteins thereby producing the radicals (e.g., HO•, e[−], and H• for water)

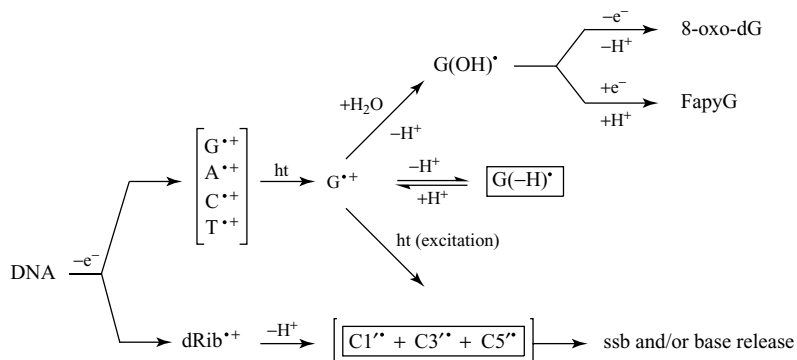


Scheme 2 Formation of DNA radical via indirect effect by HO• mostly (circa 80%) at the DNA bases. H-atom abstraction by HO• from the deoxyribose sugar moiety (circa 20%) leads to the formation of neutral sugar radicals.

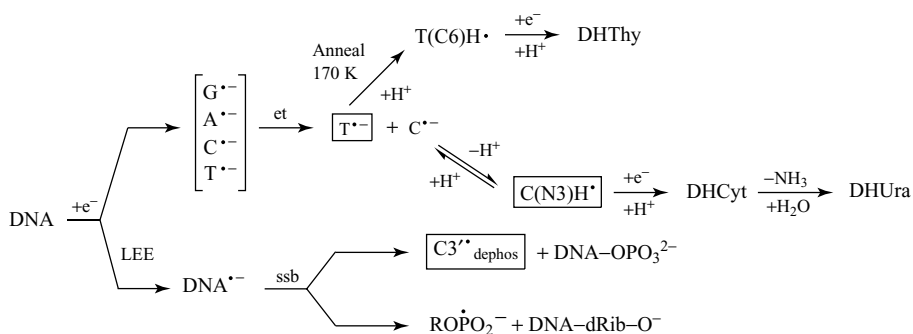
(see **Radiation-Induced Radical Reactions**). The most damaging radical is HO• which diffuses to and reacts with DNA to produce DNA radicals with almost diffusion-controlled rates (Scheme 2). The HO• reacts by addition to the base moiety or by abstraction of an H-atom from the deoxyribose sugar moiety in DNA leading to the formation of neutral sugar radicals^{7,21–23} (see also **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA** and **Oxidatively Formed Sugar Radicals in Nucleic Acids**).

G(-H)•	C(N3)H•	T• [−]	T(C6)H•
A• ⁺	C1'•	C3'•	C5'•
C4'•	ROPO ₂ • [−]		C3'• dephos

Scheme 3 Structures of DNA radicals discussed in this article.



Scheme 4 DNA radicals formed via oxidative (i.e., electron loss) pathway. Via hole transfer processes, the hole is localized on the guanine base. The sugar radicals, especially $C3''\cdot$ and $C5''\cdot$, which are known as *strand break precursor radicals*, are produced either via direct ionization of the sugar–phosphate backbone or via excitation of $G^{\bullet+}$. Here, “ht” denotes hole transfer and “ssb” means single strand break.



Scheme 5 DNA radicals formed via the reductive (i.e., electron gain) pathway. Via electron transfer, the electrons are localized on cytosine and thymine bases, where subsequent reversible ($C(N3H)\cdot$) and irreversible ($TH\cdot$) protonation reactions occur. The sugar radicals, especially $C3''_{\text{dephos}}\cdot$ and $C5''_{\text{dephos}}\cdot$, which are immediate strand break radicals, are produced via dissociative electron attachment of the low-energy electrons (≤ 20 eV) at the sugar–phosphate backbone. Here, “et” denotes electron transfer and “ssb” means single strand break.

For the structural formulae of sugar radicals see Scheme 3.

- (ii) *DNA radical formation by metal-mediated formation of oxyl radicals*: DNA radicals are produced via attack of oxyl radicals formed by complexed metals (e.g., Fe^{2+} and Cu^{2+}) with endogenous hydroperoxides.^{7,23,24}
- (iii) *Other methods*: DNA radicals are also produced via other exogenous methods, for example, UV photolysis (e.g., via Norrish type I and II reactions), and also endogenously via attack of reactive oxygen and reactive nitrogen species.^{7–9}

It has already been mentioned in Section 1 that the thrust of this article is to review radical formation

and trapping in low temperature irradiated DNA, and, to describe the radical processes that likely lead to strand breaks. Ionizing radiation, such as γ -radiation, X-rays, or ion beams initially results in formation of cation radicals, anion radicals, and excited states (Schemes 1, 4, and 5) in the medium being irradiated. Secondary radicals (see Schemes 3–5 and also Section 3) result from the chemical reactions of these primary radicals.

At 77 K in DNA, these radicals can be trapped and observed using ESR spectroscopy. In Figure 1, the ESR spectrum, at 77 K, of DNA, hydrated to $\Gamma = 12$ D_2O /nucleotide, and γ -irradiated to 8.8 kGy is shown.^{10–12} Computer analysis of the spectrum using a least squares method and the benchmark spectra shown in Figure 1 indicates that

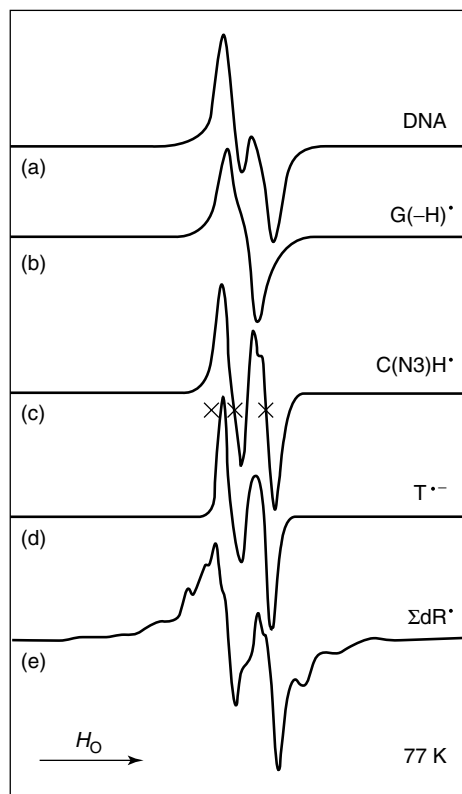


Figure 1 (a) ESR spectrum of hydrated ($\Gamma = 12$ D₂O/nucleotide) DNA, γ -irradiated to 8.8 kGy; the DNA was irradiated and the spectrum recorded at 77 K. This spectrum is a composite, arising from at least seven trapped radicals. (b)–(e) Benchmark spectra used to computer analyze the DNA spectrum. See narrative for description of each species. The three reference markers in this figure and in other figures show the position of the Fremy's salt resonances with the central marker at $g = 2.0056$. Each of these markers is separated from each other by 13.09 G.

the spectrum is actually a composite that results from the presence of at least seven radicals. Three of these are the base radicals: G(–H) $\cdot$, C(N3)H $\cdot$, and T $\cdot^-$ (Scheme 3). Individual benchmark ESR spectra (Figure 1) for each of these have been developed. The other four radicals are the sugar radicals: C1' $\cdot$, C3' $\cdot$, C5' $\cdot$, and C3' $\cdot_{\text{dephos}}$ (Scheme 3). These are radicals in which the unpaired electron resides on the deoxyribose sugar ring. Invariant individual benchmark spectra cannot be successfully developed for each these radicals as they change couplings with conformation, but a composite spectrum from them, labeled $\Sigma\text{dR}\cdot$, can be successfully used as a single benchmark for analysis of the overall DNA spectrum. Spectral components from C1' $\cdot$, C3' $\cdot$,

C5' $\cdot$, and C3' $\cdot_{\text{dephos}}$ are present in $\Sigma\text{dR}\cdot$, indicating that these radicals are present in the DNA radical composite spectrum. However, analysis of $\Sigma\text{dR}\cdot$ has been able to account for only circa 85% of the spectral intensity present; hence, there may be other, as yet unidentified, radicals present. Theoretical calculations have been critical in determining the nature and origin of all seven of the known radicals in γ -irradiated hydrated DNA (*vide infra*).

A large number of the initial DNA radicals, including those shown above, result from the DNA cation and anion radicals originating with ionizations via direct-type effects (Scheme 1). The two principal ionization pathways for DNA radical formation are the electron loss (or oxidative path, Scheme 4) and the electron gain (or reductive path, Scheme 5).^{7,10–16,20} In Schemes 4 and 5, those radicals that contribute to the ESR spectrum shown in Figure 1 are shown with boxes around them.

1.1.2 DNA Radicals and the Oxidative (Electron-Loss) Pathway

For the oxidation pathway (Scheme 4), the ionization of DNA occurs at both the bases and the sugar group. Ionization through the Compton effect is roughly proportional to the number of valence electrons; thus, about half the ionization occurs at the DNA bases and half at the sugars as indicated in the scheme.¹⁰ Of the four possible oxidized bases, only G(–H) $\cdot$ is trapped and observed at 77 K in double stranded (ds) hydrated DNA.^{25–27} This is quite reasonable since guanine has the lowest ionization energy of the four bases.^{28–30} To explain this observation, hole transfer (ht) must occur as indicated to localize the hole on guanine to first give C : G $^{+\cdot}$, which then undergoes intra-base pair proton transfer from the N1 of guanine to the N3 on cytosine to give C(+H $^{+\cdot}$) : G(N1–H) $\cdot$, the radical that is trapped and observed at 77 K (Section 3.1.4).^{25–27,31} Owing to the nucleophilic addition of water at the C-8 atom in the guanine moiety of C : G $^{+\cdot}$, and via subsequent deprotonation, a guanine OH-adduct radical (GOH $\cdot$) is formed.^{32,33} The diamagnetic compounds 8-*oxo*-G and FapyG are formed via one-electron oxidation and one-electron reduction of GOH $\cdot$, respectively.^{7,34}

Electron loss at the deoxyribose sugar results in a hole on the sugar (dRib $^{+\cdot}$) (Scheme 4). Sugar cationic radicals have not been observed

in polymeric DNA at 77 K. It is assumed that rapid deprotonation from C1', C3', or C5' sites in dRib⁺ leads to formation of C1'', C3'', and C5'', respectively.^{7,12} These radicals contribute to the Σ dR⁺ benchmark spectrum shown in Figure 1. On warming, they cause base release and/or a single strand break.^{7–9}

One remaining pathway in the electron loss regime involves proton-coupled hole transfer (PCHT) from an excited base cation radical to the deoxyribose sugar. As shown in the scheme, the deoxyribose sugar cation radical thus formed rapidly deprotonates, resulting in a neutral sugar radical such as C1'', C3'', or C5'' (see also Section 3). Deprotonation is expected to occur within the lifetime of the excited state (circa 10^{-12} s (Section 3.2.1)); hence, formation of a neutral sugar radical contributing to product formation should be very rapid.^{10–12,16,18,19,35,36}

1.1.3 DNA Radicals and the Reductive (Electron-Gain) Pathway

The electron gain path results from the localization of ionization produced electrons principally on DNA bases after electron thermalization. The actual DNA base locations of initial electron trapping are likely to be random on all four bases. However, the trapped radicals observed are from electron addition to C and T bases^{7,10–16,20}; thus, only T^{•−} and C(N3)H^{•−} are trapped and observed at 77 K.^{10–16,20} This is plausible because the pyrimidine bases have greater electron affinities than the purines.^{18–20} It is reasonable to postulate that electron transfer (et) must occur in order to explain the trapping of only the pyrimidine base anionic radicals and not any purine base anionic radicals in the electron gain path.^{10–16,20} Reversible proton transfer from N1 on guanine to N3 on the anionic cytosine radical (C^{•−}) results in ultimate formation and trapping of C(N3)H^{•−} at 77 K.^{7,10–16,20}

Nonthermal electrons, that is, low-energy electrons (LEEs), have been shown to induce reactions at the sugar phosphate backbone. This provides a second pathway for the electron gain product formation (Section 3, Scheme 10).³⁷ LEEs are electrons that have energies of near 0 to circa 20 eV and which have not been solvated.^{10–16,18–20,37} They can add to the DNA and cause an immediate strand break

through a dissociative electron attachment (DEA) process (see Section 3.2.2 for a comprehensive discussion).

1.2 Identification of DNA Radical Hyperfine Interaction: Theory and Experiment

The identification of DNA radicals using ESR spectroscopy in conjunction with theory is briefly outlined below. Those further interested should also consult article **Analysis of Radicals by EPR**.

From Section 1.1, it is evident that in the absence of molecular oxygen, two main types of DNA radicals are produced via ionization processes, purine and pyrimidine radicals, and carbon-centered sugar radicals.⁷ In these DNA radicals, the unpaired spin on the radical site interacts with nuclei that have magnetic moment, such as, ¹H, ²H, and ¹⁴N. This electron spin–nuclear spin interaction gives rise to hyperfine coupling, which is characterized by the hyperfine coupling constant (HFCC) values. The HFCC values along with the *g*-value affect the ESR spectra of these radicals.^{38–43} The HFCCs, represented by a tensor (see Section 2 for details), consists of (i) an isotropic (Fermi contact term) and (ii) anisotropic (dipolar) terms.^{38–43} The isotropic part depends on the interaction of the unpaired electron at a magnetic nucleus and is known as the *Fermi contact interaction*. Its measurement is directly proportional to the electron spin density at the nucleus. On the other hand, the anisotropic coupling is obtained from the classical expression of two interacting magnetic dipoles and its value depends on the overall distribution of spin in the molecule away from the nucleus.^{38–43} The anisotropic hyperfine couplings average to zero for rapidly tumbling radicals in nonviscous solutions at room temperature. Thus, in solutions, only the isotropic interactions are observed by EPR. The isotropic hyperfine coupling is dealt with in detail in article **Analysis of Radicals by EPR**. Owing to the nature of systems involving biomolecules at low temperatures (e.g., hydrated biomolecules, biomolecules in frozen aqueous solutions at low temperatures, or irradiated single crystals of model compounds), both the isotropic and anisotropic hyperfine couplings are observed in these systems.^{10–16,20} Hence, in

Section 2, the theoretical background of the hyperfine interaction with special emphasis on anisotropic hyperfine couplings is presented.

The anisotropic portion of the HFCC is more easily calculated by theory than the contact term. Theoretical calculation of accurate isotropic HFCCs (contact term) is a complex task because the spin density at the nucleus depends on the radical structure and conformation, electron correlation effects, and a number of mechanisms of spin delocalization, such as, spin polarization for an α -proton coupling and direct hyperconjugation for a β -proton coupling.^{44–49} Computation of HFCCs by quantum chemical methods have employed all levels of theory including Hartree–Fock (HF), Møller–Plesset perturbation theory (MP2), coupled cluster (CC), multiconfiguration self-consistent field (MCSCF), multireference configuration interaction (MRCI), and density functional theory (DFT). From a number of studies, it was found that the HF method is not adequate to compute the isotropic HFCCs; the post-HF electron correlated methods (MP2, CC, MCSCF, and MRCI) are very computationally expensive and feasible for small molecules only.^{50–53}

DFT using the B3LYP functional is found to predict isotropic HFCCs with good accuracy.^{51,54–64} The use of DFT has several advantages such as (i) reduced computational cost comparable to HF methods. (ii) It can be applied to large molecules of up to approximately 1000 atoms. (iii) It takes into account electron correlation through the exchange–correlation function. Finally, (iv) it provides reasonably accurate molecular geometries.⁵³ In this context, we mention recent reports by Hermosilla *et al.*,^{65–67} in which, these authors extensively considered a large number of radicals, anionic, cationic, and neutral, containing ¹H, ⁹Be, ¹¹B, ¹³C, ¹⁴N, ¹⁷O, ¹⁹F, ²³Na, ²⁵Mg, ²⁷Al, ²⁹Si, ³¹P, ³³S, and ³⁵Cl nuclei and calculated the isotropic HFCCs using B3LYP, B3P86, and B3PW91 density functionals and 6-31G*, TZVP, EPR-III, and cc-PVQZ basis sets. The calculated 274 HFCC values were compared with the available 174 experimental HFCC values.⁶⁵ They also calculated the ¹⁴N isotropic HFCCs of 109 radicals containing a nitrogen atom. From a regression analysis,^{65,66} they find the B3LYP method to be reliable in predicting the isotropic HFCCs of these radicals. Furthermore, the B3LYP method has showed its applicability in predicting a variety of the properties

of DNA ion radicals, for example, conformation, spin density distribution, energies for hole and anion formation, acid/base properties of DNA base radicals, potential energy surfaces for proton transfer between one-electron oxidized Watson–Crick DNA base pairs, and sugar radical formation from excited one-electron oxidized nucleosides, nucleotides, and oligomers. These will be elaborated, along with experimental ESR findings in subsequent sections. In addition to HFCC computation, B3LYP and PBE0 density functionals with the N07D basis set by Barone and Cimino⁶⁸ were found to predict “remarkably accurate” electronic *g*-tensor values for a number of free radicals of second row elements.

2 ANISOTROPIC HYPERFINE INTERACTION AND COUPLING

2.1 The Complete Spin Hamiltonian

Usually DNA radicals (see Section 1.1) have the unpaired electron located in a p-orbital or a delocalized π -MO.³⁹ The electron in a p-orbital is distributed away from nucleus in space; so, the interaction between the electron spin and nuclear spin produces a magnetic dipole–dipole interaction that is called the *dipolar hyperfine interaction*. This type of interaction is anisotropic in nature, that is, the magnitude of this interaction as well as its sign depends on the orientation of the radical to the external magnetic field. The hyperfine splitting resulting from this type of interaction is called *anisotropic hyperfine splitting*.

The Hamiltonian for the electron–nuclear magnetic dipole–dipole interaction is given by (1)^{38–43}:

$$\hat{H}_{\text{dipolar}} = \frac{\vec{\mu}_e \cdot \vec{\mu}_N}{r^3} - \frac{3(\vec{\mu}_e \cdot \vec{r})(\vec{\mu}_N \cdot \vec{r})}{r^5} \quad (1)$$

where $\vec{\mu}_e$ is the magnetic moment of the electron, which is equal to $-g_e\beta_e S$, $\vec{\mu}_N = g_N\beta_N I$ is the magnetic moment of the nucleus, and $\vec{r}$ is the vector joining the unpaired electron and the nucleus. Here, g_N is the nuclear *g*-value, g_e is the *g*-value of the free electron, β_N is the nuclear magneton, and β_e is the Bohr magneton. Equation (1) expresses the classical dipole–dipole interaction between two magnetic moments.^{38–43}

The magnetic moments can be replaced by their corresponding operators in a quantum mechanical

system. Therefore, the anisotropic interaction in (2) can be modified as^{38–43}

$$\hat{H}_{\text{dipolar}}(r) = -\frac{\mu_0}{4\pi}(\mathbf{g}_e\beta_e\mathbf{g}_N\beta_N) \times \left[\frac{\hat{\mathbf{S}} \cdot \hat{\mathbf{I}}}{r^3} - \frac{3(\hat{\mathbf{S}} \cdot \vec{r})(\hat{\mathbf{I}} \cdot \vec{r})}{r^5} \right] \quad (2)$$

Here, $\hat{\mathbf{S}}$ is the electron spin operator and $\hat{\mathbf{I}}$ is the nuclear spin operator. Here, $\hat{\mathbf{S}} = \hat{S}_x\hat{\mathbf{i}} + \hat{S}_y\hat{\mathbf{j}} + \hat{S}_z\hat{\mathbf{k}}$, $\hat{\mathbf{I}} = \hat{I}_x\hat{\mathbf{i}} + \hat{I}_y\hat{\mathbf{j}} + \hat{I}_z\hat{\mathbf{k}}$, and $\vec{r} = x\hat{\mathbf{i}} + y\hat{\mathbf{j}} + z\hat{\mathbf{k}}$.

Application of this Hamiltonian in (2) to an electron in an orbital leads to its average over the entire electron spatial distribution and that is abbreviated as follows^{40–43}:

$$\hat{H}_{\text{dipolar}}(r) = \hat{\mathbf{S}} \cdot \mathbf{T} \cdot \hat{\mathbf{I}} \quad (3)$$

Here, $\mathbf{T}$ is the dipolar interaction tensor (in units of MHz or Gauss), which expresses the anisotropic nuclear hyperfine interaction. Hence, the complete static Hamiltonian operator is^{40–43}

$$\hat{H} = \beta_e\hat{\mathbf{S}} \cdot \mathbf{g} \cdot \vec{H} + \hat{\mathbf{S}} \cdot \mathbf{A} \cdot \hat{\mathbf{I}} - g_N\beta_N\vec{H} \cdot \hat{\mathbf{I}} \quad (4)$$

where $\beta_e\hat{\mathbf{S}} \cdot \mathbf{g} \cdot \vec{H}$ represents the electron Zeeman term, $\hat{\mathbf{S}} \cdot \mathbf{A} \cdot \hat{\mathbf{I}}$ is the hyperfine interaction term, and $g_N\beta_N\vec{H} \cdot \hat{\mathbf{I}}$ is the nuclear Zeeman term. H is the external magnetic field. Note that the contribution from the nuclear Zeeman term is generally neglected in the interpretation of ESR spectra as it does not affect the EPR spectrum. Thus, (4) becomes^{40–43}

$$\hat{H} = \beta_e\hat{\mathbf{S}} \cdot \mathbf{g} \cdot \vec{H} + \hat{\mathbf{S}} \cdot \mathbf{A} \cdot \hat{\mathbf{I}} \quad (5)$$

In (4) or (5), $\mathbf{g}$ and $\mathbf{A}$ are tensors and are 3×3 matrices representing the anisotropic electron Zeeman and nuclear hyperfine interactions. In general, a coordinate system can be found (the principal axes) in which $\mathbf{g}$ and $\mathbf{A}$ are diagonal. If $\mathbf{g}$ and $\mathbf{A}$ are diagonal in the same coordinate system, their principal axes are said to be coincident. $\mathbf{A}$ is the sum of the scalar term a , which is the isotropic component (Fermi contact term), and $\mathbf{T}$, which is the anisotropic component (the dipole–dipole interaction term), that is,^{40–43}

$$\mathbf{A} = \mathbf{T} + a \cdot \mathbf{1} \quad (\mathbf{1} = \text{unit matrix}) \quad (6)$$

These expressions are valid for any orientation of the radical with respect to the applied field. For

a spherical electron cloud or for radicals which are rapidly tumbling in solution, $\hat{H}_{\text{dipolar}} = 0$, and both $\mathbf{g}$ and $\mathbf{A}$ become scalar quantities. For those cases, the hyperfine coupling becomes isotropic and is equal to one third of the trace of the anisotropic $\mathbf{A}$ diagonalized tensor. In solid samples such as single crystals or aqueous glasses, where $\hat{H}_{\text{dipolar}}$ is not equal to 0, for interpretation of the ESR spectrum of a radical, the evaluation of the full anisotropic $\mathbf{g}$ (the $\mathbf{g}$ -tensor) and of the full anisotropic $\mathbf{A}$ (the $\mathbf{A}$ -tensor) in (5) are necessary.

2.1.1 The $\mathbf{g}$ -Tensor

The anisotropic $\mathbf{g}$ -tensor can be represented by the following 3×3 matrix (Scheme 6)^{40–43}:

On diagonalization of the $\mathbf{g}$ -tensor, three principal values, g_{xx} , g_{yy} , and g_{zz} , are found whose principal eigenvectors correspond to directions in the molecular framework (g_{zz} , e.g., is usually coincident with the z -axis of the p_z orbital in a π -electron-type radical). For a particular radical, the deviation of the radical $\mathbf{g}$ -value from the $\mathbf{g}$ -value of the free electron ($g_e = 2.0023$) arises from the coupling of spin and orbital angular momenta ($\lambda L \cdot S$), λ is the spin-orbit coupling constant. This effect is increased with atoms of higher atomic number (Z), which have greater tendency to couple spin and orbital angular momenta than do lighter atoms. Thus, N, O, S, and Cl atoms show a progressive increase in deviation from g_e with increasing atomic number (Z). As a rule of thumb, the greater the spin on the heteroatom in the radical, the greater is the deviation from g_e .

For most DNA radicals (see Section 1.1), the $\mathbf{g}$ -values found (2.002–2.006) are close to the free spin value ($g_e = 2.0023$).^{10–16,20,39} For these radicals, only small differences in the three principal $\mathbf{g}$ -values are experimentally detected. Often

$$\begin{bmatrix} g_{xx} & g_{xy} & g_{xz} \\ g_{yx} & g_{yy} & g_{yz} \\ g_{zx} & g_{zy} & g_{zz} \end{bmatrix} \xrightarrow{\text{Diagonalization}} \begin{bmatrix} g_{xx} & 0 & 0 \\ 0 & g_{yy} & 0 \\ 0 & 0 & g_{zz} \end{bmatrix}$$

Scheme 6 Schematic representation of the $\mathbf{g}$ -tensor. Here, x , y , and z -axes are arbitrary axes, which can be the crystal axes in a single crystal. The diagonalized tensor gives the principal axes that correspond to directions in the molecular framework.

the large linewidths in solids, especially for carbon-centered sugar radicals with β -proton couplings only, the small g -value differences cannot be discerned and only one g -value (g -apparent, g_{app}), at the center of the experimentally recorded ESR spectrum is assigned. We note here that the heteroatom (mostly, nitrogen)-centered DNA base radicals have near axial symmetry for both g and hyperfine (A) tensors and hence can be approximated by two g -values, $g_{\parallel}$ and $g_{\perp}$; since g_{xx} is close to g_{yy} , they are both designated as $g_{\perp}$.³⁹ $g_{\parallel}$ is oriented along the direction of the axis of symmetry for the radical p_z orbital and $g_{\perp}$ in the plane of the radical.³⁹

2.1.2 The A-Tensor

Equation (6) shows the nuclear hyperfine interaction term with A diagonalized.

The Fermi contact term (a) in (6) depends on the amount of unpaired electron spin density at the nucleus. Only s-orbitals have spin density at the nucleus and thus only unpaired spin in an s-orbital gives rise to a Fermi contact interaction. The magnitude of this isotropic hyperfine coupling can be used to compute the fraction of s character in the radical if the coupling for unit spin in the s-orbital is known.

The most frequently encountered interacting nucleus is ^1H , which has a nuclear spin $I = 1/2$, and thereby splits the singlet due to an electron into a doublet. In the solid state, two types of proton (^1H) hyperfine interactions exist, viz., isotropic and anisotropic. It is frequently found that the unpaired electron is localized in a single p-orbital on an essentially sp^2 hybridized carbon atom and this circumstance will be used to illustrate the nature of the anisotropic versus isotropic hyperfine interactions. In this discussion, we will also distinguish between an α -proton, which is the one bonded to the carbon atom on which the unpaired electron resides, and which exhibits considerable anisotropy in its hyperfine coupling, and a β -proton, which is a proton bonded to an adjacent carbon, and for which the hyperfine coupling is almost entirely isotropic.

In case of DNA radicals, different types of isotropic hyperfine couplings can be generalized³⁹:

- (i) For π -type radicals in a C–H fragment, this interaction is mediated via spin polarization

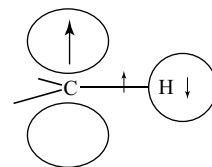


Figure 2 Schematic representation of isotropic α -hyperfine interaction via spin polarization. The arrows for the hydrogen and bond must be the same size as they are restricted by the Pauli principle.

(Figure 2), that is, the electrons in the C–H σ -bond are polarized by the unpaired spin and generate a small unpaired spin on the H-atom that is opposite to the unpaired spin density in the carbon p_z orbital (as shown in Figure 2). This is an example of α -proton isotropic hyperfine coupling as the H-atom is directly bonded to the C-atom having the radical site. This induces a small *negative* spin density (circa 4.5%) in the H 1s orbital for a full spin in the p_z on the C-atom. Since the hydrogen atom (for unit spin in 1s orbital) has a HFCC of 506 G, the 4.5% spin gives rise to a -23 G isotropic coupling, which is easily observed experimentally.

- (ii) When the proton is β to the radical site (β -proton) (Figure 3a), its isotropic hyperfine coupling is directly related to the π -spin density (ρ^π) and the dihedral angle (θ) between the C–H bond and z -axis of the carbon p_z orbital at the radical center (Figure 3b) and is given by the following equation:

$$a = B_0\rho^\pi + B_2\rho^\pi\cos^2\theta \quad (7)$$

The value B_2 is near 50 G for typical neutral radicals, for cation radicals, it can be as large as 90 G and for anion radicals as small as 25 G. B_0 is small (0–5 G) and is often neglected. As a result, for a neutral radical, the β -proton isotropic hyperfine coupling for unit spin, ρ^π ranges from near 0 ($\theta = 90^\circ$) to 50 G ($\theta = 0^\circ$) (Figure 3b).

For the anisotropic components (T_{xx} , T_{yy} , and T_{zz}) of the α -coupling in the π -type radicals in a C–H fragment (Figure 2), the three eigenvectors defining the principal axis system are shown in Figure 4. The hyperfine coupling values shown are

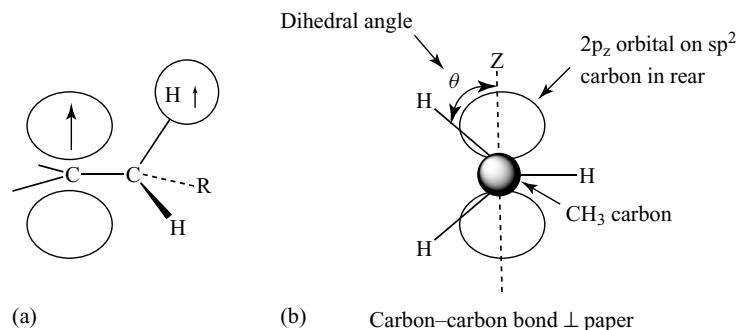


Figure 3 (a) The $\text{R-CH}_2\text{-C}^*$ fragment with its p_z -orbital at the radical center. (b) The same radical viewed along the C–C bond axis from the right. The angle θ is the dihedral angle between the C–H bond and the z -axis of the p_z -orbital. The β -proton hyperfine splitting varies with θ .

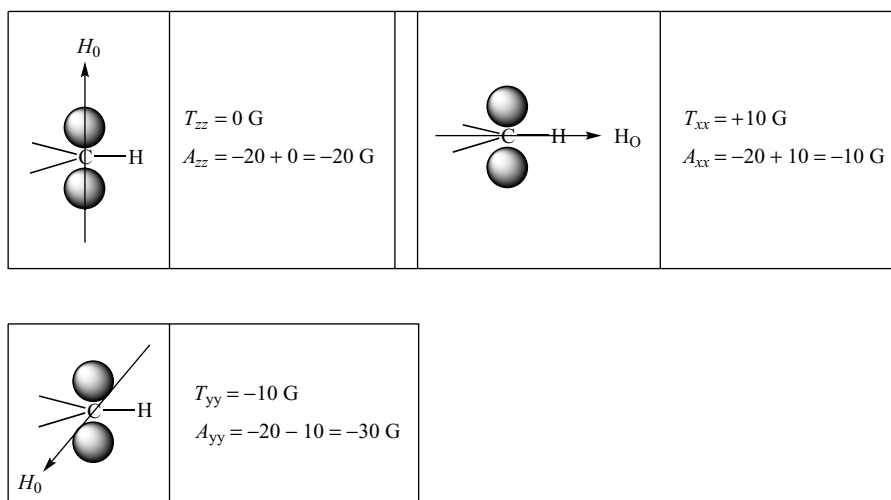


Figure 4 The figure shows the anisotropic (T_{ii}) and total hyperfine couplings ($A_{ii} = a_{\text{iso}} + T_{ii}$) along the three principal axes in a π -type radical C–H fragment. The external magnetic field, H_0 , when applied along each axis results in the different values of the anisotropic HFCC (T_{ii}).

typical for an α -proton. The observed coupling in the figure for each magnetic field orientation is also calculated using a typical isotropic coupling for an α -proton, circa -20 G . Of course, the actual measured couplings depend on the details of the chemical structure and electronic structure of the radical being investigated. In amorphous solids, all random orientations of the radical relative to the magnetic field (whose direction is fixed) are present, and the observed spectrum is a sum of the individual spectra from each orientation.

A simulated ESR spectrum for a radical with couplings of -10 , -30 , and -20 G , in the x , y , and z directions, as shown in the Figure 4, is shown

in Figure 5a. The spectrum shows the presence of the anisotropic features. In a nonviscous media, in which a radical can tumble rapidly relative to the molecular correlation timescale for the ESR experiment,^{39–43} the anisotropic hyperfine couplings average to zero and only the -20 G isotropic component of the hyperfine coupling is observed resulting in a 20 G doublet (Figure 5b).

For *nitrogen* atoms in DNA base radicals, the unpaired spin is usually localized in the p_z -orbital system, and experimentally, a dipolar hyperfine coupling is observed. The principal values of the anisotropic tensor (T_{xx} , T_{yy} , and T_{zz}) are $(-B, -B, \text{ and } 2B)$. With the applied magnetic field aligned

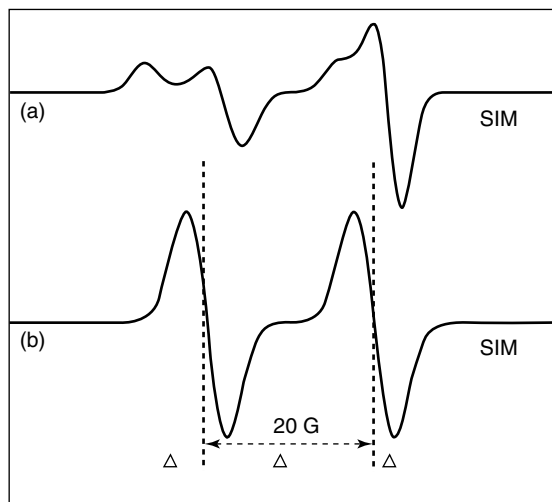


Figure 5 Simulated ESR spectra for (a) a radical with α -proton couplings of -10 , -30 , and -20 G, in the x , y , and z directions, g (2.0032, 2.0049, 2.0020); for (b), the same radical shown in (a), as it would appear if rapidly tumbling with an α -proton isotropic coupling of -20 G, $g = 2.0034$. These spectra were simulated using 3 G linewidth and a Lorentzian/Gaussian lineshape = 1. The simulated spectra in this figure and in other figures shown in this article were obtained using WIN-EPR and SIMFONIA (Bruker) program.

with the p_z -orbital axis, the magnitude of the anisotropic portion of the coupling is maximum ($2B$). When the external field is perpendicular to the p_z -orbital, the coupling is smaller and reversed in sign ($-B$). Addition of the anisotropic and isotropic terms (a) provides two A -values shown in (8):

$$A_{||} = A_{zz} = (a + 2B), A_{\perp} = A_{xx} = A_{yy} = (a - B) \quad (8)$$

From these values, the sp hybrid character of the radical site can be calculated from the following relationships:

$$\begin{aligned} \%s \text{ character} &= (a/a^\circ) \times 100, \\ \%p \text{ character} &= (B/B^\circ) \times 100 \end{aligned} \quad (9)$$

Here, a° and B° are the isotropic and anisotropic hyperfine couplings calculated for unit populations in pure s - or pure p -orbitals, respectively.

In the past several years, a number of review articles have been published, which have summarized numerous evidences of employing ESR to the identification of DNA radicals.^{7–16,20}

2.1.3 Theoretical Prediction of Radical Properties

ESR provides important information, for example, g -values and HFCCs that can be employed to identify free radicals species. The HFCCs provide the most important information as to the number and kind of magnetic nuclei and their degree of interaction with the unpaired electron in the radical. The HFCCs as well as the molecular geometry of a radical can also be calculated using theory which can confirm radical assignments or prove them poor choices. In recent years, DFT employing the B3LYP functional has been found to be very successful in characterizing DNA radicals.^{69–76} In addition to reliable HFCCs, it provides accurate optimized radical geometries and the relative stabilities of different conformations, vibrational frequencies, and the location of the unpaired electron in the radical. The latter is visualized by plots of spin density distributions as well as plots of the single occupied MO (SOMO). As we have mentioned in Section 1.2, the calculation of an accurate isotropic (Fermi contact term) is difficult for any theoretical method because it is a purely local property and it is very sensitive to the net spin density residing at the nucleus. The isotropic HFCC ($a_{\text{iso}}(n)$) for a nucleus n is directly proportional to the net spin density at the nucleus and is given by^{44,45,58,77}

$$a_{\text{iso}}(n) = \frac{4\pi}{3} g_e g_N \beta_e \beta_N \langle S_z \rangle^{-1} \rho(n) \quad (10)$$

$$\rho(n) = \sum_{\mu\nu} \rho_{\mu\nu}^{\alpha\beta} \langle \phi_\mu | \delta(r_N) | \phi_\nu \rangle \quad (11)$$

In 10, g_e and g_N are electron and nuclear g -factor; β_e and β_N are electron and nuclear Bohr magneton; S_z is the value of the spin quantum number (1/2 for a single unpaired electron) and $\rho(n)$ is the Fermi contact integral for the nucleus. In (11), $\rho_{\mu\nu}^{\alpha\beta}$ is the value of the one electron spin density matrix; ϕ_μ and ϕ_ν are the atomic orbitals and $\delta(r_N)$ is Dirac delta operator.

Generally, all the commonly used quantum chemical methods, for example, HF, B3LYP, MP2, and CCSD, can calculate HFCCs, but the accuracy of the calculated HFCCs is very method dependent. The simple HF method is not suitable because it cannot describe spin polarization and electron correlation, which are necessary for

the hyperfine coupling calculations.⁷⁸ MP2 includes electron correlation, but it severely contaminates the spin ($S^2 \neq 0.75$) and generally the calculated HFCCs are not close to the experimental values. In addition, MP2 is less feasible for large molecular systems owing to large central processing unit (CPU) time. The B3LYP method includes a small contribution (20%) of HF exchange and electron correlation. But it also has some drawbacks, for example, as with all DFT methods it suffers from the self-interaction error and needs correction.⁷⁹ It delocalizes spin densities over several DNA bases more than that found experimentally. Even so, the use of the DFT-based B3LYP method is well tested for a large number of organic and inorganic radicals^{65–67} and DNA radicals^{69–77} for HFCC calculations. Also, it is a good choice for a compromise between accuracy and computational feasibility; the computational cost is comparable to the HF method. It should also be noted that a well-defined basis set is also required to accurately compute the isotropic HFCCs (a_{iso}), although satisfactory anisotropic HFCCs (T_{ii}) can be obtained with almost any method and basis set with the condition that the radical structure is reasonably correct. This is important because the experimental structures of radicals are often not available. Considering this aspect, special basis sets known as *EPR-II* and *EPR-III* were developed to compute HFCC by Barone.⁸⁰ These basis sets are especially designed for computing HFCCs by the DFT method, particularly, B3LYP. The *EPR-II* basis set is a double ζ basis set with a single set of polarization functions. *EPR-III* is a triple- ζ basis set including diffuse functions, double d-polarizations, and a single set of f-polarization functions; for details see the Gaussian web site.⁸¹ Recently, Barone and Cimino⁸² calculated HFCCs for a large data set of 200 radicals using B3LYP and PBE0 methods and 6-31G* and a newly devised N07D basis sets. The calculated mean absolute deviation ($\text{MAD} = \sum |a_{\text{calc}} - a_{\text{exp}}|/N$, where a_{calc} and a_{exp} are calculated and experimental isotropic HFCC values and N is the number of data points) for hydrogen and second row elements C, O, N, and F reported in Gauss are 2.1 (H), 3.5 (second row) for B3LYP/6-31G*, 1.9 (H), 3.2 (second row) for B3LYP/*EPR-III*, 4.2 (second row) for B3LYP/TZVP, and 1.9 (H), 2.1 (second row) for PBE0/N07D, respectively.^{82,83} Thus, the use of the B3LYP/6-31G* method is able to treat the

differential spin polarization and thus provides as good a description of the magnetic properties of hydrogen and second row atom couplings as found for other specifically designed basis sets and functionals. The theoretical calculation provides a and $T_{ii} = [T_{xx}, T_{yy}, T_{zz}]$ and the principal values of the diagonalized hyperfine tensor can then be obtained employing (6) by adding $a + T_{ii}$. The calculation also provides the direction cosines for each T_{ii} which rotate the diagonalized T_{ii} to a common axis system that allows for the simulation of the experimental ESR spectrum.

3 ESR AND THEORETICAL STUDIES THAT ELUCIDATE VARIOUS PROPERTIES OF DNA RADICALS WITH SPECIFIC EXAMPLES

3.1 Ground-State Properties of DNA Radicals

3.1.1 Conformation of DNA Radicals

The DNA (or RNA) sugar radicals discussed in Section 1.1 adopt various conformations as defined by the pseudo-rotation cycle.^{72,84–87} Since HFCC values depend on conformation, the identification of sugar radicals solely on the basis of the HFCC can be difficult.^{70–72,88–90} Using B3LYP/6-31G(d,p) method and considering C4'• as an example of a DNA sugar radical, Parr and Wetmore⁷² have shown that the lowest energy conformation for C4'• depends on the model system chosen. A combination of ESR spectral studies and DFT calculations has established that C5'• in an aqueous (D₂O) glass at low temperature shows only one ca. 20 G doublet splitting from the α -hydrogen at C5'. Even though a β -hydrogen is present on C4', the conformation of the C5' radical is such that only a small and unresolved coupling from it is present.^{70,71,88,89} However, for C5'• in 3'-AMP, there are two different pD-dependent conformations in the pD range of circa 6 to circa 9, which lead to different β -couplings from the hydrogen on C4' (Figures 6 and 7, Ref. 70).

In Figure 6, the ESR spectra of C5'• formed via photoexcitation of A^{•+} in glassy (7.5 M LiCl/D₂O) samples of 3'-AMP at various pDs are shown. The spectrum in Figure 6a obtained at pD circa 6 was assigned to C5'•; the lineshape, center of the spectrum, and the total breadth of this spectrum

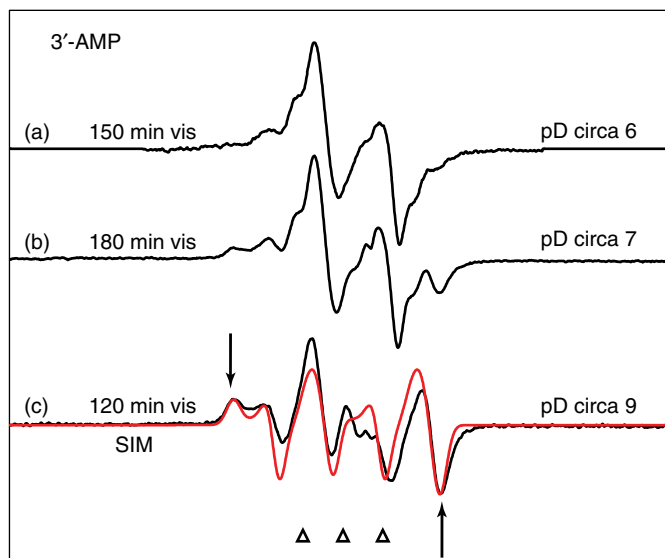


Figure 6 Spectra, attributed to $C5'^{\bullet}$, obtained after illumination of one-electron oxidized 3'-AMP in 7.5 M LiCl/D₂O glass at pD 6, 7, and 9. The spectrum from any remaining $A^{\bullet+}$ has been subtracted from each spectrum. $C5'^{\bullet}$ changes its conformation with increasing pD resulting in an increase in the β -hydrogen coupling to the $C4'$ -H atom, as indicated by an increase in the intensity of the line components in the wings of the spectra. The simulated spectrum in C (red) uses the principal hyperfine values: $1\alpha H$ (−9.0, −33.0, and −15.0) G, $1\beta H$ (34.5, 34.5, and 34.5). The g -value principal values used are 2.0032, 2.0049, and 2.0020, and a 4.5 G linewidth with a mixed Lorentzian/Gaussian (1/1) lineshape is also used. [Reprinted with permission from Ref. 70. Copyright 2008 American Chemical Society.]

agrees very well with the reported $C5'^{\bullet}$ spectrum from dGuo,⁸⁸ 3'-dGMP,⁸⁸ dAdo,⁸⁹ 3'-dAMP,⁸⁹ and Guo.⁷¹ The principal feature of this spectrum is a ca. 19 to 21 G anisotropic doublet from the α -hydrogen on $C5'$. A large increase in the isotropic hyperfine coupling from the β -hydrogen on $C4'$ from circa 5 to 34.5 G is observed on increasing the pH from 6 to 9. This can be seen in the wings of the spectra shown; line components arising from the 34.5 G coupling dramatically increase in intensity as the pD increases. At pD circa 7, the spectrum found (6b) is a combination of spectrum a (65%) and spectrum c (35%). Spectrum a (at pD circa 6) has been assigned to the form of the nucleotide that has a HPO_4^- group adjacent to $C3'$ and spectrum c (at pD circa 9) to that with a PO_4^{2-} group (Scheme 7).

The simulated spectrum in 6c (red) employed the following principal values for the hyperfine couplings and g -values: $1\alpha H$ (−9.0, −33.0, −15.0) G; $1\beta H$ (34.5, 34.5, 34.5) G; $g = (2.0032, 2.0049, 2.0020)$. A mixed Lorentzian/Gaussian (1/1) linewidth of 4.5 G was also employed.

Employing B3LYP/6-31G* method, the theoretically calculated value of the isotropic β -hyperfine coupling from the $C4'$ -H atom for the optimized geometry of the higher pD form of 3'-AMP (Figure 7b) was found to be 28.3 G, which is reasonably close to the experimentally obtained value of 34.5 G.⁷⁰

The spectrum found in Figure 6a corresponds to a conformation of the radical site that has a dihedral angle of circa 90° between the z -axis of the singly occupied p_z -orbital on $C5'$ radical and the H- $C4'$ bond. This is equivalent to the dihedral angle $H4'-C4'-C5'-O5'$ equal to 0° (Figure 7a and c). In this particular conformation, the β - $C4'$ proton is in the nodal plane of the $C5'$ radical p_z -orbital and a small hyperfine coupling results (Section 2.1.2). On the other hand, the spectrum in Figure 6c corresponds to a conformation in which the H- $C4'$ bond has a dihedral angle of circa 36° (dihedral angle $H4'-C4'-C5'-O5' = 54^\circ$). In this conformation, a large β - $C4'$ proton hyperfine coupling is found (Figure 7b).⁷⁰ The $C5'$ - αH hyperfine coupling (−21 G), which is found both theoretically and experimentally for both

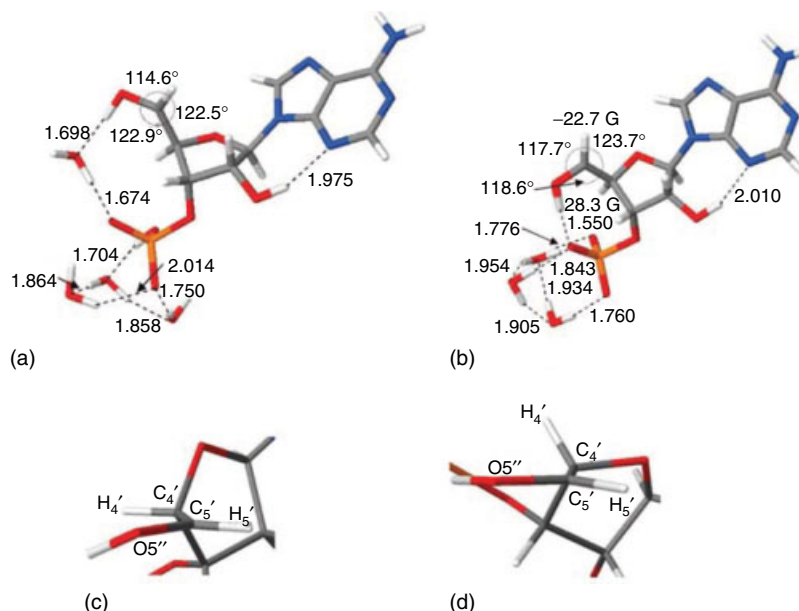
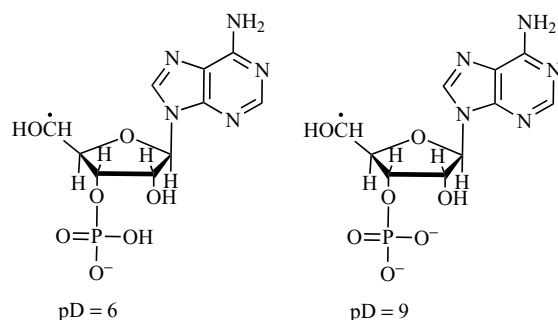


Figure 7 B3LYP/6-31G* optimized geometries of C5'• in 3'-AMP. (a) Mono-protonated phosphate (PO_4H^-) in the presence of four waters and (b) deprotonated form (PO_4^{2-}) in the presence of three waters. The atoms O5', C5', H5', and C4' are constrained in the same plane in (a) and (b). In (a), the dihedral angle $\text{H4}'\text{--C4}'\text{--C5}'\text{--O5}'$ was constrained to 0° , whereas in (b), it is 54° . (c) and (d) are the exposed views of the atoms O5', C5', H5', and C4' shown in (a) and (b). (c) shows that the C4'–H atom in (a) is in the nodal plane of the p-orbital of C5' radical, whereas (d) points out that it is lifted significantly out of the nodal plane and results in a large β -proton hyperfine coupling from the C4'–H atom in the C5'•. [Reprinted with permission from Ref. 70. Copyright 2008 American Chemical Society.]



Scheme 7 Structure of C5'• in 3'-AMP at low and high pH/pD. The optimized geometries and resulting conformations of these two forms of C5'• are shown in Figure 7.

conformations, is consistent with a C5' radical site in a near-planar conformation.⁹¹

The increase in the C4'β-proton hyperfine coupling with increasing pH is associated with the deprotonation of the phosphate group at $\text{pH} > 7$. This allows for subsequent hydrogen bonding of the C3'–OH to a negatively charged phosphate oxygen

(Figure 7b). As indicated by the fit of the simulated spectrum with experiment in Figure 6c, the hyperfine couplings suggested by theory match nicely with experiment and strongly support the theoretical structure shown in Figure 7b.

3.1.2 Effect of Solvation (Hydration) on DNA Radicals

DNA solvation is fundamentally important to its biological processes that take place in an aqueous environment. It is well known that DNA base cation radicals become more acidic and anion radicals more basic in nature than their corresponding neutral bases.^{7,28} As a result of this enhanced acidic or basic character, DNA cation radicals tend to deprotonate to nearby proton acceptors and the DNA anion radicals tend to protonate from proton donors, for example, from the complementary base in the base pair or the surrounding solvent. These proton transfer processes lead to more stable radicals and

tend to slow or stop hole and electron transfer from base to base. In recent works,^{31,35,69,70,72–75} it was found that when solvation was considered, the experimental properties of DNA ion radicals were well modeled by theory. For example, the HFCCs of G^{+} in monomers,⁶⁹ intra-base pair proton transfer in the ground state of one-electron oxidized $G:C$,³¹ and sugar radical formation by a PCHT in G^{+} in dGuo³⁵ were all nicely described by DFT calculations taking into account the effect of solvation. In theoretical calculations, the effect of solvation is incorporated either by considering the effect of full solvation through the polarized continuum model (PCM) or by placing a number of water molecules around the solute.⁶⁹ From computational points of view, PCM is simple and represents the effect of the bulk solvent; however, PCM lacks the contribution of the solute–solvent interaction, which is established through specific hydrogen bonding interactions. The inclusion of explicit water molecules describes these solute–solvent interactions better, though it is computationally more expensive than the PCM model. The best approach is to include the first few waters and to use the PCM model on the entire system so that both the local and bulk solvation effects are taken into account.

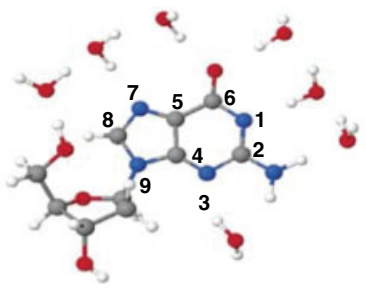
3.1.3 Protonation States of One-Electron Oxidized Guanine in Monomers

Employing ESR and UV–Vis spectroscopy, the deprotonation reactions of G^{+} in dGuo in aqueous medium at low temperatures have been elucidated.⁶⁹ The presence of specific protonation states

of one-electron oxidized guanine in dGuo were observed: (i) guanine cation radical (G^{+}) was found at pH range 3–5, (ii) the singly deprotonated species $G(N1-H)^{\bullet}$ was found in the pH range 7–9, and (iii) doubly deprotonated species $G(-2H)^{-\bullet}$ was shown to be present at $pH \geq 11$. Through ^{15}N substitution at specific nitrogen atoms (N1, N2, and N3), and deuterium substitution at the C8–H atom in the guanine moiety in dGuo, the nitrogen HFCCs were specifically assigned to each of the labeled nitrogen atoms in dGuo.⁶⁹

Using the B3LYP/6-31G* method, the geometries of G^{+} , $G(N1-H)^{\bullet}$, $G(N2-H)^{\bullet}$ (syn- and anti-conformations), and $G(-2H)^{-\bullet}$ in dGuo were fully optimized in the gas phase and in the presence of a single water molecule. The calculation predicted $G(N1-H)^{\bullet}$ to be less stable than the $G(N2-H)^{\bullet}$ by $\sim 3 \text{ kcal mol}^{-1}$.⁶⁹ Although the calculation predicted $G(N2-H)^{\bullet}$ to be more stable, the calculated HFCCs did not match with the experimental ESR HFCCs.⁶⁹ To resolve this problem, the complete first layer of hydration around G^{+} , $G(N1-H)^{\bullet}$, and $G(N2-H)^{\bullet}$ was modeled by placing seven waters in the preferred hydrogen bonding arrangement, fully optimizing the geometries, and calculating the HFCCs using the B3LYP/6-31G* method (for details see Ref. 69). The calculation predicted that $G(N1-H)^{\bullet} + 7H_2O$ was more stable than $G(N2-H)^{\bullet} + 7H_2O$ by $\sim 3 \text{ kcal mol}^{-1}$. Also, the calculated HFCCs for $G^{+} + 7H_2O$ and those for $G(N1-H)^{\bullet} + 7H_2O$ matched very well the experimental HFCC values (Table 1). For $G(-2H)^{-\bullet}$, 8–10 waters were needed to obtain a good agreement between theoretically predicted HFCC values and those obtained from experiment.⁶⁹

Table 1 Experimental and theoretical ESR HFCCs for $G(-H)^{\bullet}$ in Gauss (see Ref. 69 for details). The optimized geometry of $G(-H)^{\bullet}$ with seven water molecules is also shown along with the numbering scheme for $G(N1-H)^{\bullet}$.

	8-D-dGuo/dGuo			dGuo					
	$^{14}N3$ Couplings (G)			$^{14}N2$ Couplings (G)			C8(H) Coupling (G)		
	A_{zz}	A_{xx}	A_{yy}	A_{zz}	A_{xx}	A_{yy}	A_{zz}	A_{xx}	A_{yy}
Exp.	12.0	~ 0	~ 0	8.0	~ 0	~ 0	–7.2	–10.5	–3.5
Theory									
$G(N1-H)^{\bullet} + 7H_2O$	13.5	0.8	0.9	9.1	0.6	0.7	–8.4	–11.3	–3.0
$G(N2-H)^{\bullet} + 7H_2O$	15.0	1.0	1.0	17.6	0.8	0.8	–6.6	–8.8	–2.3

The site of deprotonation of $G^{+\bullet}$ in monomers had been proposed in previous studies to be either from N1 or from N2 nitrogen sites.^{7, 10–16, 18–20, 69} A more recent study using a combination of experiment and theory has led to the identification of the preferred site of deprotonation in dGuo.⁶⁹ This study predicts that even at low temperature, the N1–H site is the preferred site for deprotonation of $G^{+\bullet}$ in monomers. In a gas phase calculation of the conversion of $G(N2-H)^{\bullet}$ to $G(N1-H)^{\bullet}$ employing the B3LYP/6-31G* method and a single water molecule, a substantial barrier (~ 19 kcal mol⁻¹) is obtained.⁶⁹ In an experimental pulse radiolysis investigation, in aqueous solution at ambient temperature, a much lower activation energy for the conversion of $G(N2-H)^{\bullet}$ to $G(N1-H)^{\bullet}$ of 5.5 kcal mol⁻¹, was reported.⁹² The difference between the theoretical and experimental values of the activation barrier clearly points out that full solvation needs to be employed to obtain a reasonable theoretical value of the activation barrier (Section 3.1.2).

3.1.4 Intra-Base Pair Proton Transfer in One-Electron Oxidized G : C

The intra-base pair proton transfer between N1 of G to N3 of C in the G : C cation radical ($C : G^{+\bullet}$)

has been of considerable interest as this reaction is important with regard to hole transfer and reactions of the cation radical.^{7, 12, 25–27} Selective deuteration at C8 in the guanine moiety was employed to study this process. One-electron oxidation of 8-deutero-dGuo (G^*) led to the ESR spectrum of the cation radical ($G^{+\bullet}$) whose $g_{\perp}$ differs from that of the corresponding deprotonated cation radical ($G^*(N1-H)^{\bullet}$) spectrum.²⁵ Using G^* incorporated into dsDNA oligomers, only the ESR spectrum of $G^*(N1-H)^{\bullet} : C(+H^+)$ was found (Figure 8a and b).²⁵ Thus, it was concluded that on one-electron oxidation of G : C in dsDNA, proton transfer occurs in $C : G^{+\bullet}$ from N1 of guanine to N3 of cytosine. This intra-base pair proton transfer reaction was thoroughly investigated using theoretical methods in the gas phase and was found to be endothermic.^{7, 18–20, 93–96} Recently, this reaction was considered by taking into account the effect of the first hydration shell by including 11 water molecules surrounding the G–C base pair. The zero point energy-corrected reaction energies for proton transfer from $G^{+\bullet}$ (N1) to C(N3) was evaluated using the B3LYP/6-31+G** method. The forward barrier for proton transfer was found to be 1.4 kcal mol⁻¹ and the reaction was found to be exothermic in nature (Figure 8c). The proton-transferred $C(+H^+) : G(N1-H)^{\bullet} + 11H_2O$

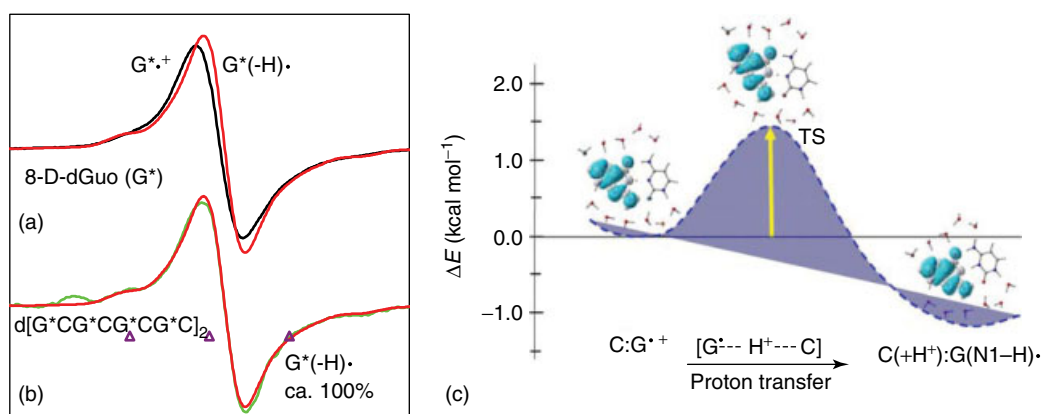


Figure 8 (a) ESR spectra of $G^{+\bullet}$ and $G^*(-H)^{\bullet}$ obtained from glassy (7.5 M LiCl in D_2O) samples of G^* ($G^* = 8\text{-D-dGuo}$, 96% D) (3 mg ml^{-1}). [Reprinted with permission from Ref. 25. Copyright 2009 American Chemical Society.] (b) Spectrum of the one-electron oxidized dsDNA oligomer $d[G^*CG^*CG^*CG^*C]_2$ (2 mg ml^{-1}), again with $G^*(-H)^{\bullet}$ from (a) in red superimposed. The match of green and red spectra in (b) shows that one-electron oxidized guanine in dsDNA oligomer $d[G^*CG^*CG^*CG^*C]_2$ exists as $G^*(-H)^{\bullet}$. Consult Ref. 25 for details. [Reprinted with permission from Ref. 25. Copyright 2009 American Chemical Society.] (c) The B3LYP/6-31+G** calculated potential energy surface (PES) of proton transfer (PT) in $C : G^{+\bullet}$ in the presence of 11 waters with zero point energy (ZPE) correction. Energy is given in kcal mol⁻¹. Spin density distributions during proton transfer are also shown. [Reprinted with permission from Ref. 31. Copyright 2009 American Chemical Society.]

was found to be $1.2 \text{ kcal mol}^{-1}$ more stable than $\text{C}:\text{G}^{\bullet+} + 11\text{H}_2\text{O}$.³¹

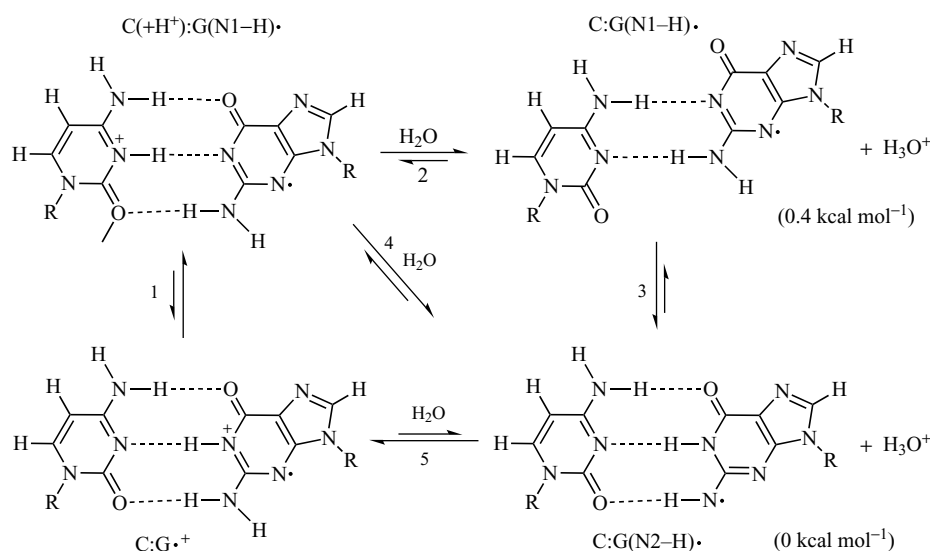
3.1.5 Duplex-to-Solvent Proton Transfer from the Exocyclic Amine (N2) of Guanine in One-Electron Oxidized G:C

The prototropic equilibria of one-electron oxidized G:C (Scheme 8) is crucially influenced by the two reversible proton transfer processes: (i) the intra-base pair proton transfer (process 1) and (ii) the proton transfer from the cation radical (parent or intra-base pair proton-transferred form) to the surrounding solvent (processes 2 and 4). The experimental and theoretical efforts outlined in Section 3.1.4 have established that the site of intra-base pair proton transfer in the G:C cation radical ($\text{C}:\text{G}^{\bullet+}$) is from $\text{G}^{\bullet+}(\text{N1})$ to $\text{C}(\text{N3})$.

Employing B3LYP/DZP++ method, the difference between the energies of the optimized geometries of $\text{C}:\text{G}(\text{N1-H})^{\bullet}$ and $\text{C}:\text{G}(\text{N2-H})^{\bullet}$ (Scheme 8) in the gas phase has been calculated to be 1 kcal mol^{-1} .²⁶ On the basis of this theoretical

result, it is suggested that the site of deprotonation of one-electron oxidized guanine in dsDNA to the surrounding water could be either at N2 or at N1 (see Scheme 8) or more likely a mixture of the two.

The authentic N2 deprotonation radical ($\text{C}:\text{G}(\text{N2-H})^{\bullet}$) in one-electron oxidized d[TGCGCGCA]₂ has been characterized using an authentic $\text{G}(\text{N2-H})^{\bullet}$ spectrum obtained from 1-methyl-2'-deoxyguanosine (1-Me-dGuo) (Figure 10).²⁶ The fact that the methyl-substituted compound, 1-Me-dGuo, or its corresponding RNA analog 1-methyl-guanosine (1-Me-Guo) is a good model for the one-electron oxidized guanine is confirmed through theoretical calculations. Using the B3LYP/6-31G* method, it is found that $\text{G}^{\bullet+}$ and 1-Me- $\text{G}^{\bullet+}$ have identical spin density distributions, as do $\text{G}(\text{N2-H})^{\bullet}$ and 1-Me- $\text{G}(\text{N2-H})^{\bullet}$ (Figure 9). In 1-Me-dGuo or 1-Me-Guo, the N1-H atom is replaced by a methyl group and deprotonation occurs *only* from the N2 site as reported in pulse radiolysis studies by Steenken.^{28–30} The UV–Vis spectrum of 1-Me- $\text{G}(\text{N2-H})^{\bullet}$ obtained via pulse radiolysis studies in aqueous solution at ambient temperature^{28–30} is further supported by the ESR



Scheme 8 Schematic representation of prototropic equilibria in the one-electron oxidized G:C. The intra-base pair proton transfer within the one-electron oxidized G:C (process 1) and proton transfer to water either from the N1 atom (process 2) or from the nitrogen atom in the exocyclic amine (N2) of the guanine moiety in the one-electron oxidized G:C (process 4) are shown. The interconversion between $\text{C}:\text{G}(\text{N1-H})^{\bullet}$ and $\text{C}:\text{G}(\text{N2-H})^{\bullet}$ is represented by process 3. Employing the B3LYP/6-31+G** method, the fully optimized geometries of $\text{C}:\text{G}(\text{N1-H})^{\bullet}$ and $\text{C}:\text{G}(\text{N2-H})^{\bullet}$ in the presence of 11 water molecules have been used to calculate the relative stabilities between $\text{C}:\text{G}(\text{N1-H})^{\bullet}$ and $\text{C}:\text{G}(\text{N2-H})^{\bullet}$ and these near identical values are provided in parentheses. Consult Ref. 26 for details. [Adapted from Ref. 26. © 2010, Royal Society of Chemistry.]

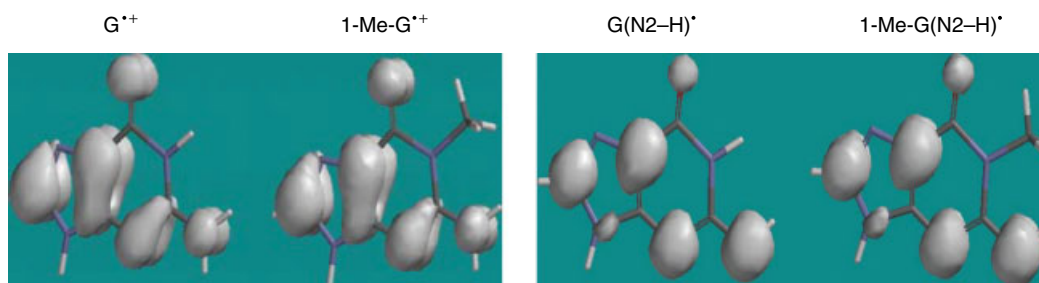


Figure 9 Comparisons of spin density distribution of $G^{\bullet+}$ and $1\text{-Me-G}^{\bullet+}$ as well as of $G(\text{N2-H})^\bullet$ and $1\text{-Me-G}(\text{N2-H})^\bullet$ calculated using B3LYP/6-31G* method for guanine (G) and 1-methyl-guanine (1-Me-G).

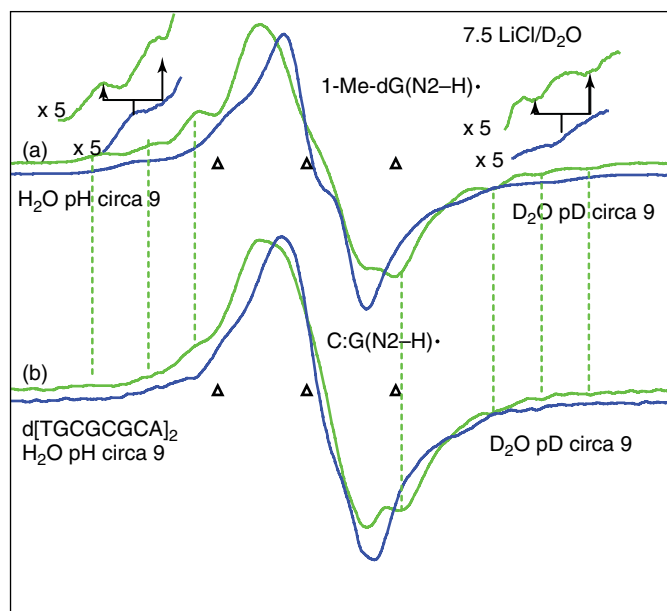


Figure 10 (a) ESR spectra of authentic $1\text{-Me-dG}(\text{N2-H})^\bullet$ obtained from glassy (7.5 M LiCl) in D_2O (blue) and in H_2O (green) samples of 1-Me-dGuo by one-electron oxidation. Expansion of the wings by factor of 5 shows the A_{zz} component of the N2-H coupling in H_2O —which is lost in D_2O . (b) Comparison of the spectrum of one-electron oxidized $\text{d}[\text{TGCGCGCA}]_2$ in D_2O from (a) (blue) with that found in H_2O (green) for an otherwise identical sample. Similar to the spectra (see arrows) shown in (a), the A_{zz} component of the remaining N2-H proton hyperfine coupling of $G(\text{N2-H})^\bullet$ is visible (as indicated by the dotted lines in green) in the wing spectrum (green) in (b). All ESR spectra were recorded at 77 K. [Consult Ref. 26 for details.]

and UV–Vis spectroscopic studies of one-electron oxidized 1-Me-dGuo or 1-Me-Guo in glassy systems at low temperatures.²⁶

In Figure 10a, the ESR spectrum of $1\text{-Me-dG}(\text{N2-H})^\bullet$ (green) formed via one-electron oxidation by $\text{Cl}_2^{\bullet-}$ of 1-Me-dGuo in 7.5 M LiCl (H_2O) is shown. For comparison, the ESR spectrum of $1\text{-Me-G}(\text{N2-H})^\bullet$ in D_2O (7.5 M LiCl) (blue) has been superimposed on it. The expanded wings in Figure 10a show the 8 G A_{zz} hyperfine coupling

of the N2-H proton of $1\text{-Me-G}(\text{N2-H})^\bullet$ in H_2O (green), which is lost in D_2O glasses (blue). In Figure 10b, we have compared the spectrum of the one-electron oxidized $\text{d}[\text{TGCGCGCA}]_2$ (green) obtained in H_2O glass with the spectrum of the one-electron oxidized $\text{d}[\text{TGCGCGCA}]_2$ found in D_2O glass (blue). Comparison of Figure 10a and b establishes that one-electron oxidized $\text{d}[\text{TGCGCGCA}]_2$ (green) in H_2O also shows the A_{zz} component of hyperfine coupling of the

exchangeable N-H atom in d[TGCGCGCA]₂. Thus, the G(N2-H)[•] spectrum in one-electron oxidized d[TGCGCGCA]₂ has been identified. Moreover, analyses using authentic G(N1-H)[•] and G(N2-H)[•] spectra show that the radical cohort in spectrum B (either in H₂O or in D₂O) is an equilibrium mixture of C:G(N2-H)[•] (circa 60%) and C:G(N1-H)[•] (circa 40%)—which is expected from the near identical stabilities of these radicals obtained by DFT calculations (Scheme 8).

3.2 Excited-State Processes

The ground states of a variety of DNA radicals (Section 1.1) have been well characterized experimentally and theoretically (Section 3.1). However, very little is known about the excited-state properties of DNA radicals. Excited states are copiously produced as ionizing radiation interacts with DNA.^{10–16,18–20} For radiations with low linear energy transfer (LET), excited states are usually isolated and rapidly deactivate, so they likely result in a small extent of DNA damage. On the other hand, high LET radiations produce dense ionization tracks that have excitations and ionizations in proximity in the core of the track.^{10–16} With this in mind, the fact that irradiation of DNA by a high-energy argon ion beam produces a large number of sugar radicals along the ion-track has led to the suggestion that fast deprotonation from excited-state cation radicals lead to the formation of neutral sugar radicals.⁹⁷ To test this hypothesis, ESR spectral studies of photoexcited one-electron oxidized purines in DNA and RNA model systems (nucleosides, nucleotides, and oligomers) as well as one-electron oxidized highly polymerized dsDNA (salmon sperm) were carried out and formation of sugar radicals was observed.^{12,27} Subsequently, time-dependent (TD)-DFT calculations were carried out to support these experimental results.^{18,19,35,36}

3.2.1 Hole Transfer Processes and Sugar Radical Formation

As shown in Scheme 4, a deoxyribose sugar cation radical once produced rapidly deprotonates, resulting in the formation of a neutral sugar radical such as C1'[•], C3'[•], or C5'[•].¹² Deprotonation is expected to

be especially rapid (< ps range) in an excited state; hence, formation of a neutral sugar radical should readily occur.¹² Employing UV–Vis illumination at 77 K as a means of inducing excited states in trapped G^{•+} in highly polymerized dsDNA (salmon sperm), ESR studies showed that C1'[•] was indeed formed from excited G^{•+}.⁸⁸ Furthermore, in dsDNA, formation of C1'[•] was found to depend on the wavelength of the light used for photoexcitation. In the wavelength range 310–480 nm, C1'[•] formation was observed; at wavelengths ≥ 520 nm, no sugar radical formation was observed (Figure 11).⁸⁸

Further experiments (at 77 and 143 K) in a variety of model DNA and RNA purine mononucleosides, nucleotides, and a variety of ss and ds oligonucleotides showed formation of sugar radicals (C1'[•] and C5'[•]) via excitation of previously trapped purine

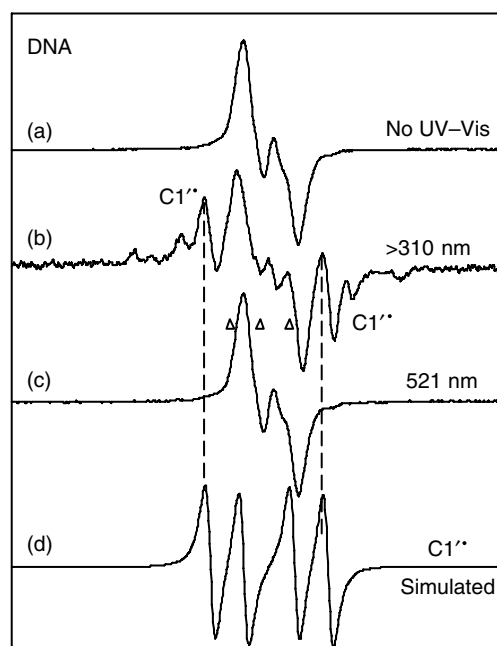
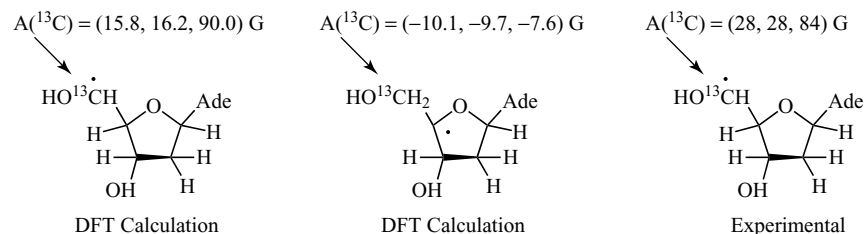


Figure 11 (a) ESR spectrum of DNA ice samples (50 mg ml⁻¹ D₂O) γ -irradiated to 15.4 kGy dose, annealed to 130 K to eliminate [•]OH. (b) After illumination at 77 K for 1 h with light >310 nm. (c) After illumination of an identically prepared sample as in (a), at 521 nm for 30 min. (d) Isotropic simulation of spectrum of C1'[•] using the parameters (15 G (1 β H), 37 G (1 β H), 5 G linewidth, and g (2.0029, 2.0029, 2.0029)). This spectrum matches line components in spectrum (b). Consult Ref. 88 for details. [Reprinted from Ref. 88. © 2005, Oxford University Press.]



Scheme 9 Experimental $^{13}\text{C}5'$ HFCC values for $\text{C}5'^{\bullet}$ and DFT calculated $^{13}\text{C}5'$ HFCC values and structures for $\text{C}5'^{\bullet}$ and for $\text{C}4'^{\bullet}$ in dAdo. [Reprinted from Ref. 89. © 2006, Oxford University Press.]

cation radicals.^{27,70,71,88,89,98,99} Observable formation of $\text{C}3'^{\bullet}$ was found in nucleosides with circa 15–35% conversion of the purine cation radical to $\text{C}3'^{\bullet}$.^{70,71,88,89} However, the formation of $\text{C}3'^{\bullet}$ via photoexcitation of $\text{G}^{+\bullet}$ in the dinucleoside phosphate TpdG was found to be small (circa 10%)⁹⁸, decreases substantially (circa $\leq 10\%$) in ssDNA oligomers (e.g., TGT, TGGT, and TGGGT)^{27,98}, and has not been observed in ds oligomers.²⁷

Specific sugar radicals were identified and their hyperfine couplings were characterized by employing nucleosides having isotopic substitutions at specific sites in the sugar moiety, for example, deuterium substitution at $\text{C}3'$ and $\text{C}5'$ sites in dGuo,⁸⁸ at $\text{C}1'$, $\text{C}2'$, $\text{C}3'$, and $\text{C}5'$ sites in Guo,⁷¹ at $\text{C}1'$, $\text{C}2'$, and $\text{C}5'$ sites in Ado, and at the $\text{C}5'$ site in 5'-AMP.⁷⁰ ^{13}C isotopic substitution at the $\text{C}5'$ site in dAdo has led to the unequivocal identification of $\text{C}5'^{\bullet}$.⁸⁹ To determine whether the prominent doublet (circa 19–21 G) observed in sugar radical cohorts (e.g., Figure 6a) was due to $\text{C}5'^{\bullet}$ or $\text{C}4'^{\bullet}$, ^{13}C isotopic substitution at the $\text{C}5'$ site in dAdo was employed.⁸⁹ B3LYP/6-31G(d) fully optimized geometries indicated that the ^{13}C hyperfine couplings at $\text{C}5'$ in $\text{C}5'^{\bullet}$ differ substantially from the corresponding ^{13}C hyperfine couplings at $\text{C}5'$ in $\text{C}4'^{\bullet}$ (Scheme 9). The comparison of experimental and calculated values clearly pointed out that the prominent doublet originated with $\text{C}5'^{\bullet}$ rather than $\text{C}4'^{\bullet}$.

With the aid of the ESR spectral data obtained from selectively isotopically substituted model compounds, a benchmark spectrum of each sugar radical ($\text{C}1'^{\bullet}$, $\text{C}3'^{\bullet}$, and $\text{C}5'^{\bullet}$) was constructed and these were employed to analyze the experimental spectra of the sugar radical cohort found in various DNA and RNA systems. Analyses showed that *no* observable formation of either $\text{C}4'^{\bullet}$ or $\text{C}2'^{\bullet}$ was found via photoexcitation of purine cation radical in DNA and

RNA model systems (monomers to oligomers) and in highly polymerized dsDNA.^{12,27,70,71,88,89,98,99}

The type and yield of various sugar radicals (i.e., $\text{C}1'^{\bullet}$, $\text{C}3'^{\bullet}$, and $\text{C}5'^{\bullet}$) are crucially influenced by various factors: (i) site of phosphate substitution (at $3'$ or $5'$), (ii) pH (i.e., the protonation state of the purine cation radical), (iii) wavelength or the excitation energy, (iv) temperature during photoexcitation, (v) length and sequence of the oligomer, and (vi) type of the oligomer (ss or ds).^{12,27,71} The effects of these factors to the sugar radical formation via excited purine cation radical have recently been reviewed.¹²

Contrary to the wavelength-dependent formation of $\text{C}1'^{\bullet}$ via photoexcitation of $\text{G}^{+\bullet}$ in dsDNA,⁸⁸ the formation of sugar radicals in dGuo, and in ssDNA oligomers with four or fewer bases was not found to be wavelength dependent.^{12,27,98} However, sugar radical formation was found to be wavelength dependent for a longer ssDNA oligomer (10-mer)^{12,27,98} and for dsDNA oligomers.²⁷ The reason for this has been explained with the aid of TD-DFT calculations for excited states of DNA base cation radicals (Figure 12).

In order to understand the mechanism of sugar radical formation due to photoexcitation of cation radical of purines, TD-DFT calculations were performed. In these calculations, the ground-state geometries of $\text{G}^{+\bullet}$ in dGuo and several dinucleoside phosphates (TpdG, dGpdG, dApdA, dApT, TpdA, and dGpT) in their cation radical states were optimized by the B3LYP/6-31G* method and their vertical excited states were studied.^{88,99,100} For example, the vertical excited states of $\text{G}^{+\bullet}$ in dGuo were calculated employing the TD-B3LYP/6-31G* method (Figure 12a). In the ground state of $\text{G}^{+\bullet}$ in dGuo, the hole is localized on the guanine base as evident from the plot of the SOMO shown, in direct agreement with the ESR studies.⁸⁸ The TD-DFT calculations

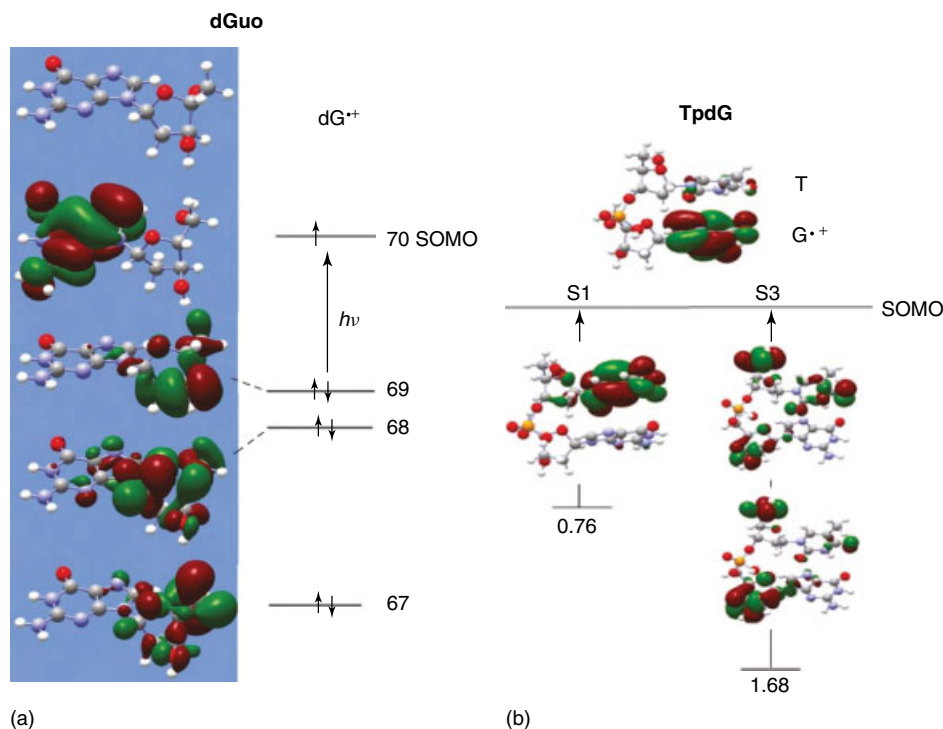


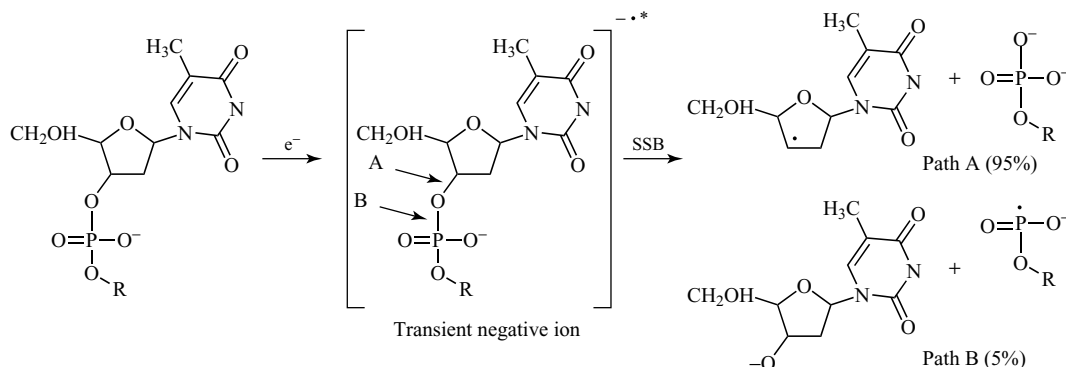
Figure 12 (a) Molecular orbitals and energy level filling diagram for G^{*+} in dGuo. MOs were computed by TD-DFT (6-31G* and B3LYP) and visualized via Gaussview. The SOMO is the expected MO for G^{*+} with the hole localized on the guanine base. A number of inner shell MOs are localized on the sugar ring. [Reprinted from Ref. 88. © 2005, Oxford University Press.] (b) Schematic representation of base-to-base hole transfer, which is favored at longer wavelengths, and base-to-sugar–phosphate hole transfer, which is favored at shorter wavelengths, on photoexcitation of $TpdG^{*+}$. Two of the 20 transitions calculated are shown for the 0.76 and 1.68 eV transitions. The MOs were obtained by employing TD-DFT/B3LYP/6-31G(d) calculations. [Adapted with permission from Ref. 99 Radiation Research, Copyright (2006), Radiation Research Society.]

predict that during excitation, electronic transitions take place from inner MOs to the SOMO, as shown by the arrow thereby showing that, on excitation, the hole transfers from the guanine moiety to the sugar. The sugar cation radical, thus formed in the excited state, deprotonates quickly to produce a neutral sugar radical. These TD-DFT calculations also indicate that the light-induced transitions occur in the whole UV–Vis spectral range (1.5–3.7 eV) from inner MOs to the SOMO, thereby agreeing with the experimental observation (*vide supra*) that sugar radical formation via photoexcitation of G^{*+} in dGuo is wavelength independent.⁸⁸ However, the excited states of dinucleoside phosphates gave a different result.^{99,100} The lowest transition for all the dinucleoside phosphates showed *base-to-base* hole transfer and higher transitions showed the *base-to-sugar* hole transfer (Figure 12b). This provided the explanation for the observation that DNA

sugar radicals were not formed at wavelengths >520 nm.

3.2.2 DNA Damage via Low-Energy Electrons

Secondary electrons formed by ionizing radiation lose their kinetic energy and after thermalization are captured by the bases in DNA.^{10–16,21} Electron transfer thereafter results in the formation of the thymine and cytosine anion radicals (Scheme 5). Secondary electrons having significant kinetic energy before thermalization can lead to DNA damage. Such electrons with kinetic energies between 0 and 20 eV are known as LEEs.^{37,101,102} Recently, LEEs have been recognized to cause single- and double-strand breaks (SSB and DSB) in plasmid DNA through a DEA mechanism.^{37,103,104}



Scheme 10 Schematic diagram showing the formation of SSB due to attachment of LEE to a thymidine moiety in DNA. Paths A and B show the two possible paths for the SSB. The percentage of each path is determined by the relative concentrations of $C3'_{\text{dephos}}^{\bullet}$ and $ROPO_2^{\bullet-}$. In theoretical calculations (Refs 106–112), one of the oxygen atoms of the phosphate group is protonated to neutralize the charge of the phosphate group.

LEEs have been proposed to account for two of the free radicals produced in $^{16}\text{O}^{8+}$ ion beam-irradiated hydrated DNA.¹⁰⁵ From ESR measurements, a new phosphorus-centered radical species was identified by its large ^{31}P parallel hyperfine coupling of circa 775 G as a phosphoryl radical ($ROPO_2^{\bullet-}$). This radical was proposed to be produced by the dissociation of P–O bond through DEA (path B, Scheme 10).¹⁰⁵ In other experiments, hydrated DNA samples at 77 K were irradiated with argon ion beams (^{36}Ar or ^{40}Ar having energies between 60 and 100 MeV/nucleon).⁹⁷ The ESR spectra of these samples indicated the presence of a radical with an unusually large number of hydrogen hyperfine couplings. A variety of considerations led to the conclusion that this was the dephosphorylated $C3'$ radical ($C3'_{\text{dephos}}^{\bullet}$ (path A, Scheme 10)) formed by the rupture of the deoxyribose $C3'$ – $O3'$ bond.⁹⁷ The formation of these two radicals was proposed to be the result of LEE-induced formation of a transient negative ion (TNI) that resulted in bond cleavage in the DNA–sugar–phosphate backbone as shown in Scheme 10.

Employing 3'-thymidine monophosphate (3'-TMP) as a model for DNA (Scheme 10), two alternative paths occur for SSB formation after LEE attachment. At present, there is experimental and theoretical evidence in model systems that the initial capture of the electron may be a “shape” resonance in a π^* state mainly on the DNA base.^{18,19,37} In path A (Scheme 10), C–O bond cleavage at $C3'$ occurs resulting in the formation of $C3'_{\text{dephos}}^{\bullet}$ and a diamagnetic polymeric remnant. In

path B (Scheme 10), a P–O bond is broken, resulting in the formation of $ROPO_2^{\bullet-}$ and a diamagnetic polymeric remnant. The relative amounts of the radicals $C3'_{\text{dephos}}^{\bullet}$ and $ROPO_2^{\bullet-}$ trapped at 77 K, greatly favor $C3'_{\text{dephos}}^{\bullet}$ formation, with circa 95% of the reaction occurring along path A and circa 5% along path B.^{10–12,15,16,97,105} The reactions of LEEs are rather remarkable because the electrons involved have energies lower than the ionization energy of DNA, yet bond cleavage and strand breaks are formed from them. Section 3.2.3 reveals that DFT calculations confirm that these processes can occur through direct resonant processes.

One radical depicted in Scheme 10, $ROPO_2^{\bullet-}$, has a very large hyperfine coupling^{97,105} so that its ESR spectrum is outside the magnetic field range shown in Figure 1. Its ESR spectrum is shown in Figure 13. In this figure, the three Frey salt resonances are shown with three vertical lines in the middle of the spectrum and the full ESR spectrum spans a range of about 1000 G rather than the 250 G shown in Figure 1. The off-scale sections of this spectrum arise from the central DNA spectrum shown in Figure 1, which has a much greater intensity than that of the $ROPO_2^{\bullet-}$ spectrum. The spectrum of $ROPO_2^{\bullet-}$ shown was observed using ^{36}Ar ion beam-irradiated DNA¹⁰²; it is also present in γ -irradiated samples, but at very low concentrations.

It should be noted that $ROPO_2^{\bullet-}$ can originate with P–O bond cleavage at a $C3'$ -phosphate group or at a $C5'$ -phosphate (Scheme 10). ESR investigations of this radical in polymeric DNA samples, which are

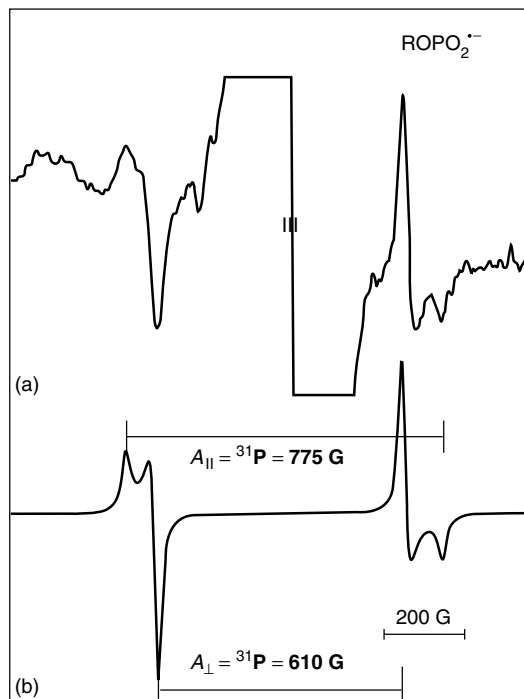


Figure 13 ESR spectra of phosphorus-centered radical ($\text{ROPO}_2^{\bullet-}$). (a) Spectrum of DNA hydrated to $\Gamma = 9$ and irradiated with an ^{36}Ar ion beam, 80 MeV/nucleon ($\text{LET} = 650 \text{ keV}/\mu\text{m}$), with a dose of 170 kGy at 77 K. The spectrum of a phosphoryl radical, $\text{ROPO}_2^{\bullet-}$, is evident in the wings. (b) Simulated spectrum of $\text{ROPO}_2^{\bullet-}$ ($A_{zz} = A_{||} = 775 \text{ G}$, $A_{yy} = A_{xx} = A_{\perp} = 610 \text{ G}$, $g_{xx} = g_{||} = 2.00$, $g_{yy} = g_{zz} = g_{\perp} = 2.01$ and a Gaussian line shape with linewidth 12 G). The spectrum is calculated to second order because of the large phosphorus hyperfine coupling constants involved. [Adapted with permission from Ref. 97 Radiation Research, Copyright (2003) Radiation Research Society.]

amorphous, cannot distinguish between these two sites. The presence of both $\text{C3}'_{\text{dephos}}^{\bullet-}$ and $\text{ROPO}_2^{\bullet-}$ supports the role of LEE in these processes.

Recent theoretical efforts (Section 3.2.3) have shown that LEE addition to DNA may effectively create an anion excited state (TNI, Scheme 10) by addition to a unoccupied MO of higher energy^{18,19,111,112} than the LUMO.^{106,107}

3.2.3 Theoretical Studies of DNA Damage via Low-Energy Electrons

Using TD-DFT calculations, three types of mechanisms were proposed in the literature for

LEE-induced strand break formation: (i) LEE attachment to the lowest energy π^* MO of the base followed by transfer to dissociative σ^* MOs on the sugar phosphate group, resulting in rupture of the C–O bond,^{106,107} (ii) direct addition of LEE to the sugar–phosphate backbone of DNA to create the strand break,^{108,109} and (iii) LEE-induced formation of the various shape resonances producing a TNI that leads to strand breaks^{110–112} (Scheme 10). The TNI is formed when an electron is vertically attached to a neutral molecule without changing its neutral ground-state geometry, as shown in Scheme 10. Mechanisms (i) and (ii) are specific examples of the more general mechanism (iii).

It is well known that during LEE–molecule interactions, shape resonances effectively produce transient excited states of the incipient anion radical.¹¹¹ Thus, a fruitful understanding of the SSB formation in DNA can be obtained from the study of the excited states of the TNI (TNI^*). Hence, the excited states of the anion radical of 5'-TMP (as a model of DNA) were investigated using TD-DFT.¹¹¹ The geometries of 5'-TMPH in their neutral state were fully optimized using the B3LYP/6-31G* method. The lowest three excited states of the TNI were calculated using the TD-BHandHLYP/6-31G* method. In this study, the ground and three lowest excited-state potential energy surfaces were generated as the C5'–O5' bond length was increased in 0.1 Å increments, and at each fixed C5'–O5' bond length, the vertical excited states of the TNI were calculated (Figure 14). The three lowest calculated transition energies of the TNI were found to be $\pi(\text{T}) \rightarrow \sigma(\text{PO}_4)^*$, $\pi(\text{T}) \rightarrow \pi(\text{T})^*$, and $\pi(\text{T}) \rightarrow \sigma(\text{S})^*$ in nature and have transition energies 1.42, 1.68, and 2.06 eV, respectively. The calculated 1.68 eV transition is in good agreement with those obtained from electron transmission spectroscopy experiments of thymine.¹¹³ From Figure 14, we see that the ground-state anion radical surface (lowest surface) is a π -type ground state and has a barrier height of circa 18.7 kcal mol⁻¹ at 1.7 Å for the C–O bond cleavage. This makes the first mechanism (i) suggested above unlikely as the barrier height is substantial. The second and third excited-state surfaces corresponding to $\pi(\text{T}) \rightarrow \pi(\text{T})^*$ and $\pi(\text{T}) \rightarrow \sigma(\text{S})^*$ transitions also exhibit a bound-state character. However, the first ($\pi(\text{T}) \rightarrow \sigma(\text{PO}_4)^*$) surface shows a dissociative nature. Such a dissociative nature for the $\pi \rightarrow \sigma^*$ transitions in excited states are well documented in the literature.¹¹¹ The presence of the

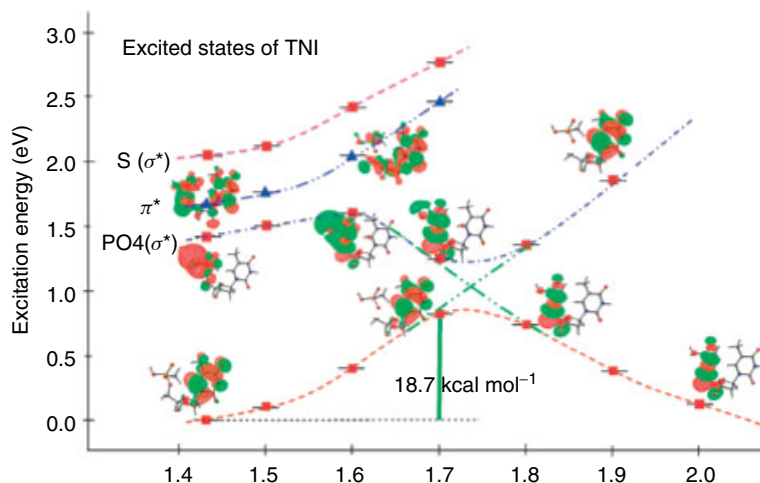


Figure 14 Lower curve: Potential energy surface (PES) of the 5'-TMPH transient negative ion (TNI); calculated in the neutral optimized geometry of 5'-TMPH with C5'-O5' bond elongation. SOMO is shown at selected points. Upper curves: calculated vertical excitation energies of the radical anion at each point along the PES, MOs involved in excitations are also shown. Energies and distances are given in eV and Å, respectively. The lowest $\pi\pi^*$ state (triangles) and lowest $\pi\sigma^*$ states (square) are shown. [Reprinted with permission from Ref. 111. Copyright 2008 American Chemical Society.]

$\pi(T) \rightarrow \sigma(PO_4)^*$ transition at <2 eV clearly indicates that LEEs with this energy can directly attach to the sugar-phosphate group during TNI formation and result in a prompt SSB formation in DNA.

4 CONCLUSION

This article describes work that combines the utility of ESR spectroscopy with modern computational chemistry methods such as DFT to elucidate free radical processes in irradiated DNA systems at low temperatures. DFT calculations aid in the identification of DNA base and sugar-phosphate radicals by prediction of stabilization energies, conformations, and most importantly for ESR, predicting accurate values of the HFCCs. ESR spectral studies carried out by employing isotopic substitution (D, ^{13}C , and ^{15}N) at selective sites in the DNA (or RNA) base,^{25,69} in the DNA (or RNA) sugar moiety,^{70,71,88,89} as well as in the solvent (H_2O^{17} in place of H_2O^{16})³³ have made substantial contributions toward identification of these radicals by characterization of the sites having major hyperfine couplings. The powerful combination of ESR spectral studies and DFT calculations is found to clarify various properties of DNA radicals, which are important to the biological consequences of radiation damage.

These include likely sites of deprotonation in the base cation radical, intra-base pair proton transfer processes, excited-state reactions, and many others. In the future, increasing computational power along with advances in DFT methods, combined with corresponding improvements in ESR spectroscopy, such as high field spectroscopy,¹¹⁴ double resonance,²⁰ and pulse techniques¹¹⁵ will answer still more interesting questions about radiation-produced DNA radicals.

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Radical-Based Damage of Sulfur-Containing Amino Acid Residues

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1 INTRODUCTION

Sulfur (S)- and selenium (Se)-containing amino acids serve a variety of important functions in peptides and proteins such as the maintenance of structure (e.g., through disulfide bonds),¹ the binding of metals,² as sites for redox regulation³ or mediators of redox processes,⁴ as target sites for electrophiles,⁵ and as constituents of active sites. Inherent to S- and Se-containing amino acids is their efficient reaction with free radicals and reactive oxygen species, which may lead to conformational changes and/or both activation and inactivation of enzymes dependent on the extent of modification and the nature and location of the reaction products. Such radical- and/or oxidation/reduction-based modifications are of significance for an increasing number of cellular signal transduction processes^{3,5} and also for protein damage, which is frequently observed under biologic conditions of oxidative stress (see **Oxidative Damage to Proteins**).⁶ Importantly, a radical reaction with a primary target amino acid will lead to secondary radicals. These may engage in radical- and/or electron-transfer processes with additional protein amino acids such that the ultimate location of a radical damage may evolve potentially far from the site of initial radical attack. Such processes have been documented for radicals derived from S-containing amino acids.⁷ Hence, the reaction of radicals with S- and Se-containing amino acids has the potential for

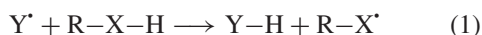
generating a wide array of reaction products and a thorough understanding of such processes would ultimately be of great benefit for biomedical studies attempting to correlate the oxidative damage of specific proteins under conditions of oxidative stress with physiologic observations. For this purpose, this article will cover both the reactions of free radicals with S- and Se-containing amino acids and the radical chemistry of the product radicals from these amino acids. The scope of reactions has mostly been limited to radicals of biological relevance.

This article focuses predominantly on radical reactions of specific S- and Se-containing amino acids important for mammalian proteins and physiology, which are introduced in the following (the respective structures are displayed in Figure 1). In native mammalian proteins, S- and Se-containing L-amino acids are present as cysteine (Cys, **1**), selenocysteine (SeCys, **2**), methionine (Met, **3**), and selenomethionine (SeMet, **4**), where the number of SeCys- and SeMet-containing proteins is very small relative to the total number of proteins.⁸ Cys is also key to the activity of the tripeptide glutathione (GSH, **5**), which is present in tissue at concentrations up to millimolar range. The amino acid homocysteine (Hcys, **6**) does not represent a building block of proteins, but can bind to proteins through the formation of mixed disulfides or reaction of its thiolactone form with protein nucleophiles.^{9,10} Hcys can form through a free radical reaction of Met¹¹

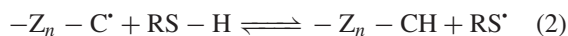
(*vide infra*). Hcys displays pro-inflammatory activity and its physiologic levels represent an important risk factor for several pathologies, including cardiovascular disease and stroke.^{9,12}

2 THIOLS AND SELENOLS

On the basis of the relatively low bond dissociation energies (BDEs) of RS-H (BDE = 367 kJ mol⁻¹¹³) and RSe-H (BDE = 310 kJ mol⁻¹¹⁴), thiols and selenols are excellent hydrogen donors for hydrogen transfer reactions to radicals. These reactions generate thiyl (X=S) and selenyl (X=Se) radicals, respectively (reaction 1):



Rate constants for such hydrogen transfer processes depend on the nature of the radical Y[•] and, representatively measured for RXH = dithiothreitol (DTT), can be as low as 7.4 × 10⁷ M⁻¹ s⁻¹ for Y[•] = [•]CH₃¹⁵ or as high as 1.4 × 10¹⁰ M⁻¹ s⁻¹ for Y[•] = HO[•].¹⁶ The reaction of heteroatom (Z)-substituted carbon-centered radicals from alcohols, ethers, and amines with thiols is reversible¹⁷⁻²¹ (equilibrium 2; for more details on such reversible reactions of Cys, Hcys, and GSH, *vide infra*):



For synthetic organic reactions, the reverse reactions, that is, hydrogen transfer from C-H bonds to thiyl radicals, have been explored in epimerization processes, and thiols have been referred to as “polarity reversal catalysts.”²² Thiyl radicals also play an important role in enzymatic processes such as that catalyzed by the ribonucleotide reductases,²³⁻²⁵ pyruvate formate lyase,^{23,25-28} benzylsuccinate synthase,^{29,30} and glycerol dehydratase.³¹ Here, intermediary Cys thiyl radicals abstract hydrogen atoms from substrate during the catalytic cycle of ribonucleotide reductase, benzylsuccinate synthase, and glycerol dehydratase, while in pyruvate formate lyase, an intermediary Cys thiyl radical adds to the carbonyl group of the substrate pyruvate (see **Radical Enzymes**).

2.1 Cysteine, Homocysteine, and Glutathione

2.1.1 Formation and Properties of Thiyl Radicals

The mercapto group of the free amino acids Cys and Hcys ionizes with pK_a values of 8.15 and 8.7,³² respectively (measured at 30 °C, μ = 0.3) (isothermal titration microcalorimetry of Cys confirms a thiol pK_a of 8.22 ± 0.16³³), while the thiol pK_a of GSH is 8.93 ± 0.04 (at 25 °C).³⁴ A significantly wider pK_a range is observed for protein Cys residues, which display pK_a values as low as 5³⁵ and as high as ca. 10.75.³³ Thiol ionization has a profound effect on the reaction of thiol/thiolate with free radicals as well as the potential stabilization of thiyl radicals. For example, nonoxidizing carbon-centered radicals react preferentially with the protonated thiol form (reaction 1), while oxidizing radicals prefer reaction with the deprotonated, thiolate form (reaction 3).³⁶:



The resulting thiyl radicals associate with a second, nonoxidized thiolate to produce a 2σ/1σ* three-electron-bonded disulfide radical anion [RS : SR]⁻ (equilibrium 4).³⁷:



Equilibrium constants for thiyl radical/thiolate complex formation (equilibrium 4) have been measured for Cys and Hcys and are of the order of 706 and 600 M⁻¹, respectively.³⁸ In contrast, intermolecular complexes between thiyl radical and protonated thiol display low stability and either dissociate (reaction 5) or eliminate a proton to yield the disulfide radical anion (equilibrium 6):



This situation can change for proteins, where Cys residues may stay in close contact through conformational restrictions. In fact, both the disulfide radical anion and its protonated form have been detected on one-electron reduction of bovine IgG

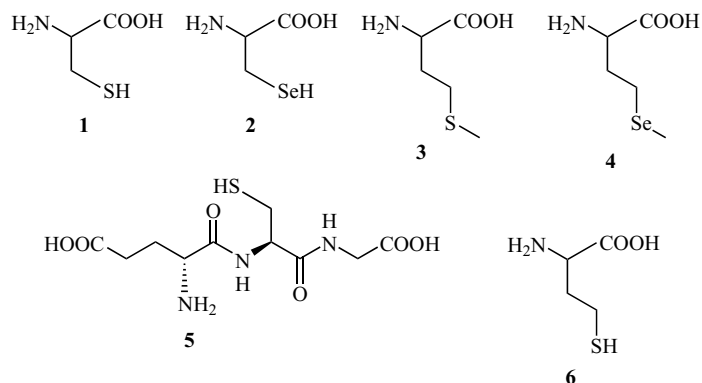
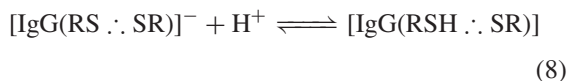
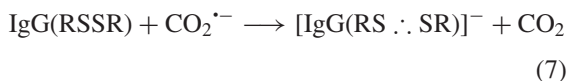
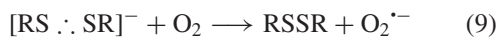


Figure 1 Structures of S- and Se-containing amino acids and GSH.

by $\text{CO}_2^{\cdot-}$ in a pH-dependent manner (reaction 7), and the pK_a for equilibrium (8) in bovine IgG is between 4.5 and 6.5³⁹:



The disulfide radical anion is a strongly reducing species, with $E^0 = -1.60 \text{ V}$ (for the half reaction $\text{e}^- + \text{RSSR} = [\text{RS} \cdot \text{SR}]^-$),⁴⁰ which efficiently reduces molecular oxygen to superoxide (reaction 9).⁴¹ In contrast, thiyl radicals are oxidizing species with $E^0 = 1.33 \text{ V}$ for the half reaction $\text{RS}^\cdot + \text{e}^- + \text{H}^+ = \text{RSH}$ (determined for 2-mercaptoethanol)⁴⁰ and $E^0 = 0.74 \pm 0.01 \text{ V}$ for the half reaction $\text{RS}^\cdot + \text{e}^- = \text{RS}^-$ ⁴⁰ ($E^0 = 0.73 \text{ V}$ reported for Cys thiyl radicals, $\text{CysS}^\cdot$ ⁴²). More recent electrochemical experiments on the oxidizing power of glutathione thiyl radical ($\text{GS}^\cdot$) reveal $E_m = 0.92 \pm 0.03 \text{ V}$ at pH 7.4⁴³:



Hence, through the association with thiolate, an oxidizing thiyl radical converts into a reducing radical anion, and the net availability of oxidizing and reducing species in a given biologic environment will be a function of thiol concentration and thiol pK_a . Thiyl radicals and disulfide radical anions can be monitored directly with time-resolved UV spectroscopy (coupled to laser flash photolysis or pulse radiolysis), where thiyl radicals have

a reported absorbance maximum at 330 nm with reported absorption coefficients between 100 and $1200 \text{ M}^{-1} \text{ cm}^{-1}$ depending on the nature of the thiyl radical.^{44,45} If experimentally possible, thiyl radicals should be detected complementary also through their disulfide radical anion complexes, which absorb around 420 nm with absorption coefficients of the order of $8000 \text{ M}^{-1} \text{ cm}^{-1}$ ($[\text{RS} \cdot \text{SR}]^-$ from Cys and GSH)⁴⁶ (see **Radiation-Induced Radical Reactions**).

2.1.2 The Reaction of Cys with Carbon-Centered Radicals

The forward reaction of equilibrium (2) represents a hydrogen transfer from a thiol to a carbon-centered radical. Experimental and theoretical data indicate that the kinetics of hydrogen transfer are influenced by polar effects,^{15,47,48} that is, the stabilization of polar transition states through substituents on the carbon-centered radical. For example, experimental values for k_2 increase in the series $\cdot\text{CH}_3 < \cdot\text{CH}_2\text{OH} < \cdot\text{C}(\text{CH}_3)_2\text{OH}$, while the experimental activation energies E_a show the opposite trend.¹⁵ Theoretical calculations (gas phase) reveal decreasing activation enthalpies for the series $\cdot\text{CH}_3 > \cdot\text{CH}_2\text{OH} > \cdot\text{C}(\text{CH}_3)_2\text{OH}$, consistent with the experiment¹⁵ (in equilibrium 2, $\cdot\text{CH}_3$ is represented by $-\text{Z}_n-\text{C}^\cdot$ for which $n = 0$). They also reveal increasing charge separation in the transition state for the series $\cdot\text{CH}_3 < \cdot\text{CH}_2\text{OH} < \cdot\text{C}(\text{CH}_3)_2\text{OH}$,¹⁵ in support of the polar effect already suggested by Roberts and Steel.⁴⁷ Polar transition states can be expressed through a series of valence-bond

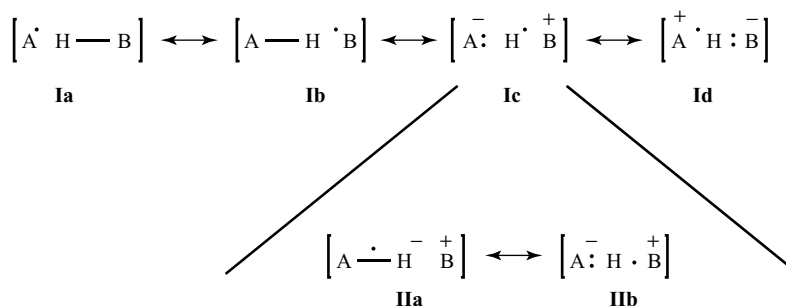


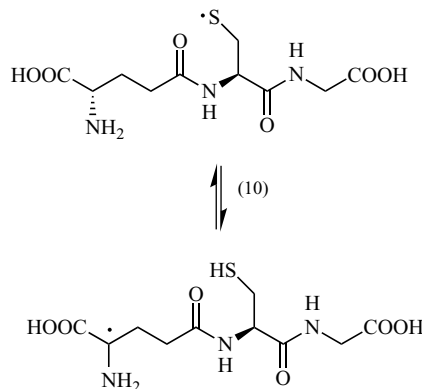
Figure 2 Valence-bond structures of transition states for hydrogen transfer reactions. [Adapted from Refs 15 and 47.]

structures **Ia–Id**, where structure **Ic** may be better expressed as three- and one-electron bonded structures **IIa** and **IIb**, respectively, displayed in Figure 2.^{15,47} With reference to equilibrium (2), A in Figure 2 corresponds to RS and B corresponds to $-\text{Z}_n-\text{C}$, that is, for the reaction of hydroxymethyl radicals with a thiol, structures **IIa** and **IIb** would translate into $[\text{RS} \cdot : \text{H}^+ \text{CH}_2\text{OH}]$ and $[\text{RS}^-\text{H} \cdot \text{CH}_2\text{OH}]$, respectively.

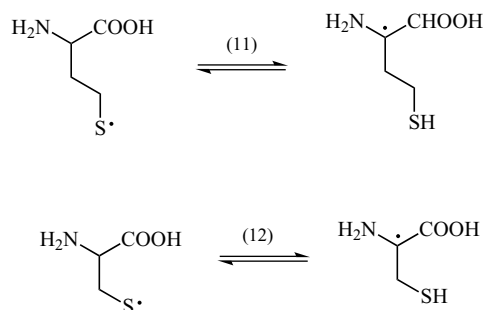
Importantly, the oxidizing carbon-centered radical $\cdot\text{CH}_2\text{CHO}$ reacts only very slowly with GSH,³⁶ an observation that can be rationalized by the lack of stabilization of a positive charge on the methylene carbon in the transition state. In fact, oxidizing carbon-centered radicals such as $\cdot\text{CH}_2\text{CHO}$ will react predominantly with thiolate, RS^- .

Values for k_2 and k_{-2} have been obtained through isotope exchange of C–H bonds,^{49–51} radiation chemical isomerization,¹⁷ and time-resolved pulse radiolysis experiments.^{18,19,38} For alcohols and ethers, $k_2 = 10^7\text{--}10^8 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-2} = 10^3\text{--}10^4 \text{ M}^{-1} \text{ s}^{-1}$,^{17–19} and for amino acids at pH 10.5 (i.e., the anionic form), $k_{-2} = 3.2 \times 10^5 \text{ s}^{-1}$ (Gly) and $7.7 \times 10^5 \text{ s}^{-1}$ (Ala).³⁸ In contrast, for amino acids within model peptide structures such as *N*-acetyl amino acid amides, and for cyclic amino acid anhydrides, diketopiperazines, $k_{-2} = 10^3\text{--}10^5 \text{ M}^{-1} \text{ s}^{-1}$.⁵⁰ An important question is whether reversible hydrogen transfer reactions of $\text{CysS}^\cdot$ proceed *intramolecularly* in peptides and proteins, that is, whether $\text{CysS}^\cdot$ radicals are in equilibrium with other amino acid radicals and are potentially able to initiate the oxidation of other amino acids. For $\text{GS}^\cdot$, an *intramolecular* hydrogen transfer equilibrium between the $\alpha\text{C-H}$ group of the N-terminal $\gamma\text{-Glu}$ residue and $\text{CysS}^\cdot$ radical had been demonstrated through electron

spin resonance and pulse radiolysis experiments (equilibrium 10), where $k_{10} = 1.8 \times 10^5 \text{ s}^{-1}$.^{38,52} This hydrogen transfer is facilitated through deprotonation of the N-terminal amino group of GSH ($\text{p}K_{\text{a,NH}_3^+} = 9.28 \pm 0.1$; 25°C ³⁴) but proceeds well at neutral pH unless thiyl radicals are directed toward competitive pathways such as reaction with thiolate (equilibrium 4) or with oxygen (*vide infra*) (especially in physiological environment also the reaction of thiyl radicals with ascorbate has to be considered):

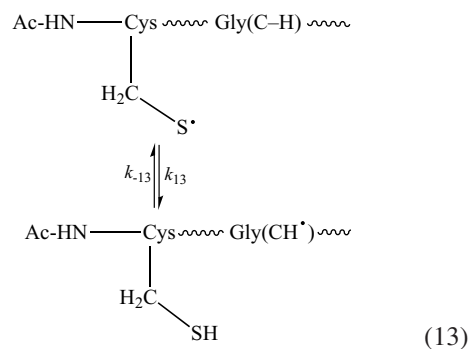


Analogous hydrogen transfer reactions have been documented for thiyl radicals from Hcys (equilibrium 11) and Cys (equilibrium 12),³⁸ where the rate constants for the forward reactions, $k_{11} = 2.2 \times 10^5 \text{ s}^{-1}$ and $k_{12} = 2.5 \times 10^4 \text{ s}^{-1}$. Reaction (12) represents a 1,3-H-shift, and generally activation energies for 1,3-H-shifts (and 1,2-H-shifts) in radicals are significantly higher than that for 1,4- and 1,5-H-shifts,^{53,54} rationalizing that $k_{12} < k_{11}$:

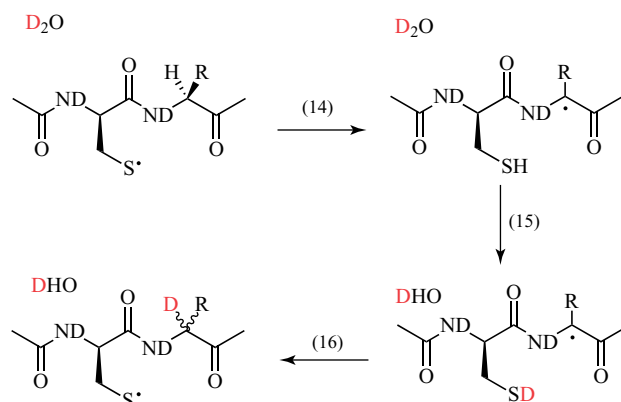


Theoretical calculations for the gas phase indicate that hydrogen transfer from the γ -Glu α C-H group in GS• to the thiyl radical represents the preferred pathway, associated with a free energy of activation, $\Delta G^\ddagger = 40 \text{ kJ mol}^{-1}$,⁵⁵ though thermodynamically all α C-H bonds in GS• are expected to have a lower BDE compared to the BDE of the S-H bond ($\text{BDE}_{\text{S-H}} \approx 367 \text{ kJ mol}^{-1}$): $\text{BDE}_{\alpha\text{C-H, Gln}} \leq 329 \text{ kJ mol}^{-1}$ for the configuration $\text{H}_2\text{N}-\text{C}^\alpha\text{H(R)}-\text{CO}_2\text{H}$ (experimental value), $\text{BDE}_{\alpha\text{C-H, Cys}} = 346 \text{ kJ mol}^{-1}$,¹³ and $\text{BDE}_{\alpha\text{C-H, Gly}} \leq 350 \text{ kJ mol}^{-1}$. However, recent pulse radiolysis experiments have expanded the range of possible hydrogen transfer reactions of GS•, suggesting, based on time-resolved UV spectroscopy, that not only the α C-H but also the β C-H group of the γ -Glu residue are targets for hydrogen abstraction by the thiyl radical in GS•.⁵⁶ The latter is counter-intuitive based on a comparison of BDEs, where the α C-H bond of the γ -Glu residue (experimental: $\text{BDE} \leq 329 \text{ kJ mol}^{-1}$ for the configuration $\text{H}_2\text{N}-\text{C}^\alpha\text{H(R)}-\text{CO}_2\text{H}$ ⁵⁷) should be considerably lower than the BDE of β C-H (BDE is expected to be of the order of 395 kJ mol^{-1} when compared to the secondary C-H bond in propane⁵⁸). However, clearly the time-resolved experiments by Hofstetter *et al.*⁵⁶ suggest the presence of more than one carbon-centered radical in GS•. Some additional apparent discrepancies between theory and experiment need to be addressed: calculations for Hcys reveal an activation energy for reaction (11) of circa 50 kJ mol^{-1} ⁵⁹; nevertheless, the rate constants for reactions (10) and (11) are comparable, where the experimental value of $k_{11} = 2.2 \times 10^5 \text{ s}^{-1}$ was discussed as possibly being even too low.³⁸ On the other hand, calculations predict a high activation enthalpy for reaction (12), $\Delta H^\ddagger = 83 - 115 \text{ kJ mol}^{-1}$.^{13,55} Nevertheless, a rate constant of $k_{12} = 2.5 \times 10^4 \text{ s}^{-1}$

was reported. Although it was discussed that this value may be too high, the fact remains that reaction (12) was observed for CysS• despite the calculated high activation enthalpy. Calculations also revealed a very high free energy of activation for hydrogen transfer between the Gly residue and the thiyl radical in GS•, $\Delta G^\ddagger = 134 \text{ kJ mol}^{-1}$ for the more stable peptide conformation,⁵⁵ consistent with the original reports of exclusive hydrogen transfer between the γ -Gln α C-H bond and the thiyl radical in GS•. However, pulse radiolysis and laser flash photolysis experiments established rate constants for reversible hydrogen transfer equilibria in radicals from several Cys-, Gly-, and Ala-containing peptides. For example, for radicals from *N*-acetyl-CysGly₆, equilibrium (13) is characterized by rate constants of $k_{13} = 1 \times 10^5 \text{ s}^{-1}$ and $k_{-13} = 8.9 \times 10^5 \text{ s}^{-1}$, that is, $k_{13} \approx 0.1$.⁴⁵



Of course with six available Gly residues in *N*-acetyl-CysGly₆, the possibility exists that hydrogen transfer does not involve the residue at position $n + 1$, but Gly residues further along the model peptide chain. On the other hand, mass spectrometry experiments on products originating from thiyl radicals of several model peptides suggest that CysS• within a model peptide can react via hydrogen transfer with amino acids at the $n + 1$ position.⁶⁰ For example, when the disulfide-containing peptide (GlyGlyCysGlyGlyLeu)₂ was photolyzed with 253.7-nm light in D₂O, both Gly residues in position $n + 1$ and $n - 1$ underwent covalent H/D exchange, analyzed in the final products.⁶⁰ The suggested mechanism for covalent H/D exchange is displayed in the following reactions:

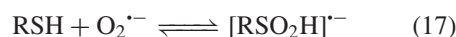


Further evidence for thiol radical-dependent $\alpha\text{C}^\bullet$ radical formation at amino acid residue at positions $n + 1$ and $n - 1$ comes from photochemical studies of the disulfide-bound dimer (LeuGlyAlaCysAlaGlyLeu)₂, where initial thiol radical formation resulted in the conversion of L-Ala into D-Ala.⁶¹ Experimental mass spectrometry studies confirm the potential for CysS $^\bullet$ radicals to abstract hydrogen atoms from amino acid residues at positions $n + 1$ and $n - 1$ in the gas phase.⁶² Under mass spectrometry conditions, the mobile proton model allows for the protonation of the carbonyl functions of various amide bonds, rendering the protonated amides more powerful electron-withdrawing functionalities, which can result in a higher captodative stabilization of some $\alpha\text{C}^\bullet$ radicals. In calculations for solution conditions, Himo⁶³ showed that hydrogen bonds with both amides in the Gly model CHO–NH–CH₂–CO–NH₂ reduced the Gly $\alpha\text{C}^\bullet$ –H bond energy by circa 4.2 kJ mol^{−1}, and solvation also led to a reduction by circa 5.4–8.8 kJ mol^{−1}. However, the effects of hydrogen bonding on the free energy of activation for hydrogen transfer are currently unknown.

2.1.3 The Reaction of Cys with Superoxide

Superoxide anion (O₂ $^{\bullet-}$) represents the initial one-electron reduction product of molecular oxygen, and several enzymatic routes generate superoxide under conditions of oxidative stress. Superoxide serves as a precursor for various reactive oxygen species, most of which react with thiols (e.g.,

peroxynitrite, the product of nitrogen monoxide (NO), and superoxide, or the carbon trioxide radical anion, CO₃ $^{\bullet-}$, which forms via homolysis of ONO₂CO₂ $^-$, a complex of peroxynitrite and CO₂).⁶⁴ A biologically important and controversially discussed question is the *direct* reaction of superoxide with Cys (and thiols, in general). The exposure of various biologically relevant thiols to a superoxide-generating system (xanthine/xanthine oxidase) resulted in a superoxide-dependent, that is, superoxide dismutase (SOD)-inhibitable, loss of these thiols via a short chain reaction, paralleled by the consumption of oxygen.⁶⁵ Importantly, only Cys and penicillamine (Pen) promoted the formation of H₂O₂, while no H₂O₂ formation was detected for cysteamine (Cya), GSH, *N*-acetylcysteine (NAC), and DTT. These results were interpreted such that the reaction of superoxide with Cya, GSH, NAC, and DTT proceeds to generate sulfinyl radicals and HO $^-$ (reactions 17 and 18) via an intermediary thiol/superoxide complex:



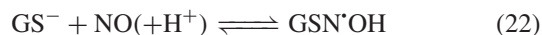
Theoretical calculations confirmed the possibility for a three-electron-bonded superoxide-thiol complex and the likelihood for decomposition into sulfinyl radical and hydroxide.^{66,67} However, the hydrogen peroxide formation observed for the

reaction of superoxide with Cys and Pen suggests that these two thiols may additionally react via hydrogen/electron transfer, directly leading to hydrogen peroxide and thiyl radicals (reaction 19). This reaction could require a proton transfer before electron transfer, that is, conversion of the couple $\text{RSH}/\text{O}_2^{\cdot-}$ to $\text{RS}^-/\text{HO}_2^{\cdot}$ before electron transfer. Interestingly, Jones *et al.*^{68,69} detected $\text{GS}^{\cdot}$ through spin trapping when GSH was exposed to superoxide, suggesting that either a small fraction of the reaction of superoxide with GSH proceeds via reaction (19) or that thiyl radicals are generated subsequently, possibly through the reaction of sulfinyl radicals with GSH (reaction 20). The reported rate constants for the reaction of superoxide with thiols vary between 10^2 and $10^5 \text{ M}^{-1} \text{ s}^{-1}$,⁶⁸ but it appears that values between 10^2 and $10^3 \text{ M}^{-1} \text{ s}^{-1}$ appear most reasonable. On the basis of these relatively low rate constants, thiols will not be able to compete with SOD for superoxide unless specific local conditions allow for a high effective thiol/thiolate concentration in the vicinity of superoxide generation, and/or thiols are part of a transition metal complex (e.g., iron–sulfur clusters).

2.1.4 The Reaction of Cys with NO and NO₂

The S-nitrosation of Cys is key to the regulation of various proteins and biologic pathways.⁴ Nonradical mechanisms of S-nitrosation involve the reaction of thiolate with N_2O_3 , the reaction product of two radicals, NO and nitrogen dioxide (NO_2), as well as *trans*-nitrosation. In addition, a free radical mechanism of S-nitrosation has been suggested, involving the reaction of a thiyl radical with NO (reaction 21)⁷⁰; an alternative mechanism suggested the reaction of NO with thiol in the presence of an electron acceptor.⁷¹ Recently, rate constants of $k_{21} = (2\text{--}3) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ have been reported for the reaction of thiyl radicals from Cys, GSH, and PenSH with NO,⁷² indicating an efficient radical–radical reaction, which is in contrast to earlier studies suggesting that the reaction of $\text{GS}^{\cdot}$ with NO proceeds with $k < 2.8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.⁷³ Of biologic relevance is the question whether thiols react directly with NO,⁷⁴ especially under physiologic conditions of submicromolar concentrations of NO, and $[\text{NO}] \ll [\text{RSH}]$. This question was addressed by Folkes and Wardman,⁷⁵ showing that the anaerobic

reaction of NO with GSH most likely proceeds via reactions (22)–(24):



A kinetic simulation based on reactions (22)–(24) satisfactorily fits not only their results obtained under conditions of $[\text{NO}] \ll [\text{RSH}]$ but also the data of others, obtained under reverse conditions where $[\text{RSH}] \ll [\text{NO}]$. However, the authors conclude that the reaction of NO specifically with GSH is too slow to be of physiological significance. In contrast, the reaction of Cys and GSH with NO_2 proceeds with rate constants of the order of 2×10^7 and $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, respectively, at pH 7.4 (reaction 25).⁷⁶

2.1.5 The Reaction of Cys with Tyrosyl Radicals

The reaction of tyrosyl radicals with Cys (equilibrium 26) represents an important step in the mechanism of ribonucleotide reductase class I²³:

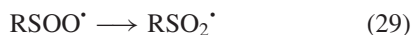


In addition, pulse radiolysis studies have revealed the importance of equilibrium (26) in several electron-transfer cascades.⁷⁷ More recently, the nitration of Tyr by peroxynitrite has been investigated, where especially in the presence of CO_2 , peroxynitrite decomposes into NO_2 and $\text{CO}_3^{\cdot-}$.⁶⁴ These radicals act in concert, where the reaction of $\text{CO}_3^{\cdot-}$ with Tyr generates the tyrosyl radical, which subsequently recombines with NO_2 . Importantly, no Tyr nitration was observed for model peptides which simultaneously contained both Tyr and Cys, rationalized by the fact that initially generated tyrosyl radicals would be reduced by Cys before recombination with NO_2 .⁷⁸ The rate constant

for the forward reaction of equilibrium (27) was recently determined as $k_{27} = 2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ (pH 7.15).⁷⁹

2.1.6 The Reaction of Cys Thiyl Radicals with O₂

In aerobic environment, thiyl radicals can convert into oxy acids, RSO_nH ($n = 1-3$), via multiple pathways. Thiyl radicals react reversibly with molecular oxygen (equilibrium 28), where $k_{28} = (2.0-2.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-28} = 6.2 \times 10^5 \text{ s}^{-1}$.^{80,81} The electronic structure of the thiyl peroxy radical can be partially described by a charge-transfer state, $\text{RS}^+\text{OO}^{\cdot-}$,⁸² and this species is characterized through a weak absorbance with $\lambda_{\text{max}} = 540 \text{ nm}$.⁸⁰ The chemistry of thiyl peroxy radicals in aerobic solution is complex, and various radical intermediates and products have been characterized for thiyl radicals from GSH, cysteine, penicillamine, and cysteamine through ESR studies in frozen matrices, while kinetic information mostly originates from pulse radiolysis of “simpler” organic thiols, for example, 2-mercaptoethanol. The unimolecular rearrangement (reaction 29) to sulfonyl radicals, $\text{RSO}_2^{\cdot}$, proceeds with $k_{29} \approx 10^3 \text{ s}^{-1}$ ⁸¹ and is associated with a high energy of activation (circa 45 kcal mol^{-1})⁸³:



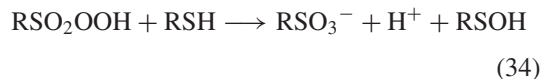
The sulfonyl radical can further react with oxygen, to yield sulfonyl peroxy radicals (equilibrium 30), where, measured representatively for methyl sulfonyl radicals, $k_{30} = 1.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{-30} < 10^5 \text{ s}^{-1}$.⁸⁴:



Excess thiols serve as hydrogen donors to thiyl peroxy radicals, sulfonyl radicals, and sulfonyl peroxy radicals, yielding sulfenic acid, sulfinate acid, and sulfonate (reactions 31–34).^{85,86}:



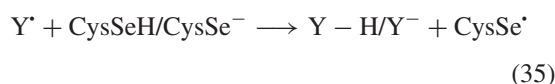
Reaction (33) leads to peroxysulfonic acid, which may be reduced through excess thiol to sulfonic acid (reaction 34):



Sulfinate and sulfonate have been observed as stable oxidation products of Cys in peptides and proteins. In contrast, sulfenic acid is unstable and rapidly reacts with excess thiol to form disulfide unless such a reaction is prevented through the location of the sulfenic acid in a protein domain that does not permit access of thiol.⁸⁷

2.2 Selenocysteine

The low BDE of the Se–H bond (310 kJ mol^{-1}),¹⁴ the low standard reduction potential $E^0(\text{RSe}^{\cdot} + \text{e}^- + \text{H}^+) = +0.77 \text{ V}$ (compare with $E^0(\text{RS}^{\cdot} + \text{e}^- + \text{H}^+) = +1.33 \text{ V}$), and the selenol $\text{pK}_a \approx 5.2$ render selenocysteine (CysSeH) a powerful antioxidant, which has been observed to catalyze the reduction of benzyl viologen by DTT.¹⁴ As for thiols, hydrogen or electron transfer from selenocysteine generates selenyl radicals, $\text{CysSe}^{\cdot}$:



On the basis of the thermodynamic properties listed above, selenyl radicals are expected to be significantly weaker oxidants compared to thiyl radicals. However, $\text{CysSe}^{\cdot}$ radical chemistry has not been explored to the same extent as has been for $\text{CysS}^{\cdot}$ radicals. Critical to the time-resolved detection of $\text{CysSe}^{\cdot}$ are its UV properties, where some open questions remain to be addressed. When Kolano *et al.*⁸⁸ photolyzed (266 nm) dimethyl bis(*N*-*tert*-butoxycarbonyl)-L-selenocysteine in acetonitrile, they observed two transients absorbing with $\lambda_{\text{max}} = 335$ and 450 nm . In contrast, no 450-nm absorbance was detected on photolysis of [(fluorenylideneamino)oxycarbonyl]methyl(*N*-*tert*-butoxycarbonyl)-L-selenocysteine. Tamba and Badiello⁸⁹ used pulse radiolysis to generate $\text{CysSe}^{\cdot}$ via one-electron reduction of low concentrations of selenocystine, and observed a 460-nm absorbance,

assigned to CysSe[•], an observation also made by Nauser *et al.*¹⁴ when they oxidized CysSeH with azide radicals (N₃[•]) in acidic solution. Both groups also described the spectral properties of a diselenide radical anion, for which they reported an absorption with $\lambda_{\text{max}} = 440$ and 455 nm, respectively. Especially the latter value is very close to the reported absorption for CysSe[•] so that both species may not be easily distinguishable. Complicating matters, Mishra *et al.*^{90,91} oxidized various concentrations of selenocystine with HO[•] radicals and other one-electron oxidants and observed that especially at high concentrations of selenocystine and pH > 4, an initial selenocystine radical cation, [CysSeSeCys]⁺⁺ (absorbing with $\lambda_{\text{max}} = 560$ nm), converted into a species absorbing with $\lambda_{\text{max}} = 460$ nm, assigned to a complex of CysSe[•] with nonoxidized selenocystine. Analogous complexes had been observed for thiyl radicals in the presence of high concentrations of disulfides.⁹² Hence, to date, the formation of CysSe[•] has been associated with at least three transient species absorbing around 460 nm, CysSe[•] itself, its diselenide radical anion complex with CysSe[•], and a complex of CysSe[•] with selenocystine. This manifold of transients will require careful experimental optimization when reactions of CysSe[•] need to be studied.

2.3 Protein Cysteine

The reactions outlined above for Cys, GSH, and CysSeH will proceed to various extents for protein Cys and CysSeH, where radical and product yields will depend largely on the respective pK_a values (note that Cys pK_a values can vary between 5.0 and ca. 10.75),^{33,35} conformational properties, and the accessibility to reactant sites. For example, a Cys thiyl radical generated in the vicinity of a second, nonoxidized thiol/thiolate will efficiently form disulfide radical anions in an *intramolecular* reaction. The reaction of the disulfide radical anion with oxygen will then yield disulfide and superoxide, that is, the initial formation of a thiyl radical in the presence of oxygen will lead to the two-electron oxidation product (disulfide). Protein Cys thiyl radicals will also have the opportunity to abstract hydrogen atoms from suitably located amino acids within the three-dimensional structure, and evidence for such hydrogen transfer reactions was provided for human insulin.⁷

For proteins containing both Cys and CysSeH in an appropriate conformation, such as mammalian thioredoxin reductase (TRR), there is the possibility for the formation of selenium–sulfur bonds, R–Se–S–R, and selenium–sulfur bond radical anions, [R–Se–S–R]^{•–}. On the basis of model studies on the one-electron reduction of DTT, diselenothreitol, and selenothiolthreitol, Nauser *et al.*⁹³ have forwarded the hypothesis that the single CysSeH residue in TRR, located in the sequence Gly–Cys–CysSeH–Gly, may protect TRR from deleterious reactions of a thiyl radical by providing a one-electron redox equivalent such that a thiyl radical, Gly–CysS[•]–CysSeH–Gly, would react via *intramolecular* electron transfer with the deprotonated CysSeH residue ($pK_a = 5.2$) to yield a selenyl radical, Gly–Cys–CysSe[•]–Gly. Because of the low Se–H BDE (310 kJ mol^{–1}), the selenyl radicals are not expected to react with protein C–H bonds such as described for thiyl radicals.

3 THIOETHERS AND SELENOTHIOETHERS

Free radicals can react with thio- and selenoethers via homolytic substitution^{94,95} (see **Intramolecular Homolytic Substitutions in Synthesis**) or electron transfer.^{90,96,97} Electron-transfer reactions have been studied in quite detail for the thioether- and selenoether-containing amino acids methionine (Met) and selenomethionine (SeMet), and these have been reviewed in detail below. More recent reports also focused on the reaction of Met with hydrogen atoms (H[•]).

3.1 Methionine

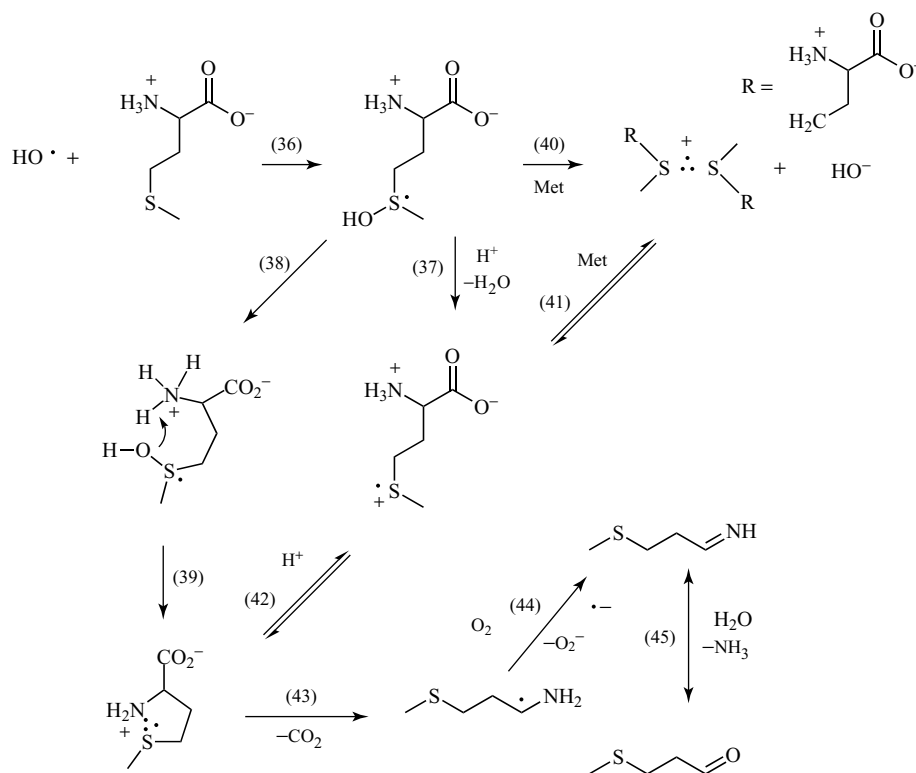
3.1.1 Reaction of Methionine with Oxidizing Radicals

Reaction of Met with the Hydroxyl Radical

The reaction of Met with hydroxyl radicals (HO[•]) was characterized in great detail through radiation chemical methods such as pulse radiolysis and γ -radiolysis.⁹⁸ This reaction proceeds via addition of HO[•] to the sulfur (reaction 36), resulting in a hydroxysulfuranyl radical. Subsequent reactions of this hydroxysulfuranyl radical depend on various parameters such as the nature of the

Met-containing substrate (i.e., whether the reaction involves the free amino acid Met, peptide-bound Met, or protein-bound Met), the concentration of the Met-containing substrate, and pH:

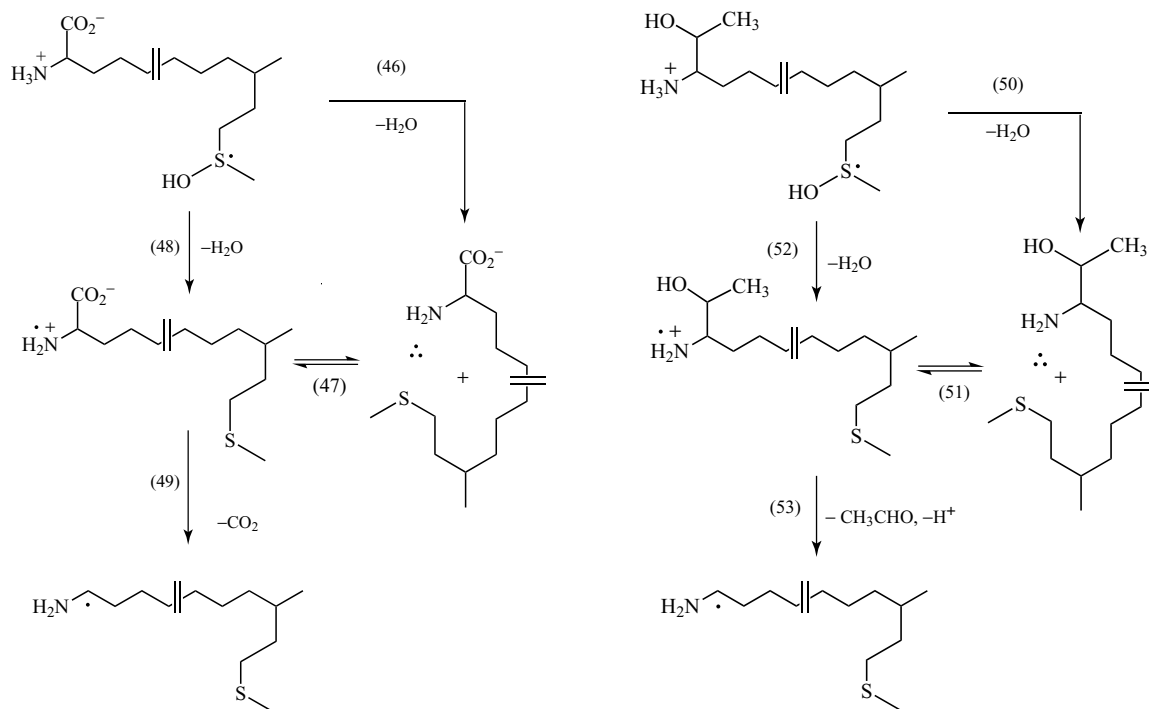
three-electron-bonded intermediate was also obtained for the reaction of HO $\cdot$ with peptides containing an N-terminal Met residue.⁹⁹ An important feature of water elimination from the



Hydroxysulfuranyl radicals of free Met decompose via three competitive pathways: protonation followed by the elimination of water, where the proton is either derived from the solvent (pH < 3; reaction 37) or the N-terminal amino group (pH > 3; reactions 38 and 39), and reaction with a second Met (reaction 40). Reactions (38) and (39) lead to a very short-lived sulfur–nitrogen three-electron-bonded intermediate ($> \text{S} \cdot \text{NH}_2\text{R}^+$), which formally exists in equilibrium with a Met sulfur radical cation. Ultimately, this reaction sequence results in the formation of CO $_2$ and an α -amino-substituted carbon-centered radical (reaction 43). The latter reacts in a diffusion-controlled manner with molecular oxygen, ultimately forming superoxide and 3-(methylthio)propanal (methional) (reactions 44 and 45).¹¹ Evidence for a sulfur–nitrogen

hydroxysulfuranyl radical at pH > 3 is the ability of the protonated N-terminal amino group to function as a proton donor. The question arises whether such proton transfer is also possible over longer distances, that is, when Met is incorporated into peptides. Experiments with γ -Glu-Met and γ -Glu-Gly-Met-Gly revealed a circa 50% efficiency for decarboxylation according to reactions (46)–(49) for both peptides at pH 5.9–6.4,¹⁰⁰ suggesting that proton transfer, followed by formation of a sulfur–nitrogen three-electron-bonded intermediate, can occur when Met is not the N-terminal amino acid:

Pulse radiolysis experiments on the nanosecond timescale revealed formation of a sulfur–nitrogen three-electron-bonded intermediate also for *S*-methylglutathione.¹⁰¹ Additional support for



the interaction of Met hydroxysulfuranyl radicals with the N-terminus is derived from experiments with Thr-(X)_n-Met,^{102,103} where a fraction of the sulfur–nitrogen three-electron-bonded intermediate suffers $C_\alpha-C_\beta$ cleavage of the Thr residue, generating acetaldehyde (CH_3CHO) (reactions 50–53). No significant difference in the efficiency of acetaldehyde formation was observed between Thr-Met and Thr-Gly-Met, while only a circa 30% reduction was observed when comparing Thr-Met with Thr-(Gly)₄-Met.¹⁰³ Hence, a flexible Gly-containing sequence permits the interaction of Met hydroxysulfuranyl radicals with the N-terminus. In contrast, incorporation of a single Pro residue between Thr and Met (i.e., in Thr-Pro-Met) results in a significant reduction (by >70%) in the efficiency of acetaldehyde formation, suggesting that the Pro residue provides a barrier for *intramolecular* proton transfer and formation of the sulfur–nitrogen three-electron-bonded intermediate:

It remains to be shown to what extent proton transfer reactions between Met hydroxysulfuranyl radicals and proton donors (His, Lys, and Arg) may promote sulfide radical cation formation in proteins. In this respect, we note that $HO^\bullet$ radicals

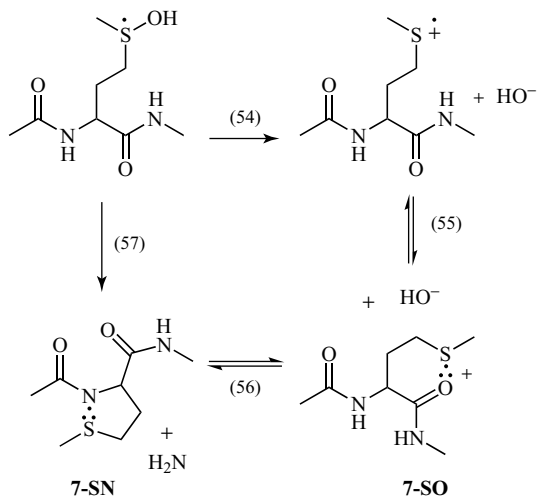
can not only originate from the exposure of aqueous solutions to ionizing radiation, but that $HO^\bullet$ (and/or their metal-bound equivalents) will be generated by Fenton reactions. In fact, acetaldehyde was observed on exposure of Thr-Met to a Fenton system consisting of $[Fe(II)(EDTA)]^{2-}$ and H_2O_2 , though control experiments with a Met-deficient peptide, Thr-Leu, suggest that under these experimental conditions, a fraction of acetaldehyde could result from a direct oxidation of the N-terminal amino group.¹⁰⁴

Theoretical calculations predict that the sulfur–nitrogen three-electron-bonded intermediate with the N-terminal amino group represents the most stable structure of a one-electron oxidized Met in aqueous solution.¹⁰⁵ This is also reflected in a calculated lower one-electron reduction potential for sulfide oxidation of an N-terminal Met residue as compared to a non-N-terminal Met residue within a peptide.¹⁰⁵ These calculations are *not* a contradiction to the experimental observations presented above, where an interaction between a non-N-terminal Met residue and the N-terminal amino group (e.g., in γ -Glu-Gly-Met-Gly and Thr-Gly-Met) was proposed based on a reaction product (i.e., formation of CO_2 and acetaldehyde). The formation of these reaction products indicates

that the interaction between a Met residue and the N-terminal amino group is kinetically possible but does not allow to quantify an equilibrium constant for the formation of the sulfur–nitrogen three-electron-bonded intermediate.

Interestingly, theoretical calculations predict that sulfur radical cations are not significantly stabilized by interaction with either the oxygen or the nitrogen of an amide bond.¹⁰⁵ These calculations are in contrast to experimental data with a series of *N*-acetyl (*N*-Ac)-substituted peptides (which do not contain a free N-terminal amino group) and with specific organic model compounds of Met, in which Met is embedded into a norbornane frame.

Pulse radiolysis experiments with *N*-Ac-methionyl amide, *N*-Ac-(Gly)₃Met(Gly)₃,¹⁰⁶ and cyclo-Met-Met¹⁰⁷ provided evidence for the formation of both sulfur–nitrogen and sulfur–oxygen three-electron-bonded intermediates with the peptide bond (such as that shown in the following reactions:



In addition, sulfur–oxygen three-electron-bonded intermediates were identified for the reaction of HO[•] radicals with (1*R*,2*S*,4*R*,6*R*)-6-(methylthio)bicyclo[2.2.1]heptane-2-carboxamide (**8-endo**) but not (1*R*,2*R*,4*R*,6*R*)-6-(methylthio)bicyclo[2.2.1]heptane-2-carboxamide (**8-exo**) (Figure 3).¹⁰⁸

Moreover, when HO[•] radicals were reacted with the diketopiperazine-substituted Met analog (1*R*,2*R*,4*S*,6*R*)-6'-methylene-6-(methylthio)spiro[bicyclo[2.2.1]heptane-2,2'-piperazin]-3'-one hydrate (**9**) (Figure 3), time-resolved UV

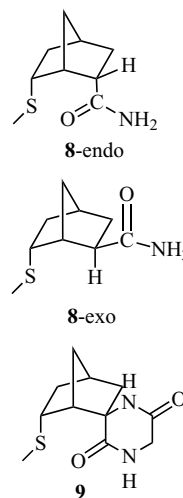
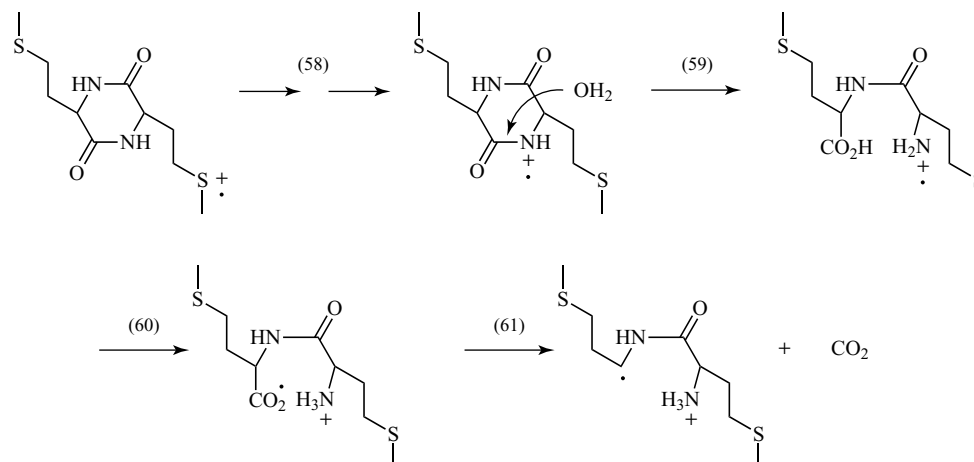


Figure 3 Structures containing Met embedded into a norbornane frame.

spectroscopy indicated the formation of a sulfur–oxygen three-electron-bonded intermediate, though the width of the UV peak with λ_{max} around 400 nm was significantly smaller compared to analogous UV peaks observed for the Met-containing peptides and **8-endo**.¹⁰⁸ Parallel electrochemical experiments in acetonitrile revealed a significantly lower peak potential for the oxidation of **8-endo** (1.07 V vs Ag/AgNO₃) compared to **8-exo** (1.40 V vs Ag/AgNO₃), consistent with the potential for stabilization of intermediary sulfur radical cations by interaction with the amide bond.

In general, sulfur radical cations decompose by deprotonation, forming α -(alkylthio)alkyl radicals.⁹⁸ However, especially for sulfur radical cations from cyclo-Met-Met, kinetic data revealed additional pathways, based on an incomplete conversion into α -(alkylthio)alkyl radicals.¹⁰⁷ While a detailed characterization of these additional pathways must await further experimental results, our hypothesis for the decomposition of sulfur radical cations of cyclo-Met-Met is summarized in reactions (58)–(60).

The reaction of HO[•] with the protein calmodulin (CaM) in the presence of Ca²⁺, investigated by pulse radiolysis, leads to the formation of an intermediate with λ_{max} circa 390 nm at circa 0.6–1.1 μ s after the pulse.¹⁰⁹ The spectral features of this intermediate display a higher resemblance to a sulfur–nitrogen three-electron-bonded intermediate as



of sulfur–nitrogen three-electron-bonded intermediates would suggest that it does not decompose via *intramolecular* proton transfer such as observed during the reaction of Met with HO[•].⁹⁸ Overall, the reaction of Met with CCl₃OO[•] proceeds with $k = 2.9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, while the reaction of Met with the less oxidizing peroxy radical CF₃CH(Cl)OO[•] proceeds with $k = 1.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.¹¹¹ For the reaction of less oxidizing peroxy radicals with organic sulfides, an alternative reaction mechanism exists, in which formally an oxygen atom is transferred to the sulfide to yield sulfoxide. However, isotopic labeling experiments in aqueous solution (H₂¹⁶O) saturated with ¹⁸O₂ indicate that the oxygen atom in the sulfoxide originates from water, leading to the mechanism proposed in reaction (63).¹¹²:

$$\begin{aligned} \text{R}^{18}\text{O}^{18}\text{O}-\cdot\text{S}< + {}^{16}\text{OH}_2 \longrightarrow \text{R}^{18}\text{O}\cdot \\ + \text{H}_2{}^{18}\text{O} + >\text{S} = {}^{16}\text{O} \quad (63) \end{aligned}$$

Of potential biological relevance is also the reaction of Met with the carbonate radical ($\cdot\text{CO}_3^-$). As indicated above, this radical is generated through the reaction of peroxynitrite with CO_2 , followed by homolytic dissociation into $\cdot\text{NO}_2$ and $\cdot\text{CO}_3^-$.⁶⁴ While $\cdot\text{NO}_2$ does not react measurably with Met, a rate constant of $3.6 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ has been derived for the reaction of $\cdot\text{CO}_3^-$ with Met.⁶⁴ On the basis of $E^0 = 1.84 \pm 0.1 \text{ V}$ for the reaction $\cdot\text{CO}_3^- + \text{e}^- + \text{H}^+ = \text{HCO}_3^-$,¹¹⁴ it can be assumed that

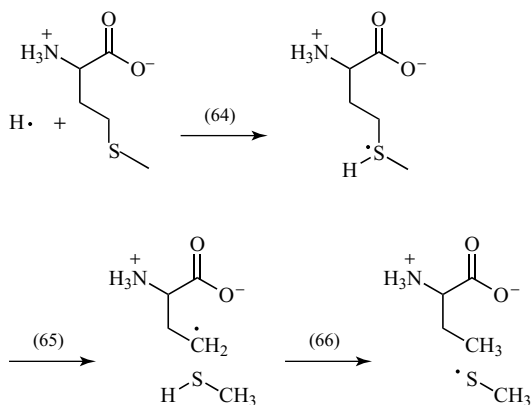


If such adduct would also form during the reaction of $\text{CCl}_3\text{OO}^\bullet$ with Met, the experimentally observed pH dependence for the formation

$\cdot\text{CO}_3^-$ reacts with Met via one-electron oxidation. However, previous time-resolved experiments have not reported the formation of a sulfur–nitrogen or sulfur–sulfur three-electron-bonded species such as observed for the reaction of Met with $\text{HO}\cdot$.¹¹⁵

3.1.2 Reaction of Met with H'-Atoms

The reaction of Met with H'-atoms is of potential relevance for radiation biology. This reaction involves bimolecular homolytic substitution ($\text{S}_\text{H}2$), via an initial addition of the H'-atom to the sulfur, followed by homolytic carbon–sulfur bond cleavage, and hydrogen transfer from the intermediary CH_3SH , ultimately generating α -aminobutyric acid and methylthiyl radicals ($\text{CH}_3\text{S}\cdot$) (reactions 64–66).¹¹ These processes have been documented for both free and peptide- and protein-bound Met.^{11,116,117}



3.2 Selenomethionine

The reactions of $\text{HO}\cdot$ radicals with selenomethionine proceed analogous to the reactions with Met, except that a selenium–nitrogen three-electron-bonded intermediate, formed via water elimination from an initial $\text{HO}\cdot\text{-Se}$ adduct, is significantly more stable.^{118,119}

4 CONCLUSION

The reactions of free radicals with S- and Se-containing amino acids are reviewed. These

reactions encompass hydrogen and electron transfer as well as homolytic substitution. Future experimental work shall focus in particular on radical transfer reactions in proteins, where sites of ultimate damage may evolve quite remote from sites of initial free radical attack. These mechanisms may rationalize some of the biological effects of free radicals.

ACKNOWLEDGMENTS

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Oxidative Damage to Proteins

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1 INTRODUCTION

Biological systems are continually exposed to both endogenous and exogenous sources of oxidants (Table 1). Under normal circumstances, the formation and subsequent reactions of such oxidants are kept in check by a battery of defensive systems within cells and organisms. These defenses include low molecular mass scavengers (e.g., ascorbic acid, tocopherols, urate, and thiols), enzymes that remove either oxidant precursors or the oxidants themselves (e.g., superoxide dismutases (SODs), catalases, peroxiredoxins, and glutathione peroxidases), and enzyme systems that can repair (methionine sulfoxide reductases (Msrs), disulfide reductases/isomerases, and sulfiredoxins) or remove (proteasomes, lysosomes, and DNA repair enzymes) damaged materials.

Despite the range and diversity of these protective systems, it is now clear that enhanced oxidative damage can occur in a wide range of human, animal, and plant pathologies. This may arise as a result of either increased oxidant formation, a failure or decrease in activity of the defense systems, or both of these simultaneously. In some diseases, it is clear as to which factor is primarily responsible for the imbalance (e.g., exposure to high energy radiation, genetic faults that result in decreased levels, or absence of repair enzymes), but in many cases, it would appear that both factors play a role, as many of the defensive systems are themselves subject to oxidation or have a requirement for cofactors that can be readily depleted/oxidized.

The processes outlined in Table 1 can result in the formation of a wide range of different oxidants (both radical and two-electron) being generated *in vivo* (Table 2). These species vary markedly in their reactivity and the damage that they induce is highly variable and complex. Some of these species are highly reactive, such as HO[•], and oxidize nearly all biological targets, with rate constants near the diffusion limit (Table 3). As a result of the abundance of such targets *in vivo*, it is likely that this radical will only cause damage within a very short distance from its locus of formation—that is, the damage induced by this species is site specific to its place of formation.

Many of the oxidants listed in Table 2 are much less reactive than HO[•], and their corresponding rates of reaction with biological materials will be somewhat slower and target/environment dependent. Some of these species can therefore diffuse through considerable distances from their sites of formation and cause damage at a distance. Furthermore, it is well established that many of these species can interconvert and give rise to secondary oxidant species, which may have very different reactivities and lifetimes than the initial species (Figure 1).

A number of groups have calculated approximate diffusion distances for biological oxidants (e.g., Ref. 2) with these values ranging from <0.2 μm for HO[•] to 1.5 mm for H₂O₂ (cf. a typical cell diameter of 20 μm). The reactivity of particular oxidants with a specific target material can vary by >10 orders of magnitude and hence the lifetime

Table 1 Examples of endogenous and exogenous factors that result in oxidant formation.

Endogenous	Exogenous
Electron transport chains (mitochondria, endoplasmic reticulum, plasma membrane)	Radiation (high energy, UV, visible light + sensitizer, thermal)
Heme protein/enzyme reactions	Sulfur oxides
Peroxidases	Nitrogen oxides
Nitric oxide synthases	Particulates (e.g., diesel particles)
NADPH oxidases	Mineral fibers and dusts (e.g., asbestos)
Xanthine oxidase	Ozone
Lipoxygenases	Metabolism of chlorinated hydrocarbons, drugs, nitro compounds, paracetamol, ethanol
Prostaglandin synthases	Oxidized foodstuffs
Auto-oxidation of glucose, thiols, catecholamines, metal ions	

NADPH, nicotinamide adenine dinucleotide phosphate.

of biological oxidants can be enormously different (submicroseconds to many days). Table 4 provides rate constants for the reaction of a number of oxidants with the amino acid methionine (Met) to illustrate this diversity. It should be noted, however, that these data must be treated with care, as the reactivity of some targets is critically dependent on the environment; this is amply illustrated by Table 5, which provides rate constant data for reaction of the amino acid cysteine (Cys) with a number of oxidants. In this particular case, there is also a vast difference in the rate constants with this encompassing ~seven orders of magnitude; however, with this amino acid, the rate constants for reaction with the *same* oxidant vary over the same range simply as a result of environmental factors that make some Cys residues (e.g., those in peroxiredoxin proteins^{3,4}) much more rapid than the same species in other proteins (e.g., bovine serum albumin⁵).

2 PROTEINS AS MAJOR TARGETS FOR OXIDATION

It is well established that the extent of damage to particular targets depends on a number of factors including

Table 2 Selected reactive oxidants postulated to be formed *in vivo*.

Hydroxyl (HO [•])	Nitric oxide (NO [•])
Superoxide radical anion (O ₂ ^{•-})	Peroxynitrite (ONOOH)
Hydroperoxyl (HOO [•])	Peroxynitrosocarbonate (ONOOCO ₂ ⁻)
Peroxyl (ROO [•])	Nitrogen oxides (NO ₂ [•] /NO ₃ [•])
Alkoxyl (RO [•])	Nitrogen-centered radicals (RNH [•])
Hydrogen peroxide (H ₂ O ₂)	Thiyl radicals (RS [•])
Alkyl/aryl hydroperoxides (ROOH)	Perthiyl radicals (RSS [•])
Dialkyl/aryl/endoperoxides (ROOR)	Disulfide radical anions (RSSR ^{•-})
Singlet oxygen (¹ O ₂)	Sulfur trioxide radical anion (SO ₃ ^{•-})
Ozone (O ₃)	Alkyl/aryl radicals (R [•])
Hypochlorous acid (HOCl)	Excited state species
Hypobromous acid (HOBr)	α-Dicarbonyls
Hypothiocyanous acid (HOSCN)	α-Hydroxycarbonyls
Phenoxy radicals (aromatic-O [•])	α-Aminocarbonyls
Semiquinone radicals	α, β-Unsaturated aldehydes
Quinones	Carbonate radical anion (CO ₃ ^{•-})
Quinimines	

Table 3 Selected rate constants for reaction of HO[•] with biological macromolecules and antioxidants.^a

Target	Rate constant (M ⁻¹ s ⁻¹)
DNA	8 × 10 ⁸
RNA	1 × 10 ⁹
Hyaluronan	7 × 10 ⁸
Linoleic acid	9 × 10 ⁹
Collagen	4 × 10 ¹¹
Albumin	8 × 10 ¹⁰
Ascorbate	1 × 10 ¹⁰
GSH	1.4 × 10 ¹⁰
Trolox C (water-soluble analog of α-tocopherol)	6.9 × 10 ⁹

^aData from Ref. 1.

1. the concentration of target
2. the rate constant for reaction of oxidant with target
3. the location of target versus oxidant
4. the occurrence of secondary damaging events
5. the occurrence of transfer reactions and
6. the possibility of repair and scavenging reactions.

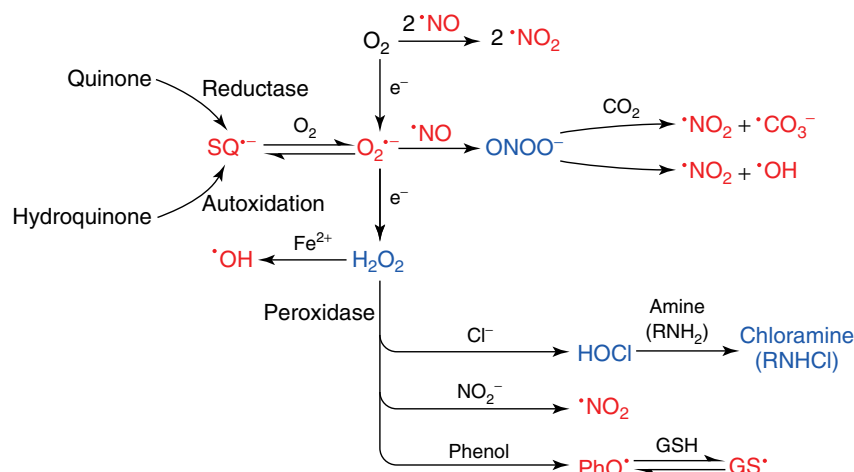


Figure 1 Interconversion of some biological oxidants. [Adapted from Ref. 2. © Nature Publishing Group, 2008.]

Table 4 Selected rate constants for reaction of some biological oxidants with the amino acid methionine.^a

Reactant	Rate constant (M ⁻¹ s ⁻¹)
HO•	7 × 10 ⁹
CO ₃ • ⁻	1.2 × 10 ⁸
HOCl	3.8 × 10 ⁷
Singlet oxygen	2 × 10 ⁷
Ozone	5 × 10 ⁶
CF ₃ CHClOO•	1.4 × 10 ⁶
N ₃ •	<10 ⁶
ONOO ⁻ /ONOOH	3.6 × 10 ²
O ₂ • ⁻	<0.3
H ₂ O ₂	2 × 10 ⁻²
NO•	Very slow

^aData from Refs 1 and 6.

Clearly, a number of these factors cannot be readily generalized; however, there is considerable evidence that (1) and (2) can be the major driving forces. In this respect, it is worth noting that proteins comprise the major (nonwater) components of most biological systems. Thus, in plasma, proteins are present at ~70 g protein dm⁻³, with all other components being present at <5 g dm⁻³; in liver tissue, proteins account for ~140 g kg⁻¹ wet mass, with lipid ~50 g kg⁻¹, and all other components <10 g kg⁻¹; and for leukocytes, proteins are present at ~100 g per 10¹² cells with all other components present at <20 g per 10¹² cells.⁶ This predominance of proteins over all other components bar water provides a strong indication that proteins

Table 5 Selected rate constants for reaction of some biological oxidants with the amino acid cysteine.^a

Reactant	Rate constant (M ⁻¹ s ⁻¹)
HOCl	3.8 × 10 ⁷
HOSCN	8 × 10 ⁴
ONOOH	9 × 10 ³
H ₂ O ₂ (Cys-34 in BSA)	3
H ₂ O ₂ (active site Cys in peroxiredoxin-2)	~10 ⁷

^aData from Refs 3–5 and 7–9.

are major targets for oxidants in most biological systems. Using such abundance data and published compilations of rate constants, it is possible to carry out very approximate “back-of-the-envelope” calculations as to the fate of particular oxidants in cells. Using such an approach, it has been concluded that for leukocyte cells, ~69% of HO• generated within these cells, by, for example, γ -radiation (a relatively “clean” source of this species), will be consumed in reactions with proteins,¹⁰ and the corresponding data for singlet oxygen (¹O₂) is ~68%.¹¹ Such figures need, however, to be treated with extreme caution as they employ an extrapolation from homogenous reaction kinetics to highly complex, compartmentalized systems. It should also be noted that *major* does not always equate to the *most important* with regard to etiology of a disease.

In the subsequent sections of this review, the chemistry and mechanisms of damage to proteins induced by some of the oxidants listed in Table 2 are discussed. The various processes that give rise to these radicals and other oxidants will not be covered further here in any detail, as they have been covered extensively in other articles and books (e.g., Ref. 12).

3 REACTION OF RADICALS WITH PROTEINS

Radicals undergo a variety of reactions, including hydrogen abstraction, electron transfer (oxidation or reduction of the substrate), addition, fragmentation and rearrangement, dimerization, disproportionation, and substitution (concerted addition and elimination) reactions with amino acids, peptides, and proteins. These reactions have been the subject of a number of previous reviews (e.g., Refs 6, 11, 13–30). This article therefore concentrates on the reactions of radicals with proteins (and some peptides) rather than free amino acids and is a broad overview of the major processes that occur, rather than an exhaustive catalogue.

A multitude of different radicals can be generated on proteins by biologically relevant radicals. This arises from reaction with both the protein backbone and the 20 common amino acid side chains, most of which have multiple possible sites of attack. The nature of the radicals formed on proteins depends critically on the nature and reactivity of the attacking radical.

Electrophilic radicals are more commonly encountered *in vivo*, and such radicals, including oxygen-derived radicals such as alkoxyl and peroxy species, preferentially oxidize electron-rich sites. Nucleophilic species (such as phenyl and some other carbon-centered radicals) preferentially attack electron-deficient sites, but these species are relatively rare *in vivo* due to the rapid reaction of these species, once formed, with molecular oxygen with subsequent formation of peroxy radicals. With free amino acids, the positional selectivity of radical attack is well understood. There is some variation in the magnitude of the rate constants for reaction of species such as HO $\cdot$, with the rate constants ranging from $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for Gly to circa $1 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ for Trp, His, and Cys.¹ This arises from preferential attack at sites remote from the powerfully electron withdrawing amine group

on the α -carbon of free amino acids. Thus, with free amino acids, attack at side-chain sites predominates. This effect of the amine group is exerted over long distances with attack on large side chains (e.g., Val, Leu, and Ile) skewed toward remote positions.^{31–34} The ratio of attack at potential sites is also partly dictated by the greater stability of the resulting tertiary > secondary > primary carbon-centered radicals.^{34–38} The selectivity of side-chain attack is also affected by functional group that can stabilize or destabilize the resulting radicals. Thus, hydrogen atom abstraction occurs preferentially adjacent to hydroxyl groups (in Ser and Thr), carboxyl and amide functions (in Asp, Glu, Asn, and Gln), and the guanidine group of Arg.^{39–50} The protonated amine of the Lys side chain results in hydrogen abstraction at sites remote from both the side chain and backbone amine groups with abstraction predominantly from C4 and C5.^{35,36,41,51}

Addition reactions are typically faster than atom abstraction reactions, due to the more favorable transition state energies, and hence addition to Phe, Tyr, Trp, and His and the sulfur atoms of Met and cystine predominate over abstraction reactions from the $-\text{CH}_2$ groups present in these species.^{52,53} In contrast, hydrogen abstraction from the thiol ($-\text{SH}$) group of Cys is very fast, resulting in thiyl radical ($\text{RS}\cdot$) formation.^{15,54–56}

In proteins, this selectivity is less marked because of the conversion of the protonated amine on the α -carbon into a peptide (amide) bond. This results in a greater rate constant, and hence extent, of reaction by hydrogen atom abstraction from α -carbon site.¹ This results in enhanced backbone oxidation and subsequent fragmentation.^{33,57} The removal of the deactivating influence of the amine function results in faster reaction at all sites, with the range of the rate constants for HO $\cdot$ attack on N-acetylated amino acids being much smaller ($2\text{--}7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) than for the free zwitterion species.²⁴ For larger peptides, the rate constants for HO $\cdot$ reaction are all $\sim 10^9\text{--}10^{10} \text{ M}^{-1} \text{ s}^{-1}$,¹ irrespective of the side chains present.

The α -carbon radical formed by hydrogen atom abstraction from the backbone is stabilized by electron delocalization on to both the amide and the carbonyl functions on the N- and C-terminal sides, respectively,^{58,59} although the extent of this effect is dependent on the nature of the side chains (due to steric and electronic interactions arising from the need for planarity) and the local

protein structure (helix, sheet, etc.). These effects result in a greater stability of the α -carbon radical formed on Gly residues compared to the tertiary α -carbon radical formed, for example, from Ala or Val residues,^{19,60,61} due to the steric constraints required to achieving planarity at the α -carbon.^{62,63} This results in significant backbone damage as well as at side-chain oxidation, although an exact quantification of this effect has not been achieved.

With larger materials, secondary and tertiary structures appear to be a major influence. Theoretical calculations indicate that α -carbon radical stability varies with secondary structure as a result of the constraints that such structure plays on radical geometries, with a preference for α -carbon radical formation at Gly residues in anti-parallel β -sheets.^{64–66} Secondary and tertiary structures may also influence the access of radicals present in bulk solution to backbone sites as a result of the protrusion of the side chains. This may indicate that side-chain reactions are of greater importance for globular or sheet proteins, than for disordered structures or random-coil peptides.

Selectivity of damage becomes more marked with less reactive attacking radicals. This can be rationalized by the presence of late transition states with less reactive radicals, in which there is significant radical character at the incipient radical site; as a result, radical stabilizing factors become more important. Thus, selective damage is typically observed on peptides and proteins by the oxidants present below HO $\cdot$ in Table 4 (see also Ref. 19). A summary of the major sites of attack by a wide range of reactive species is given in Table 6.

A confounding factor in examining sites of radical attack on proteins arises from the observation of chain reactions, with a greater concentration of

amino acids modified than initial attacking radicals generated. Chain lengths of up to 15 have been reported (i.e., 15 amino acids modified per HO $\cdot$ generated⁶⁷). Such chain lengths are modest by comparison with lipid peroxidation, where values >100 have been detected, but these are still large enough to confound analyses. The protein-derived chain-carrying species are poorly defined, but oxygen consumption during these reactions is modest (~ 2 moles per mole attacking radical), indicating that nonoxygen-dependent reactions play a major role.⁶⁷

Selective damage to particular residues of proteins can arise from metal ion binding at particular side-chain sites.²² Evidence has been presented for site-specific radical formation on proteins, including catalase,^{68,69} bovine serum albumin (BSA),⁷⁰ and β -amyloid precursor protein⁷¹ among others. In each case, well-defined protein fragments were detected and ascribed to complexation/binding of the metal ion to particular sites and subsequent generation of highly reactive species that would be expected to react in their immediate vicinity thereby inducing site-selective damage. With thyrotropin-releasing hormone, copper complexation has been proposed to occur at the His residue in the sequence $\sim$ Glu–His–Pro $\sim$, with HO $\cdot$ abstracting a hydrogen atom from the α -carbon site of Pro.⁷² Subsequent reaction with O $_2$ gives backbone cleavage, with formation of an aldehyde and a new N-terminal amide ($\sim$ Glu–His–Pro–NH $_2$). Selective modification of His residues has also been reported for glutamine synthetase^{73,74} and human growth hormone.⁷⁵ Specific side-chain modification of Met residues has been reported for peptides treated with Fe $^{3+}$ /O $_2$ /ascorbate,⁷⁶ His, and Met in human relaxin treated with similar mixtures,⁷⁷ and Trp loss in peptides exposed to Fe $^{3+}$ /O $_2$ $^{\cdot-}$.⁷⁸ The enhanced loss of particular amino acids exposed to metal ion generated, compared to radiolytic, HO $\cdot$ has been ascribed to a similar phenomenon, with the enhanced loss of His, Cys, Met, Lys, Arg, and Trp to metal ion binding (reviewed in Ref. 22). In other systems, metal ion-peroxy species, high oxidation state Ni $^{3+}$ complexes, and H $_2$ O $_2$ have been invoked.^{76,78–80} Formation of metal ion–hydroperoxide complexes (M $^{n+}$ –OOH) has been demonstrated in some systems with these used to carry out site-specific cleavage on proteins (e.g., Refs 81–83). Localization of the metal ion at a particular site allows the three-dimensional structure in the vicinity of the

Table 6 Selectivity of damage to protein side chains by reactive oxidants.

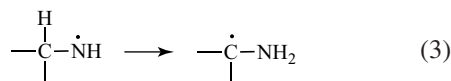
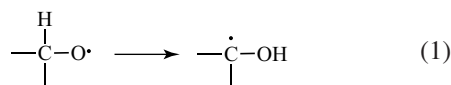
Oxidant	Major sites of damage
HO $\cdot$	Most residues
1 O $_2$	Cys, Met, Trp, Tyr, and His
HOCl/HOBr	Cys, Met, cystine, His, α -amino group Lys, Trp
Peroxynitrite	Cys, Tyr, Trp
UV light	Trp, Tyr, cystine
Reactive aldehydes	Arg, Lys, Cys, His, α -amino group
HOSCN	Cys

metal ion to be probed.^{84,85} Site-specific damage has also been defined in sugar-mediated reactions, particularly during metal-ion catalyzed oxidation, or autoxidation, of sugar molecules covalently linked to proteins as a result of glycation reactions.^{86–90}

4 FATE OF PROTEIN RADICALS

4.1 Side-Chain Carbon-Centered Radicals

Reaction of most radicals with proteins results in the initial formation of carbon-centered radicals either via hydrogen abstraction from C–H bonds (side chain or α -carbon) or from addition of an initial radical to an aromatic ring. Carbon-centered radicals can also be generated via secondary reactions of other species, such as rearrangement and fragmentation reactions of alkoxyl,^{15,91–94} peroxy,^{95–99} or nitrogen-centered radicals (reactions 1–3).^{100,101}



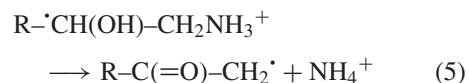
In the presence of O_2 , which is ubiquitous in most biological systems, these carbon-centered species usually yield peroxy radicals with rate constants near the diffusion-controlled limit ($k = 10^9\text{--}10^{10} \text{ M}^{-1} \text{ s}^{-1}$). In the absence of O_2 , dimerization or disproportionation is the major fate. The rate constants for the latter processes are structure dependent and this can be a major factor governing protein radical behavior. Furthermore, as dimerization/disproportionation involves two radicals, which are usually present only at very low concentrations, reaction with O_2 typically predominates. One major exception is with highly stabilized/delocalized radicals (e.g., Tyr-derived phenoxyl radicals) where dimerization (k circa $5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$), through either the oxygen atom or carbon atoms on the aromatic ring, is not markedly affected by O_2 .^{102–104}

Hydrogen atom abstraction by carbon-centered species can also occur with suitable donors containing weak X–H bonds (typically thiols). This can be of significance when the concentration of

O_2 is low, where the radical is stabilized, and/or when dimerization reactions are prevented by steric constraints (e.g., protein structure). This process typically results in “repair” of the carbon-radical and formation of a secondary species (e.g., thiyl radicals; reaction 4).^{55,105} Recent studies have shown that these reactions can be of significance with α -carbon (backbone) radicals, with repair occurring by neighboring Cys residues; a special case of this process is internal repair within Cys residues (i.e., transfer from the Cys α -carbon site to the thiol within the same residue).



Some suitably substituted carbon-centered radicals also undergo (slow) unimolecular elimination reactions. Thus, some α -hydroxyalkyl radicals with β -amino groups release ammonia (reaction 5).¹⁰⁶ This process may be significant with radicals formed at C5 on 5-hydroxylysine.



4.2 Peroxyl Radicals

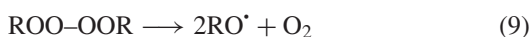
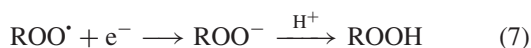
In addition to formation by O_2 addition to carbon-centered radicals, peroxy radicals can also be generated from metal ion-catalyzed decomposition of hydroperoxides (reaction 6).^{107,108}



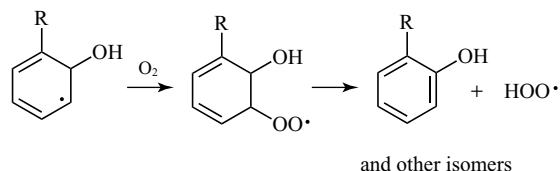
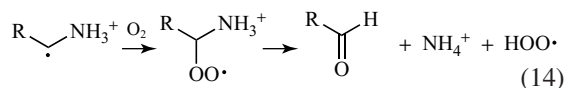
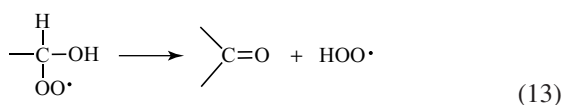
These radicals undergo multiple reactions that generate hydroperoxides, alcohols, and aldehydes or ketones. The former of these appear to arise predominantly from either hydrogen atom or electron abstraction reactions, with the latter followed by rapid protonation of the anion (reactions 2 and 7). These processes are the likely source of the high yields (up to ~65% of the initial radical yield) of hydroperoxides detected on exposure of proteins to a wide range of radicals in the presence of O_2 . These species have been detected on most side chains, and particularly those with large numbers of C–H bonds (e.g., Val, Leu, Ile, Glu, Lys, and Pro). While the nature and yield of these species have been explored in some detail with free amino

acids and small peptides,^{109,110} the nature and sites of these species on intact proteins and larger peptides is poorly understood, due to the complexity of these systems and the instability of these materials.

Peroxyl radicals can also undergo dimerization reactions with another peroxyl radical or other species (e.g., $\text{HOO}^\bullet/\text{O}_2^{\bullet-}$; reactions 8–12) that yield carbonyls and alcohols or alkoxy radicals.^{95–99}



Peroxyl radicals with α -substituted heteroatoms (α -hydroxyl or α -amino groups) undergo rapid unimolecular elimination reactions with loss of $\text{HOO}^\bullet/\text{O}_2^{\bullet-}$ (reactions 13–14).^{111–116} Thus, peroxyl radicals formed at C6 on lysine side chains (via carbon-centered radicals) readily eliminate NH_4^+ and $\text{HOO}^\bullet$ to yield α -amino adipate- δ -semialdehyde.¹¹⁷ Similar reactions are likely to occur with peroxyl radicals formed at the β -carbon on Ser and Thr residues, with this underlying the very low yields of hydroperoxides detected on irradiation of these amino acids. These reactions result in the formation of the corresponding aldehyde (from Ser) or ketone (from Thr). Similar reactions have been postulated to be of major importance in backbone fragmentation (see below). This type of elimination reaction is also of significance when peroxyl radicals are generated on aromatic rings after initial radical addition (reaction 15).¹¹⁸ These reactions may be key processes in protein chain oxidation reactions as they result in damage to one amino acid and the release of a further radical species that can propagate damage.



(15)

The factors that determine the yield of these various potential products on peptides and proteins have yet to be fully elucidated with little kinetic data available for the reactions. Factors that are likely to play a major role include (i) the rate of reaction of the initial carbon-centered radical with O_2 (usually $k = 10^9\text{--}10^{10} \text{ M}^{-1} \text{ s}^{-1}$), (ii) the rate of reaction of the peroxyl radical with hydrogen atom or electron donors, (iii) the radical flux and hence the rate of radical–radical reactions, (iv) steric and electronic constraints that will affect the partition between bi- and unimolecular reactions, and (v) the stability of intermediate species, such as hydroperoxides and tetroxides. It is however clear that this multitude of reactions can result in a wide range of different materials, principally hydroperoxides, alcohols, and aldehydes and ketones, and also some fragmented and dimerized species, from aliphatic side chains on proteins. Some of the products arising from these reactions are listed in Table 7.

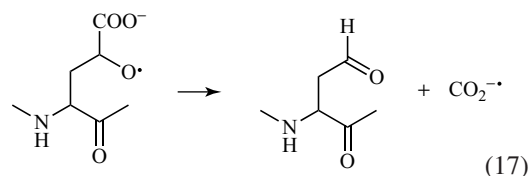
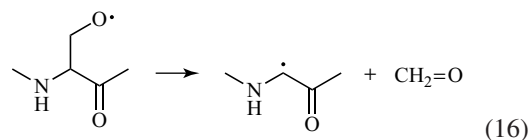
4.3 Alkoxy Radicals

Alkoxy radicals formed from peroxyl radical reactions (e.g., reaction 9) or one-electron reduction of hydroperoxides undergo rapid addition and hydrogen abstraction reactions and a number of facile unimolecular fragmentation and rearrangement reactions.^{15,91–94} Primary and secondary alkoxy radicals undergo rapid (formally 1,2-) hydrogen shift reactions in aqueous solution (reaction 1; k circa $10^6\text{--}10^7 \text{ s}^{-1}$) to give α -hydroxyalkyl radicals.^{91,92,119} These reactions compete with intramolecular hydrogen abstraction to give alcohols.^{92,119} Tertiary alkoxy radicals, where 1,2-hydrogen shift reactions are impossible, undergo rapid ($k \sim 10^6 \text{ s}^{-1}$) β -fragmentation reactions to give a carbon-centered radical and

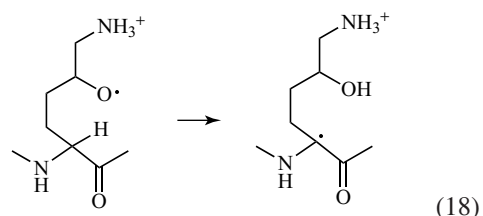
Table 7 Stable and unstable products formed on oxidation of aliphatic and sulfur-containing amino acids and protein side chains.

Amino acid	Product
Alanine	Serine
Arginine	Hydroperoxides (low yield)
	Hydroperoxides (unstable)
	5-Hydroxy-2-aminovaleric acid
	Carbonyls
Cysteine	Chloramines
	Bromamines
	Cystine (disulfide)
	Oxyacids (RSOH, RSO ₂ H, RSO ₃ H)
	Sulfenamides
Glutamic acid	Sulfenyl chloride
	Sulfonamides
	Hydroperoxides
	Decarboxylated products
Glycine	Aminomalonic acid
Isoleucine	Hydroperoxides
	Alcohols
Leucine	Carbonyls
	Hydroperoxides
	Alcohols
	α -Ketoisocaproic acid
	Isovaleric acid
	Isovaleraldehyde
	Isovaleraldehyde oxime
Lysine	Other carbonyls
	Hydroperoxides
	Alcohols
	Carbonyls
Methionine	Chloramines
	Bromamines
	Sulfoxide
	Sulfone
Proline	Sulfonamides
	Hydroperoxides
	5-Hydroxy-2-aminovaleric acid
	Other alcohols
Valine	Carbonyls
	Hydroperoxides
	Alcohols
	Carbonyls

an aldehyde/ketone.^{93,120–122} These reactions may result in transfer of damage from a β -carbon side-chain site to the backbone, as a result of the stability of the α -carbon radical, and release of the side chain from the protein as a low molecular mass aldehyde/ketone (reaction 16).^{123,124} β -Scission of an alkoxy radical formed at C4 on Glu side chain has been shown to result in the loss of the adjacent side-chain carboxyl group as CO₂^{•-} (reaction 17).¹⁰⁷

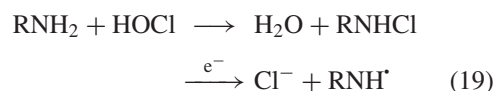


Other side chain-derived alkoxy radicals may also transfer damage to the α -carbon site. Thus, alkoxy radicals at C5 on Lys might be expected to readily abstract an α -carbon hydrogen atom via an intramolecular 1,5-hydrogen atom shift (reaction 18); direct evidence for this process is lacking, although such reactions occur rapidly with model compounds (k circa $8 \times 10^6 \text{ s}^{-1}$) even when the product radical is poorly stabilized. Similar reactions may occur with C5 alkoxy radicals on the side chains of Arg, Ile, and Leu. 1,4-Hydrogen shifts are less favorable, and hence slower, than 1,5 (and 1,6) reactions.



4.4 Nitrogen-Centered Radicals

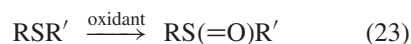
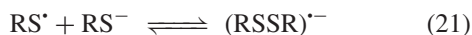
Nitrogen-centered radicals generated via cleavage of N–Cl bonds (see section on hypohalous acids; reaction 19) can undergo rearrangement reactions analogous to those of alkoxy radicals described above to give carbon-centered radicals.^{100,101} Direct formation of nitrogen-centered radicals by hydrogen atom abstraction from amine groups (e.g., that on free Gly) by HO[•] has also been demonstrated.¹²⁵ The significance of such reactions with amine and amide groups on proteins is yet to be determined.



Intramolecular hydrogen atom abstraction appears to be particularly favored with aminyl radicals (e.g., those potentially formed from the ϵ -amino group of Lys side chains), with this having the potential to generate carbon-centered radicals at other side-chain sites or at the α -carbon.^{100,101} The latter is an example of potential side chain to backbone radical transfer and may be of significance in the induction of protein backbone cleavage by these species; such reactions remain to be explored in depth.

4.5 Radicals Formed on Sulfur-Containing Amino Acids

Thiyl radicals ($RS^\bullet$) can be generated on proteins by direct hydrogen, by cleavage of disulfide linkages (e.g., by UV light or electron attachment), or by repair of other radicals (see above).^{126,127} Thiyl radicals react rapidly, but reversibly, with O_2 to form peroxy radicals $RSOO^\bullet$ (reaction 20), which can isomerize to give sulfonyl radicals $RS(=O)O^\bullet$ and hence oxyacids and sulfinyl ($RSO^\bullet$) radicals.^{27,128} At physiological pHs, reaction with a further thiolate anion (RS^-) to give a disulfide radical anion (reaction 21) can compete with reaction with O_2 .^{15,54–56} The disulfide radical anion generated by this process reacts rapidly with O_2 via electron transfer to give the disulfide and $O_2^{\bullet-}$ (reaction 22).^{15,54–56} Thiyl radicals dimerize rapidly and can thereby generate inter- or intramolecular protein cross-links. These radical–radical reactions may be severely limited by steric and electronic factors (see **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**).^{54–56}



The thioether group ($R-S-R'$) function of Met residues is readily and rapidly oxidized by many species due to its low oxidation potential (cf. data in Table 4). The major product that arises from oxidation of this residue in most peptides, or proteins, is the corresponding sulfoxide (reaction 23); further oxidation of this species gives the sulfone, although this occurs to a much lesser extent. The

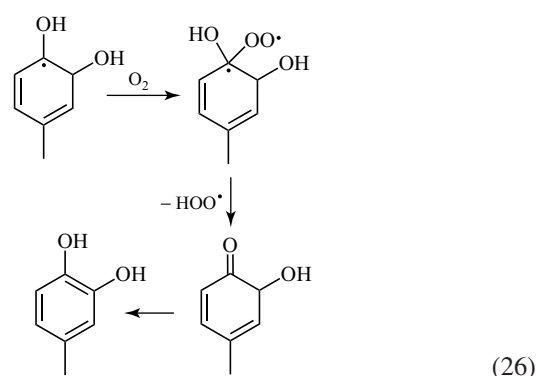
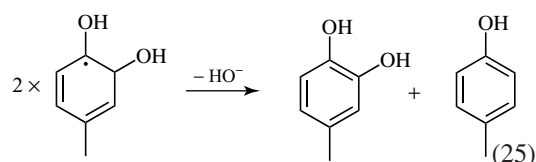
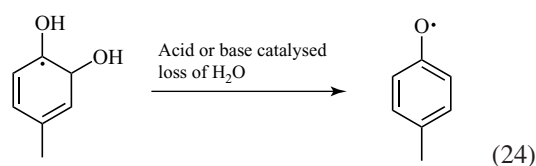
sulfoxide is the major product with a wide range of oxidants regardless of whether the initiating species is a radical or a two-electron oxidant, although the mechanism(s) by which this species is formed are different. Two stereoisomers are generated from the sulfoxide group—the *S* (D-) and *R* (L-) epimers, with this having important ramifications for the repair of this product inside cells as the enzymes (Msrs) responsible for reduction are stereospecific (i.e., each enzyme only reduces specific stereoisomers). The ratio of these isomeric products varies between different oxidants, and also between different Met residues on proteins, with the protein structure being an important controlling factor. Whether this is true *in vivo* is more difficult to ascertain as repair and protein turnover will affect the population present at any particular time.

With powerfully oxidizing radicals, such as $HO^\bullet$, the initial product formed is a transient $R-S^\bullet(OH)-R$ (hydroxy sulfuranyl) adduct. This adduct undergoes rapid further reactions to give the sulfoxide, with this occurring via multiple pathways. In some cases, loss of HO^- yields a monomeric radical cation; this can dimerize to give a dimeric radical-cation with a two-center, three-electron bond. The monomer radical-cation can react with superoxide radicals to give the sulfoxide or be stabilized by other nucleophiles (e.g., amine, hydroxyl, halide, and carboxyl groups) with the resulting formation of short-lived species containing S–N, S–O, and S–halide two-center, three-electron bonds. The formation of these species is dependent on the neighboring residues and peptide sequence. Limited oxidation is also seen at the C–H bonds flanking the sulfur atom with these yielding carbon-centered radicals that undergo typical carbon-centered radical reactions (see above).

4.6 Radicals Derived from Aromatic Side Chains

Reaction of initiating radicals with aromatic side chains (Trp, Tyr, and Phe) and related species (His) occurs predominantly by either addition of a radical to the ring or by electron transfer from the ring to the radical. The latter results in a (usually transient) radical-cation, which usually undergoes rapid deprotonation to yield a neutral species (a phenoxyl radical from Tyr or an indolyl from

Trp). Direct hydrogen abstraction from the ring or methylene ($-\text{CH}_2-$) side-chain groups are minor processes. Reaction of $\text{HO}^\bullet$ with Tyr residues occurs primarily via the formation of substituted cyclohexadienyl adduct. These rapidly eliminate water, in both acid- and base-catalyzed reactions, to give phenoxyl radicals (reaction 24) or react further to give 3,4-dihydroxyphenylalanine (DOPA).^{52,53,129} In the absence of O_2 , DOPA is formed via disproportionation of two ring-derived radicals (reaction 25), whereas in the presence of O_2 , peroxy radical formation is followed by rapid elimination of $\text{HOO}^\bullet$ (reaction 26).^{130,131} The latter pathway yields higher levels of DOPA (one per initial ring radical), whereas in the absence of O_2 , two initial ring-derived radicals yield one DOPA. This material, as well as many other aromatic radical oxidation products (Table 8), has been used as a biomarker of oxidative damage *in vivo*.



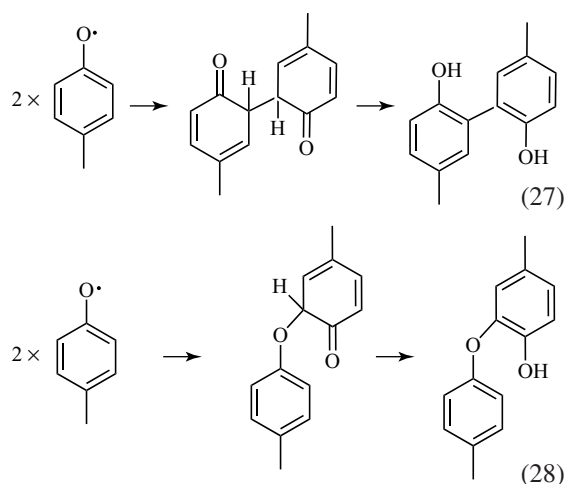
Tyr phenoxyl species are generated efficiently and rapidly by a wide range of radicals, due to the ease of ionization of the ring, and also via a range of enzymatic reactions (e.g., peroxidase- and heme protein-mediated processes).^{132,133} Phenoxyl radicals dimerize rapidly (k circa $5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$),

Table 8 Stable and unstable products formed on oxidation of aromatic amino acids and protein side chains.

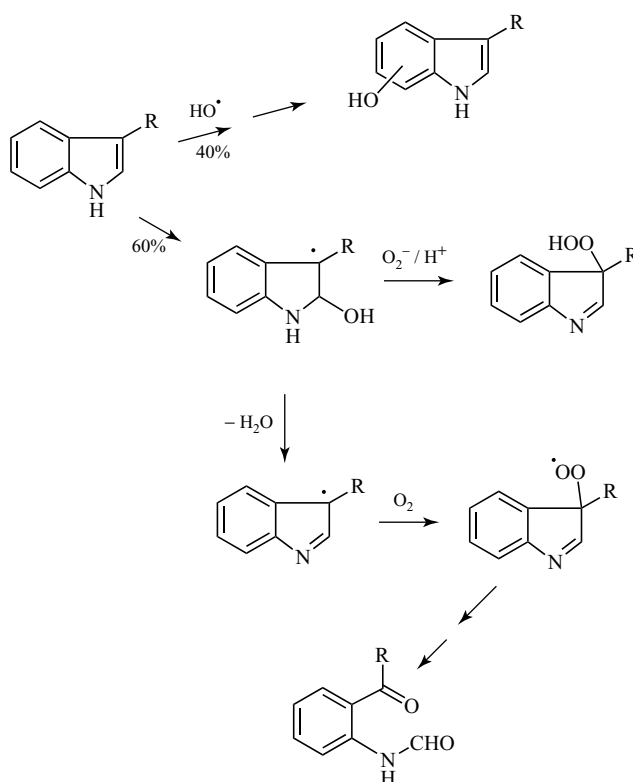
Amino acid	Product
Phenylalanine	<i>ortho</i> -Tyrosine (2-hydroxyphenylalanine) <i>meta</i> -Tyrosine (3-hydroxyphenylalanine) Tyrosine Nitrophenylalanine
Tyrosine	3,4-Dihydroxyphenylalanine (DOPA) Di-tyrosine (carbon–carbon dimer, carbon–oxygen dimer, and higher species) 3-Chlorotyrosine 3,5-Dichlorotyrosine 3-Bromotyrosine 3,5-Dibromotyrosine 3-Nitrotyrosine 3,5-Dinitrotyrosine Hydroperoxides 3-Hydroxytyrosine Alcohols and cyclized products
Tryptophan	<i>N</i> -Formylkynurenine Kynurenine 5-Hydroxytryptophan 7-Hydroxytryptophan 5-Nitrotryptophan 6-Nitrotryptophan Hydroperoxides Alcohol and cyclized products Hydropyrroloindole Oxindole
Histidine	2-Oxohistidine Chlorinated materials Hydroperoxides Alcohol and carbonyl products Ring opened products including urea and asparagine Nitrohistidine

via carbon–carbon bond formation, to yield hydroxylated biphenyls (dityrosine; reaction 27).^{134–136} Carbon–oxygen linkages have also been characterized (reaction 28).¹⁰² Addition of O_2 to a phenoxyl radical is slow ($k < 1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$), and hence, dityrosine yields are usually not significantly affected by the O_2 concentration, unless this alters the initial chemistry of radical formation.^{104,137} In contrast, reaction with $\text{HOO}^\bullet/\text{O}_2^{\bullet-}$ is fast¹⁰⁴ with this resulting in the formation of multiple hydroperoxides at different ring positions; the nature and subsequent reactions of some of these species have been characterized.^{104,138–142} Owing to their considerable lifetime, when dimerization is prevented for steric

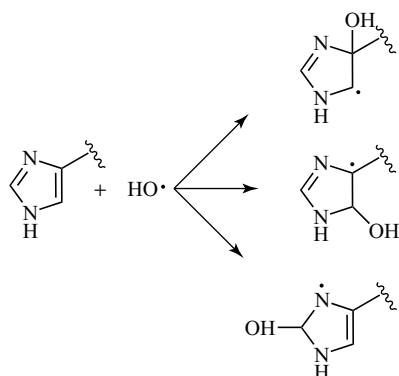
or electronic reasons, Tyr phenoxyl radicals can undergo hydrogen or electron transfer reactions with other biological molecules, with this resulting, for example, in the initiation of lipid peroxidation and antioxidant depletion.^{143–151}



Tryptophan-derived ring radicals are also formed in a facile manner due to the ease of oxidation of indole moiety. Addition can occur at either the benzene ring (circa 40%) or the pyrrole moiety (circa 60%) in the case of $\text{HO}^\bullet$ (Scheme 1).^{152–154} In the absence of O_2 , the ring-derived radicals give rise to low yields of hydroxylated products on the benzene ring (4-, 5-, 6-, and 7-hydroxytryptophans; Scheme 1) or lose H_2O to give the neutral indolyl radical (25–30% for $\text{HO}^\bullet$, Scheme 1).^{152,153,155,156} In the presence of O_2 , peroxy radicals are formed on the six-membered ring, some of which (circa 30%) eliminate $\text{HOO}^\bullet/\text{O}_2^{\cdot-}$ to give hydroxylated products. Indolyl radicals react slowly with O_2 to give a peroxy radical (at C3),^{157,158} but this can be a significant process in proteins where this species is isolated and cannot readily undergo other reactions.^{143,146,148,149,159–163} This peroxy species can undergo hydrogen atom/electron transfer reactions to give a hydroperoxide, or undergo further reactions, which result in opening of the pyrrole ring with formation of *N*-formylkynurenine



Scheme 1

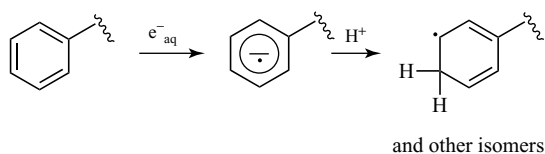


Scheme 2

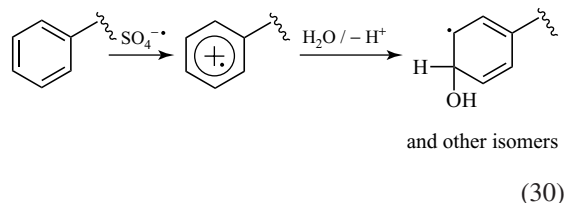
(Scheme 1).^{153,154,164} In contrast to the slow reaction with O_2 , reaction of these indolyl radicals with $HOO^{\bullet}/O_2^{\bullet-}$ is fast ($k = 4.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) yielding a hydroperoxide (Scheme 1).^{154,158,165}

The chemistry of radical reactions with His is complex and still not completely resolved. $HO^{\bullet}$ undergoes addition to the imidazole ring of histidine at C2, C4, and C5 (Scheme 2),^{166–169} with the resulting adduct radicals either undergoing addition reactions with O_2 (to give peroxy radicals) or base-catalyzed loss of H_2O to give stabilized diazacyclopentadienyl radicals.^{166,168} The final products, and yields, of these reactions have not been determined completely, but include 2-oxo-histidine, asparagine, aspartic acid, hydroxylated derivatives, and hydroperoxides.^{170,171}

Electron transfer reactions occur readily with aromatic side chains, resulting in formation of radical-anion and radical-cation. Addition of an electron to Phe generates a transient radical-anion, which rapidly protonates to give a cyclohexadienyl radical (reaction 29).¹⁷² Radical-cations can be generated from each of the side chains by powerful oxidants¹⁰⁵ and also by photo-ionization (see the following sections). The charge on these species is rapidly lost by processes including hydration (and hence hydroxylated products, reaction 30) and



(29)



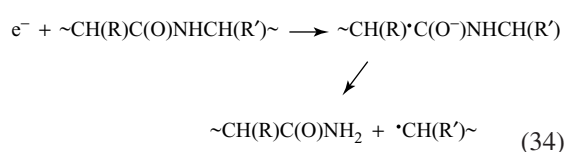
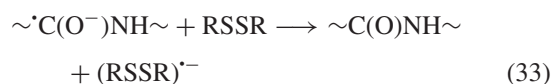
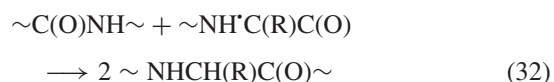
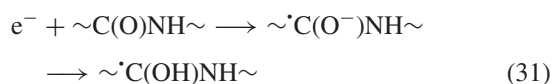
(30)

deprotonation from an adjacent C–H (Phe), N–H (with His or Trp), or O–H bond (with Tyr).^{127,173}

4.7 Backbone Radical Chemistry

Hydrogen atom abstraction from the α -carbon position can account for >90% of initial $HO^{\bullet}$ radicals with Ala-containing homopeptides, with this rationalized in terms of the greater stability of the α -carbon species over the primary alkyl radical arising from methyl side-chain hydrogen atom abstraction. This however appears to be an extreme case, with the yield of backbone-derived carbon-centered radicals being much lower when reactive side chains are present.

α -Carbon-centered radicals can also be formed from solvated electron reaction with backbone carbonyl groups (reaction 31).^{174–176} These species, when formed in the middle of peptide chains in the absence of O_2 , decay primarily via reaction with other radicals, with this resulting in the repair of both species (reaction 32).¹⁷⁷ Electron transfer can also occur with electron acceptors, such as cystine (reaction 33) or His residues.¹⁷⁸ Backbone cleavage (reaction 34) is believed to be a minor process.^{179,180}

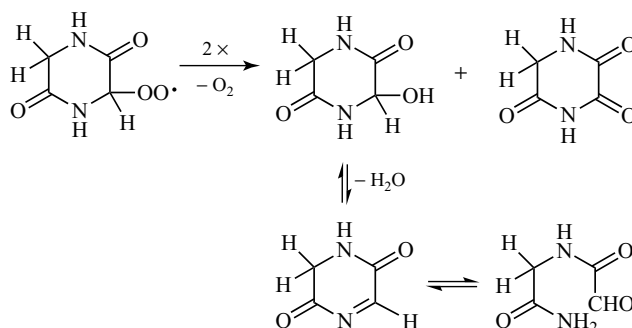


In the absence of O_2 , α -carbon radicals decay primarily by dimerization,¹⁸¹ with the resulting products characterized for some small peptides. These data indicate that cross-links are formed at all radical sites.^{57,181} With larger peptides, significant side-chain cross-links are also observed.

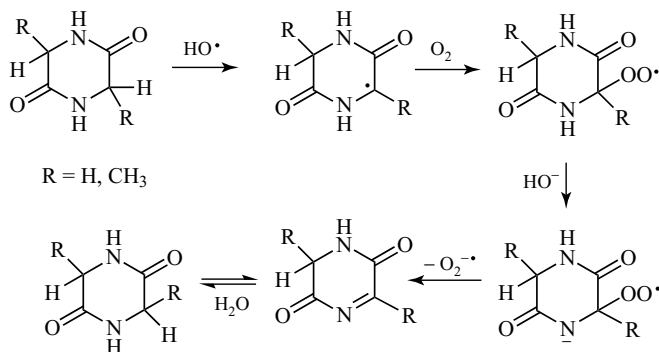
In the presence of O_2 , backbone peroxy and alkoxy species are formed, which undergo a complex series of reactions that result in backbone cleavage (reviewed in Refs 6, 16, 182). The peroxy radicals have been reported to rapidly eliminate $HOO\cdot$ to give imines that then undergo hydrolysis to the corresponding amides and carbonyl compounds. Studies on cyclo(Gly)₂ and cyclo(Ala)₂ have shown that these reactions are slow at neutral pH values and yield two major product species (Scheme 3). At higher pH, ionization of the $-NH$ group (pK_a 10.8 and 11.2 for cyclo(Gly)₂ and cyclo(Ala)₂, respectively) results in rapid base-catalyzed elimination of $O_2^{\cdot-}$ to give a single product (Scheme 4). The rate of water addition to imines is structure dependent with the $C=N$ bond from cyclo(Gly)₂ reacting with

H_2O approximately 100-fold faster than that from cyclo(Ala)₂.¹⁸³ It is clear from these data that the structure of these species can have a major influence on the rate of backbone hydrolysis.

α -Carbon peroxy radicals can also yield α -carbon hydroperoxides and alkoxy radicals via hydrogen atom abstraction and cross-termination reactions with $O_2^{\cdot-}$ and $HOO\cdot$, respectively.¹⁸⁴ Decay of such hydroperoxides (e.g., catalyzed by metal ions or UV light) yields further alkoxy radicals.^{107,108} These alkoxy radicals undergo β -scission reactions that result in the formation of carbonyl groups and acyl radicals ($\cdot C(O)NHR$) when present at mid-chain sites.¹⁰⁸ This results in cleavage of the backbone. C-terminal alkoxy radicals release $CO_2^{\cdot-}$ or $\cdot C(O)NH_2$ in the case of C-terminal amides (reaction 35). Recent studies indicate that this reaction competes with the peroxy radical/imine/hydrolysis pathway to backbone fragmentation outlined above.^{6,16,182} The contribution of these two pathways to protein backbone fragmentation is yet to be determined,

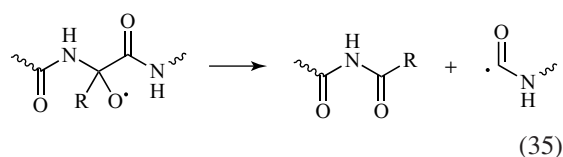


Scheme 3



Scheme 4

although fragments with new N-termini (cf. the blocked N-termini formed in the imine pathway) have been detected on peptides generated from oxidized proteins. These materials may be alkoxyl radical pathway products, as acyl radicals can give rise to isocyanates (via addition of O₂ and loss of HOO[•]) at the new N-terminus which readily hydrolyze to the amine plus CO₂.^{81,185–187} Fragments consistent with the alkoxyl radical pathway have also been detected during backbone cleavage of the R1 subunit of ribonucleotide reductase, where a backbone, Gly-derived, α -carbon radical is involved.¹⁸⁸



4.8 Radical Translocation Between Sites in Proteins

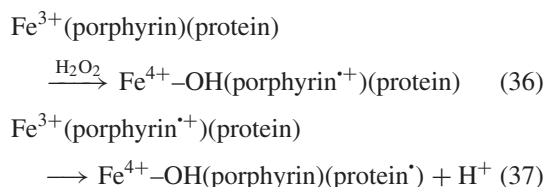
Some of the data reviewed above are consistent with radical transfer reactions occurring between sites in proteins. Transfer between side-chain sites in peptides and proteins is particularly well characterized, and primarily involves aromatic and sulfur-containing residues. These reactions have yielded important information about mechanisms and pathways of transfer of oxidizing equivalents and electrons through proteins (reviewed in Refs 179, 189–191, see also **Electron Transfer in Peptides and Proteins**). The reduction potentials of peptide radicals indicate that the ultimate sink for oxidizing equivalents in proteins are Tyr and Cys residues (or Trp in the absence of these side chains).¹⁸⁹ Some of these reactions are near equilibrium and hence are readily reversible. Thus, Tyr phenoxyl radicals can be generated by thiyl radicals and also repaired by Cys reactions,^{189,192} with the balance of this process modulated by excess thiolate anions, as thiyl radicals can be removed via reaction with these species (to give the disulfide radical anion).

Oxidation of Trp residues can, as outlined above, yield the nitrogen-centered indolyl radical. However, if such species are generated on proteins that also contain Tyr residues, rapid electron

transfer occurs between these species to yield the Tyr phenoxyl radicals over a millisecond timescale.^{179,190} Such transfer can occur over long distances in proteins, but the rate of transfer is very much dependent on the peptide/protein structure. Slow transfer can be observed even if the residues are close in distance, if they are held in an unfavorable rigid conformation.¹⁹³ In contrast, rapid transfer can occur over very long distances if the structure is flexible or if there are suitable intervening residues that can act as a conduit for electron migration.^{189,193,194} In many proteins, the transfer pathway is unclear due to the presence of multiple Tyr and Trp residues and hence alternative pathways. Transfer reactions have also been demonstrated between a number of other residues.¹⁸⁹ These types of reactions may result in a different pattern of oxidation, and kinetics of these processes, than that might be initially expected on the basis of the reactivity of the initiating radical alone.¹⁸⁹

The disulfide bond of cystine (and hence O₂ as a result of rapid electron transfer from the disulfide anion radical) is a major sink for electrons and reducing equivalents. Electron migration to disulfide bonds can compete with direct addition to O₂ in some cases.¹⁷⁹ In this case, transfer is believed to occur via hydrogen bonding networks, with the backbone acting as an efficient conduit, unlike the oxidative pathway.^{191,195} The formation of disulfide radical-anions can be of particular importance as thiyl radicals can be generated from these species via the reverse of reaction 21. The thiyl radicals can, in turn, oxidize Tyr residues, thereby providing a point of convergence of the oxidative and reductive pathways. Studies with chemically modified metalloproteins with a reactive metal ion at a defined surface site have provided some information about the mechanism and control of electron transfer within proteins.^{196,197}

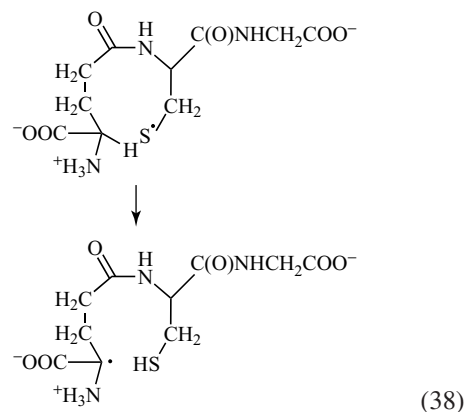
Damage transfer occurs readily in heme proteins where the initial oxidation occurs at the heme moiety. Reaction of H₂O₂ and other two electron oxidants with Fe³⁺ forms of heme proteins (e.g., hemoglobin, myoglobin, and leghemoglobin) gives rise to protein (globin) radicals via the generation of a Fe⁴⁺-oxo (ferryl) porphyrin radical-cation (reaction 36) and subsequent repair of this species by electron transfer from protein residues (reaction 37; predominantly Trp and Tyr residues; reviewed in Refs 24, 198).



Tyr-, Trp-, His-, and other carbon-centered radicals have been detected as a result of these types of reaction, and it is clear that this is a widespread process. The yield of these radicals appears to be significant in some cases, for example, with hemoglobin, myoglobin, and leghemoglobin, but much lower in “professional” peroxidases that deliberately generate such high oxidation state (compound I) species. The pathways by which these protein radicals are formed are not fully defined in all cases, and it is clear that multiple pathways (and hence residues oxidized) can occur in the same protein (cf. evidence for formation of multiple Tyr- and Trp-derived radicals in myoglobins discussed above). Some of these radicals are likely to be in equilibrium making the analysis complex. Site-directed mutagenesis studies have shown in myoglobins that removal of all the Tyr residues still results in radical formation, suggesting that the removal, or blocking of a key pathway, merely switches the site of oxidation to another available residue. In some cases, protein structure appears to play a key role, with Trp-14 being a major site in myoglobin, even though this is more distant from the oxidized heme than an alternative Trp residue (Trp-7); this has been rationalized in terms of the orientation of these residues to the porphyrin ring.^{161,199,200} The subsequent chemistry of some of these radicals has been elucidated, with evidence presented for the formation of intermolecular (protein–protein) cross-links, as well as heme–protein cross-links, and oxidation of other targets (e.g., thiol, Tyr, and Trp groups on other proteins, antioxidants, and lipids^{148,149,201–207}).

Evidence has also been obtained (see above) for radical transfer from side-chain sites to the α -carbon and occasionally for the reverse (predominantly with Cys) residues. The paucity of the latter processes is as expected in the light of the known stability of α -carbon radicals. Repair of α -carbon species by external thiols has been studied extensively as a means of protection against radiation damage.¹⁰⁵ A thiyl radical generated from the Cys residue in

reduced glutathione (GSH) can abstract a hydrogen atom from a suitably placed backbone α -carbon site (reaction 38).^{208–210} This process occurs readily, unlike most hydrogen abstraction reactions by thiyl radicals (the reverse reaction—repair—is usually favored), due to the stability of the α -carbon radical. Thus, reaction 38 occurs with GSH at pH values where the γ -glutamyl amine function is deprotonated, even though this involves a nine-membered transition state.²⁰⁹ Analogous thiyl to α -carbon transfer occurs with the thiyl radical from homocysteine when the amino group is deprotonated.²¹¹ Recent studies have also indicated that such transfer occurs with Cys despite this (apparently) involving a 1,4 rearrangement.^{212–214}



5 REACTION OF PEROXYNITRITE AND OTHER REACTIVE NITROGEN SPECIES WITH PROTEINS

NO• is generated from the amino acid arginine by nitric oxide synthase enzymes, which are widely expressed in multiple cells (e.g., endothelial, macrophage, and neuronal, reviewed in Refs 215, 216). NO• modulates a wide range of diverse biological processes including vascular tone, proliferation, and aggregation.²¹⁵ While this species has undoubted beneficial effects, high levels of NO• have been linked with cellular damage, continued inflammation, and apoptosis as a result of its rapid reaction ($k \sim 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ²¹⁷) with superoxide radicals ($\text{O}_2^{\bullet-}$) to generate peroxynitrite,²¹⁸ a process that can compete successfully with the removal of $\text{O}_2^{\bullet-}$ by SOD enzymes ($k \sim 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ²¹⁹) when the flux of NO• is high.²¹⁷

Peroxynitrite can induce considerable biological damage, through the species and chemistry involved is complex. Multiple studies have provided evidence for damage by ONOOH itself, by HO $\cdot$ and NO $_2\cdot$ formed from the homolysis of this species (in yields of circa 30%²¹⁷), by an adduct species, ONOOCO $_2^-$ (formed with physiological concentrations of CO $_2$), and by NO $_2\cdot$ and CO $_3^{\cdot-}$ formed from the latter (in yields of circa 35%²¹⁷). The reactions of the radicals formed from both ONOOH and ONOOCO $_2^-$ are covered above, and the discussion below is therefore focused on the molecular reactions of these oxidants. Considerable evidence exists for damage primarily at side-chain sites, with Cys, Met, and Trp reacting directly with ONOOH, and Tyr, His, and Phe also being modified, predominantly as a result of secondary reactions. Kinetic data on the reactions of ONOOH with proteins and free amino acids have been reviewed.²²⁰

Reaction with Cys residues has been shown to generate a wide range of products, including cystine, sulfenic, sulfinic and sulfonic acids, nitroso-cysteine (RSNO), nitrocysteine (RSNO $_2$) as well as thiyl, sulfinyl, and disulfide anion radicals.^{5, 221–226} The formation of the radical species clearly involves one-electron chemistry, and there is some evidence for the formation of nitrosocysteine and nitrocysteine likewise (i.e., the formation of the latter materials is likely to involve termination reactions of thiyl radicals with nitric oxide and NO $_2\cdot$ radicals, respectively), although evidence has also been presented for a direct reaction of ONOOH with Cys to yield RSNO.²²⁴ The formation of the disulfide, cystine, has been reported to occur via a direct nucleophilic attack of the thiolate anion on ONOOH, with this giving the sulfenic acid and nitrite as initial products. Subsequent reaction of the sulfenic acid with an additional molecule of Cys yields cystine. The higher rate constants for reaction of ONOOH with some Cys residues on proteins (for rate constants see Ref. 220) is therefore explicable in the light of the varying pK $_a$ values for the Cys residues on these proteins. The cystine formed from this reaction does not appear to have any significant reactivity with ONOOH (cf. the absence in any change in the rate of decay of ONOOH in the presence of this species²²⁷), but reaction does appear to occur with the more reactive disulfide of lipoic acid with this resulting in formation of the corresponding disulfide S-oxide.²²⁷

Peroxynitrite reacts rapidly with Met residues to give both sulfoxide and ethylene (ethene). These products may arise via three possible processes. The first of these involves the formation of radical reactions of HO $\cdot$ and NO $_2\cdot$ from decomposition of ONOOH. The second mechanism is via direct reaction of ONOOH with Met, probably via the formation of an initial adduct species, R–S $^+$ (OH)–R, with release of NO $_2^-$, and subsequent deprotonation of the former to give the sulfoxide, and the third is via peroxynitrite anion addition to the sulfur function and subsequent decomposition of this species to the sulfoxide. Of the latter two pathways, the one involving ONOOH appears to be more rapid than that involving ONOO $^-$.^{228, 229} Studies with materials that react rapidly with HO $\cdot$ have reported only marginal effects on the yields of sulfoxide and ethylene, consistent with radicals being only minor contributors.²²⁸ The ONOOCO $_2^-$ adduct appears to oxidize Met at a much slower rate than ONOOH or ONOO $^-$, suggesting that Met oxidation *in vivo* is modulated to a major extent by CO $_2$ levels.^{230, 231}

Trp residues react directly with ONOOH relatively slowly²³² ($k \sim 40 \text{ M}^{-1} \text{ s}^{-1}$), whereas the corresponding reactions of the radicals derived from ONOOH and ONOOCO $_2^-$ are very rapid. The formation of radical species has been confirmed by electron paramagnetic resonance (EPR) spin trapping.^{233–236} As such, a mixture of products is typically observed. These include radical oxidation products (hydroxytryptophan, *N*-formylkynurenine, hydropyrroloindole, and oxindole; see above) mentioned above and 5- and 6-nitrotryptophan. The yield of both the direct and radical products has been reported to be enhanced by the presence of CO $_2$ and hence the formation of ONOOCO $_2^-$.^{232, 233}

Reaction of ONOOH with Tyr does not appear to occur via direct reaction, but to predominantly occur via a radical mechanism, as the presence of this amino acid does not modulate the direct decay kinetics of ONOOH.^{220, 232} Reaction appears to occur via radical formation from either ONOOH or ONOOCO $_2^-$, with this giving rise to a Tyr phenoxyl radical (either via direct hydrogen atom abstraction or via an initial ring adduct; see above). Subsequent reactions of this species include formation of dityrosine and DOPA, as outlined above, and reaction with NO $_2\cdot$ to give 3-nitrotyrosine.^{237–244} This last species has been used extensively as a biomarker of peroxynitrite formation, although other

processes that give rise to phenoxyl radicals and $\text{NO}_2^\bullet$ (e.g., peroxidase-induced oxidation of Tyr and NO_2^-) may complicate the interpretation of the *in vivo* data.²⁴⁵ $\text{NO}_2^\bullet$ is not a very reactive radical²⁴⁶ and appears to require a cogeneration system to generate the Tyr phenoxyl radical to result in significant yields of 3-nitrotyrosine. The presence of CO_2 can enhance the usually low yield of 3-nitrotyrosine (which is typically $<10\%$ ²²⁰), as the $\text{CO}_3^{\bullet-}$ formed from the adduct species markedly enhances the yield of phenoxyl radicals from Tyr,²⁴⁷ as it shows a greater propensity for direct hydrogen atom abstraction from the $-\text{OH}$ bond on the ring. Phenylalanine is also oxidized by ONOOH to give nitrated products but again this appears to be a radical mediated process, as judged by the detection of *o*- and *m*-Tyr in addition to nitrophenylalanine; the former are typical $\text{HO}^\bullet$ products.²⁴⁸ Nonetheless, the detection of nitrophenylalanine has been used to invoke the formation of peroxynitrite *in vivo*.²⁴⁹

6 REACTION OF HYPOCHLOROUS, HYPOBROMOUS, AND HYPOTHIOCYANOUS ACIDS AND RELATED N-HALO SPECIES WITH PROTEINS

HOCl , HOBr , and hypothiocyanous acid (HOSCN) are generated by the heme peroxidase myeloperoxidase (MPO) released from activated neutrophils, monocytes, and tissue macrophages. This enzyme uses H_2O_2 generated by multiple cells to catalyze the oxidation of Cl^- , Br^- , and SCN^- to these powerful oxidants (reviewed in Refs 250–254). The analogous eosinophil-derived species, eosinophil peroxidase (EPO) generates HOBr and HOSCN , but not HOCl .^{255–260} HOCl and HOBr are both strong oxidants and capable of halogenation reactions.

HOCl and HOBr react avidly with sulfur and nitrogen atoms, such as those present in thiols, thioethers, amines, and amides; Cys and Met residues in proteins are therefore key targets for HOCl and HOBr .^{261–265} Oxidation of Cys by HOCl yields a sulfenyl chloride (RS-Cl), which undergoes rapid reaction with excess thiol, to give the disulfide²⁶¹ or water to yield sulfenic (RSOH), sulfinic (RSO_2H), or sulfonic (cysteic acid, RSO_3H) acids (reviewed in Ref. 266). Cystine can be oxidized to sulfonic acids via S-chlorinated and

S-oxygenated intermediates (reviewed in Ref. 266). HOCl can also induce the formation of sulfenamide (RSNR'), sulfinamide ($\text{RS(O)NR}'$), and sulfonamide ($\text{RS(O)}_2\text{NR}'$) cross-links in peptides (e.g., GSH) and proteins,^{267–270} via nucleophilic attack of Lys or Arg side chains on RS-Cl , sulfenic, or sulfinic acid intermediates.

The high susceptibility of Cys residues to oxidation by hypohalous acids has important implications for cells, as a number of key cellular enzymes have Cys residues in their active sites. Thus, creatine kinase and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) are readily inactivated by HOCl , with the loss of activity correlating with thiol depletion.^{265,271} Conversely, HOCl can activate the (inactive) pro-forms of matrix metalloproteinases (e.g., MMP-7) via conversion of a key Cys residue in the cysteine switch domain of pro-MMP-7 to a sulfinic acid derivative.²⁷²

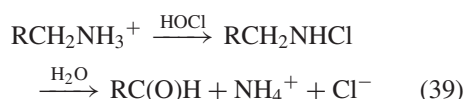
Oxidation of Met side chains results in the formation of Met sulfoxide (and with very large excesses of oxidant to Met sulfone),^{273,274} with this resulting in potential impairment of protein function and inactivation of enzymes (e.g., lysozyme and α_1 -antiproteinase^{273,275–278}). In other cases, such as with soybean trypsin inhibitor, Met oxidation did not correlate with loss of function despite the related structure and similar active site of this species to α_1 -antiproteinase.^{273,275} Recent studies have also shown that Met residues can be oxidized to dehydromethionine on peptides when this residue is present at the N-terminus.²⁷⁹

Nitrogen-containing functional groups, particularly amines and to a lesser extent amides, are readily converted to N-chlorinated and N-brominated species by HOCl/HOBr .^{253,260,280–283} The amine-derived species are generically known as halamines (chloramines, $\text{RR}'\text{NCl}$; bromamines, $\text{RR}'\text{NBr}$), while those species formed from amides are halamides (chloramides, RC(O)N(R')Cl ; bromamides, RC(O)N(R')Br). For primary halamines (where $\text{R}' = \text{H}$), further reaction with HOCl and HOBr yields dichloramines (RNCl_2) or dibromamines (RNBr_2). With chloramines, dichloramine formation only occurs to an appreciable extent when there is a large excess of HOCl over amine.^{260,280,281,284,285} However, with bromamines, rapid equilibration reactions can occur that result in dibromamine formation, even when the amine is present in large excess.²⁶⁰

Halamines and halamides can be generated on a wide variety of biological substrates. Free amino acids yield halamines on the α -amino group, and in cases such as Lys, His, and Arg where the side chain features a nucleophilic nitrogen center, halamines are also generated at these sites.^{7,253,260,281–283,286–291} Incorporation of amino acids into proteins results in derivatization of the α -amino group with halamine formation on proteins therefore restricted primarily to His, Lys, and Arg side chains, together with the N-terminal amino group. Halamide formation can occur at backbone peptide (amide) bonds with high excess of hypohalous acids, and the amide-containing side chains of Gln and Asn can also be converted to halamides.²⁹¹

Other small molecules that contain an amino residue, and are abundant *in vivo*, can also form halamines. Thus, the sulfonated β -amino acid, taurine, has been postulated to act as a cellular defense mechanism against hypohalous acid production by reacting rapidly with HOCl and HOBr to give long-lived intermediates.²⁸² However, taurine halamines are also capable of inducing further oxidation and hence detrimental cellular effects.^{271,292}

It is clear from these data that halamines and halamides are the key products of HOCl/HOBr reactions with a wide range of biological molecules. These halamines/amides retain the oxidizing capacity of the parent oxidant and can induce further reactions, some of which regenerate the parent amine as a result of halogen transfer or radical reactions, while others result in modification of the amine group. One major pathway is hydrolysis, which yields aldehydes, probably via imine intermediates (reaction 39).^{287,290,291,293–295} Aldehyde formation from bromamines occurs more readily than that from the corresponding chloramines.^{275,291,296,297} The resulting carbonyl species can react with protein or lipid amine groups to generate Schiff base imines, which can ultimately yield advanced glycation end products; the latter have strong links to vascular disease.^{298,299} Hydrolysis of His side-chain chloramines is a potential pathway for the formation of 2-oxo-His.²⁹¹



Halamines and halamides can decompose via radical pathways, with these reactions promoted by

low-valent redox-active metal ions (Fe^{2+} and Cu^+) and $\text{O}_2^{\cdot-}$. These processes yield nitrogen-centered radicals ($\text{RNH}^\cdot$)^{100,300–306} that can undergo a range of intra- and intermolecular reactions resulting in further oxidative damage (reviewed in Ref. 291).

As halamines and halamides retain the oxidizing capacity of the hypohalous acid from which they are generated, they are potentially capable of mediating cellular damage. Thus, evidence has been presented for halamines, rather than HOCl/HOBr, being major mediators of toxicity as they are long-lived species that can diffuse through cellular membranes and hence mediate oxidative damage at remote locations away from their site of generation. Halamines are capable of oxidizing thiols and thioethers, such as Cys and Met, as described above for the parent hypohalous acids,^{271,284,285,292,307,308} although halamines do not appear to produce the diversity of products observed with HOCl and HOBr. Thus, only sulfonic acids and disulfides have been detected on oxidation of thiols by halamines, with no evidence for the formation of glutathione sulfonamide.^{270,309} Halamines and halamides display a far greater selectivity in their reactions than the hypohalous acids, with low $\text{p}K_a$ thiols (e.g., those present in some enzymes) particularly susceptible to oxidation by chloramines.²⁷¹ Halamines have been shown to modulate apoptotic pathways,^{310,311} inactivate intracellular enzymes,^{271,281,311} and induce cell death.^{271,281,311}

In addition to reactions with nucleophiles, HOCl and HOBr also react with aromatic rings and double bonds, including some amino acids (Tyr and Trp), nucleobases, and fatty acid side chains (reviewed in Refs 291, 312). Similar reactions also appear to occur with chloramines and bromamines, although at slower rates and with lower efficiency. Reactions with the phenolic side chain of Tyr are of particular importance as these reactions result in the formation of 3-chlorotyrosine (3-chloro-Tyr) and 3-bromotyrosine (3-bromo-Tyr). With large excesses of oxidant, these products are further halogenated to form 3,5-dichlorotyrosine (3,5-dichloro-Tyr) and 3,5-dibromotyrosine (3,5-dibromo-Tyr). These compounds constitute the only known specific biomarkers for HOCl-, HOBr-, or halamine-mediated damage to proteins.^{254,291,312–319} A number of studies have demonstrated that halamines are important intermediates in the formation of these materials on isolated proteins,^{316,320}

although they are also formed via direct reactions with HOCl and HOBr, respectively.³²¹

Trp oxidation by HOCl yields the 2-oxindole, possibly via an initial 3-chloroindole adduct and subsequent hydrolysis;^{322–326} this product may also be generated by HOBr and halamines.²⁷⁴ Recent studies have shown that the products formed on oxidation of Trp in peptides or proteins depend on the local sequence, with a cyclized product detected when the neighboring residue is a Gly or Ala residue,^{326,327} with other side chains, mono- or dioxxygenated derivatives of Trp are formed. Whether analogous products are formed with HOBr remains to be established.

MPO, EPO, and LPO are all also capable of converting SCN[−] into HOSCN.^{256,257,328–330} This species can also be generated by direct reaction of HOCl or HOBr with SCN[−],^{331,332} and it has been suggested that the majority of HOBr generated under physiologically relevant conditions is converted to HOSCN.³³²

Product studies indicate that HOSCN is much more selective than HOCl and HOBr, with strong evidence that the major target for HOSCN is thiols (either on proteins or low-molecular mass species such as GSH).^{328,333–335} The primary products of reaction of HOSCN with thiols are RS-SCN species and disulfides; the RS-SCN adducts can react further (e.g., hydrolysis to sulfenic acids) or be repaired by reductants.^{328,334,335} There is limited evidence for damage to other targets such as aromatic residues, with modification of Tyr, His, and Trp detected following exposure of proteins and polypeptides (particularly those without Cys residues) to SCN-derived oxidants.³³⁵ It has been postulated that these reactions occur via addition of SCN⁺ from (SCN)₂ to the aromatic ring, rather than via reaction of HOSCN.³³⁵ It has also been suggested that RN-SCN species are generated with imidazole groups such as His,³³⁶ and recent studies have confirmed that HOSCN can modify Trp residues.³³⁷

Exposure of proteins to SCN-derived oxidants has been shown to result in the loss of Lys residues and the formation of carbamylated Lys derivatives (RN-C(O)NH₂).³²⁸ These products are formed via the irreversible addition of the HOSCN decay product, [−]OCN, to the Lys amine group.³²⁸ Reagent [−]OCN, and that formed via the decomposition of urea, reacts similarly and has also been shown to target other (nucleophilic) moieties such as

the α -amino groups of amino acids, peptides and proteins, and (reversibly) thiol groups.³³⁸

Although HOSCN is a much less powerful oxidant than HOCl and HOBr, there is considerable evidence that this species can exert considerable biological damage as a result of its greater specificity, particularly for thiols. Kinetic studies have shown that HOSCN reacts with both low-molecular-mass and protein thiols with rate constants in the range 10⁴–10⁶ M^{−1} s^{−1}; reactions with other amino acids were too slow to be monitored (i.e., $k < 10^3$ M^{−1} s^{−1}).^{8,339} SCN-derived oxidants, believed to be HOSCN, can inactivate a range of thiol-containing enzymes (e.g., GAPDH, glutathione-S-transferases, and membrane ATPases)^{257,328,333,340} and deplete intracellular GSH.^{341,342} It has been shown that HOSCN inactivates membrane ATPases 10–1000 times more effectively than HOCl and HOBr due to this enhanced selectivity for critical thiols.³²⁸ Exposure of endothelial cells to HOSCN has also been shown to induce tissue factor activity and promote expression of cell adhesion molecules, with these effects postulated to be due to specific oxidation of redox-sensitive thiols and resulting activation of NF- κ B.^{343–345} If this mechanism is correct, it would be expected that a large number of genes would be upregulated following exposure of cells to HOSCN.³⁴⁵ Recent studies support this suggestion with HOSCN shown to oxidize thiol groups on protein tyrosine phosphatases (which control cellular tyrosine phosphorylation levels) with a resulting loss of enzyme activity.³⁴⁶ This results in hyper-phosphorylation of cellular proteins, activation of the mitogen-activated protein kinase (MAPK) pathway, and enhanced apoptosis.^{341,346}

7 PHOTO-OXIDATION OF PROTEINS

Proteins are major targets for photo-oxidation within cells due to the presence of endogenous chromophores within some protein structures (both amino acid side chains and bound prosthetic groups such as flavins and heme), their ability to bind exogenous chromophoric materials, and their rapid rates of reaction with other excited state species. Photo-oxidation occurs via two major routes: direct photo-oxidation arising from the absorption of UV radiation by the protein structure (primarily side chains) or bound chromophores, thereby generating

excited state species (singlet or triplets) or radicals as a result of photo-ionization (type 1 processes) and secondly via the formation and subsequent reactions of singlet oxygen (molecular oxygen in its first excited singlet state, $^1\Delta_g$ O₂, or 1 O₂) generated by the transfer of energy to ground state (triplet) molecular oxygen by either protein-bound or other chromophores (type 2 processes).²¹

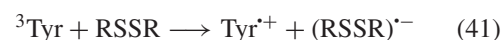
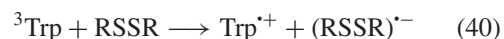
Direct oxidation of amino acids, peptides, and proteins by UV light is only a significant process if the incident light is absorbed by the protein. For most proteins without bound (covalent or noncovalent) cofactors or prosthetic groups, this only occurs with light with $\lambda \leq$ circa 320 nm. The major chromophoric amino acids present in proteins are Trp, Tyr, and Cys with the wavelengths of UV light that reach the surface of the earth. The direct photochemistry of proteins is therefore dominated by these amino acid side chains, with the contribution of each side chain depending on their abundance. The indolic side chain of Trp has the longest wavelength ground-state absorption spectrum and also has a significantly greater molar absorption coefficient for each of its major absorption bands than the other species; it is therefore the most significant chromophore in many proteins. This significance is however tempered by the lower abundance of this side chain in many proteins.

7.1 Direct (Type 1) Photo-Oxidation

The absorption of UV light by Trp, Tyr, and cystine can give both excited states and radicals via photo-ionization. The major initial species are usually in the first excited singlet state, but these are typically short lived, and readily lose energy via direct energy transfer to other groups, by collisional deactivation and vibrations, and via inter-system crossing to the triplet state. As such, most protein singlet states react via energy transfer rather than chemical reaction. The relative energies of the singlet states decrease in the order: Phe > Tyr > Trp, which can result in rapid energy transfer from Phe and Tyr to Trp; this results in the fluorescence spectra of most proteins being dominated by Trp.

The triplet states of Trp and Tyr have been studied extensively as these are longer lived than the singlets and show chemical reactivity (i.e., can undergo electron, as well as energy, transfer reactions).^{347,348} The first triplet states of Trp

and Tyr undergo electron transfer reactions with suitable acceptors such as disulfides (reactions 40 and 41), with this resulting in the formation of the disulfide radical anion and the corresponding aromatic radical-cations.^{347,348} The latter rapidly deprotonate to give the neutral indolyl radical and Tyr phenoxyl radical; the chemistry of these species is outlined above.



The disulfide radical anion ($\text{RSSR}^{\bullet-}$) formed as a result of electron transfer can dissociate, reversibly, to give the anion and a thiyl radical or react with O₂ to give a superoxide radical ($\text{O}_2^{\bullet-}$) and parent disulfide (see above).

^3Tyr can also be quenched by direct electron transfer with O₂ ($k = 4.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$), with His (with $k = 7.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7.7—this is a pH-dependent process) and with Cys (with $k = 5.2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$).^{21,347,348} In each case, ^3Tyr is converted to its phenoxyl radical via the radical-cation and the partner is converted initially to the radical-anion, although these undergo further reactions. The Tyr phenoxyl radical and the Trp indolyl radical are also generated via similar reactions by a wide range of triplet sensitizers (e.g., Ref. 349).

High-energy triplets of other chromophores can also induce direct hydrogen atom abstraction reactions with protein side chains. These reactions usually yield carbon-centered radicals (or thiyl radicals from Cys). These radical reactions have been reviewed.¹⁸²

Direct photo-dissociation of cystine to give two thiyl radicals occurs readily due to the significant absorbance of the disulfide bond between 250 and 300 nm.³⁵⁰ A major fate of such radicals is dimerization (and hence repair of the disulfide bond), but alternative reactions, such as that with O₂ (see above), can result in irreversible oxidation via formation of oxyacids. These reactions can have significant effects on the integrity of proteins, due to the role of disulfide bonds in maintaining tertiary structures. Trp, Tyr, Phe, and His can also undergo direct photo-ionization, although there is controversy in the literature regarding the quantitative significance of mono-versus bi-photon processes in such reactions, particularly when long wavelength UV light is

employed.^{21,347,348} Direct cleavage of the phenolic –O–H bond can occur with Tyr, with this yielding the phenoxyl radical, a proton, and a hydrated electron.²¹ The chemistry of the hydrated electron is well characterized with addition to O₂ to give O₂^{•−}, being very fast (k circa $10^{10} \text{ M}^{-1} \text{ s}^{-1}$).³⁵¹ Electron attachment can also occur to free carboxyl groups (e.g., the C-terminus or Asp/Glu side chains) and amine groups (e.g., the N-terminus or Lys side chains) in processes that result in deamination and elimination of H⁺, respectively. Addition can also occur at other sites, particularly with cystine (to give the disulfide radical-anion) and protonated His side chains. In peptides, the hydrated electron can also add to the carbonyl groups of the peptide backbone to give a radical-anion that can subsequently give rise to backbone cleavage. These reactions have been reviewed in Refs 13, 15.

7.2 Singlet Oxygen-Mediated Protein Damage

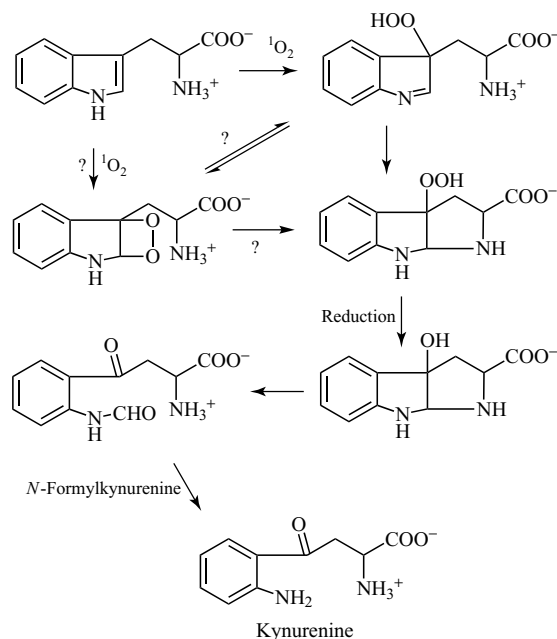
¹O₂ can interact with protein side chains by both physical quenching and chemical reaction, and rate constants have been determined for many of these reactions.³⁵² The former results in energy transfer and de-excitation of the singlet state but no chemical change in the energy acceptor. For proteins, only Trp appears to give rise to significant physical quenching,³⁵³ with k circa $2\text{--}7 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$; chemical reaction occurs at k circa $3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.³⁵³ The relative contributions of these processes with Trp is affected by multiple factors, including the environment of the residue and the presence of neighboring reactive residues.^{354,355} The rate constants for chemical reaction of ¹O₂ with the side chains of amino acids vary dramatically with only Trp, His, Tyr, Met, and Cys, undergoing rapid ($k > 1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$) chemical reaction at physiological pH values. All other side chains react with $k < \sim 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at neutral pH.³⁵², although some of these processes are pH dependent. Thus, at high pH, Arg and Lys react rapidly via their neutral (unprotonated) forms.³⁵⁶

In the case of Trp, Tyr, and His, there is considerable evidence for the initial formation of endo- and hydro-peroxides as a result of the addition of ¹O₂ to these residues. In the case of Trp and Tyr, these peroxides are reasonably well characterized; those formed with His are much less stable and

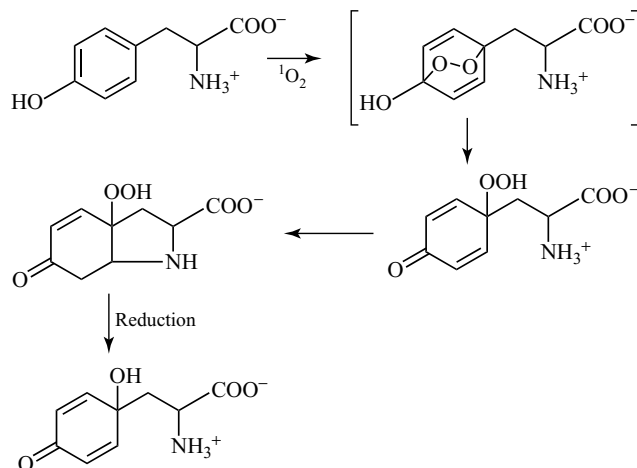
the exact nature of the (multiple) species formed remains to be completely established.^{357–369}

With free Trp, reaction with ¹O₂ yields 3*a*-hydroperoxypyrroloindole as an isolable product. It has been proposed that the initial species may be a dioxetane across the C2–C3 double bond (Scheme 5),^{367,368} although there is limited direct evidence for this with the free amino acid. Other potential intermediates include a hydroperoxide at C3 (Scheme 5).^{364,370–374} Peptide-bound Trp appears to undergo somewhat similar reactions to that of free Trp, although the ring-closing reaction to give the pyrroloindole appears to be slower due to the incorporation of the nitrogen lone pair into the peptide (amide) bond.³⁵⁹

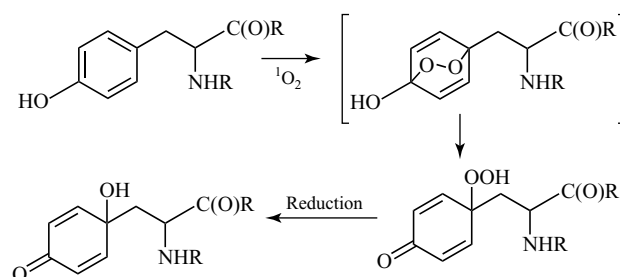
With free Tyr and peptide-bound Tyr, evidence has been presented for the generation of multiple peroxidic species, although again the initial species, probably an endoperoxide, has not been detected (Scheme 6). Ring opening of the endoperoxide has been proposed to give a hydroperoxide at C1 and direct evidence has been obtained for the presence of both these compounds³⁵⁷ and related species with other phenols.^{362,375} With free Tyr, rapid ring closure involving the nitrogen lone pair of the amine then ensues to give a bicyclic product



Scheme 5



Scheme 6



Scheme 7

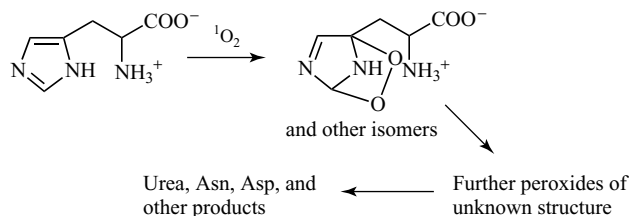
3*a*-hydroperoxy-6-oxo-2,3,3*a*,6,7,7*a*-hexahydro-1*H*-indol-2-carboxylic acid, which has been extensively characterized (Scheme 6).^{138,357,358,376,377}

With peptide Tyr residues, a peroxide formed at C1 on the ring has been detected and characterized by nuclear magnetic resonance (NMR).³⁵⁷ This is believed to arise from ring opening of an initial endoperoxide (Scheme 7). The detection of this species with peptide Tyr residues, but not the free amino acid, is believed to result from a longer lifetime of this species as a result of the slower ring closure reaction with the amine group when this is incorporated into the peptide bond.³⁵⁷ With 4-hydroxyphenylpropionic acid where such reactions cannot occur, the C1 peroxide is the major species detected.

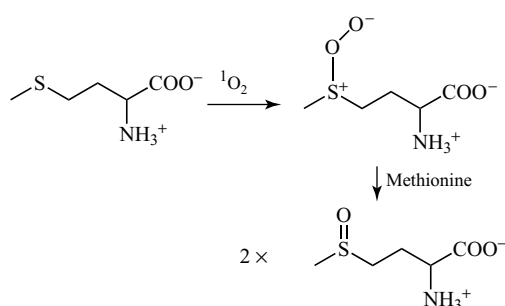
Oxidation of free His by $^1\text{O}_2$ is also believed to occur via initial endoperoxide formation and the consumption of a single molecule of O_2 per mole His (Scheme 8).³⁷⁸ Analogous endoperoxides have been detected directly by low-temperature NMR

with highly substituted derivatives in organic solvents.³⁶⁵ Decomposition of these species at elevated temperatures yielded further uncharacterized intermediates, and subsequently, stable products. Studies from the author's laboratory indicate that multiple peroxides are present in reaction mixtures from free His, with these having lifetimes of minutes to hours at room temperature. These species may be hydroperoxides formed by ring opening of an initial endoperoxide by analogy to the behavior detected with Trp and Tyr, respectively. Subsequent decomposition of these materials results in ring opening and the formation of urea, Asn, and Asp as well as other materials (Scheme 8).

Evidence has been presented for the formation of a zwitterionic peroxy species during the photo-oxidation of free Met residues (Scheme 9).³⁷⁹ This species subsequently reacts with a second molecule of Met to give up to 2 moles of sulfoxide.³⁷⁹ The stoichiometry of the latter process



Scheme 8



Scheme 9

is complex and pH dependent, with this being 1 : 1 above pH 7 and 1 : 2 below pH 5; these data suggest that other reactions also occur. Other intermediates including a nitrogen-sulfur cyclic intermediate have been reported (reviewed in Refs 380, 381), with hydrolysis of this species yielding the sulfoxide.³⁷⁹ This intermediate is only likely to be of significance with free Met, due to the involvement of the free amino group, and the situation with Met residues in peptides and proteins remains to be fully elucidated. It is however clear that the sulfoxide is a major product.^{382,383}

As with Met, the products arising from reaction of free Cys are well established (disulfide and oxyacid formation) but the mechanism is less clear.^{380,381,384} The quantitative yield of the products arising from Cys residues in proteins is not well established, and the ratio of disulfide to oxyacids is likely to vary between proteins due to steric or electronic barriers to dimer formation. Qualitative studies have shown that oxidation of free cystine occurs via a zwitterion peroxy intermediate, which reacts further with another molecule of cystine to give two molecules of RSS(=O)R.^{380,385} The effect of incorporation of cystine residues into a protein on such reactions, where steric and electronic effects

are likely to inhibit such subsequent reactions, remains to be determined.

8 CONSEQUENCES OF PROTEIN OXIDATION

Oxidation of proteins has a wide range of downstream consequences and only the general principles are reviewed here briefly. As is obvious from the above sections, oxidation can result in major physical changes in protein structure ranging from fragmentation of the backbone to oxidation of the side chains. The latter can result in either direct, or subsequent, dimerization or aggregation. Direct cross-linking can occur via intermolecular radical-radical dimerization of Tyr phenoxyl radicals to give interprotein di-tyrosine cross-links or thiyl radical termination reactions to give (reducible) disulfides. Secondary dimerization can occur via multiple pathways, including reactions of Lys, Arg, and His residues with carbonyl groups generated by oxidation on other residues, via (uncharacterized) His oxidation products, and from the reaction of quinones (e.g., those generated from DOPA generated from Tyr residues) with nucleophiles (Cys, Lys, Arg, His, and α -amino) on other proteins. The exact nature of these cross-linking reactions, and the species formed, remains to be established.

Oxidation at both backbone and side-chain sites can yield further reactive species. These include endo- and hydroperoxides, chloramines/chloramides and bromamines/bromamides, DOPA (and quinones from further oxidation), and other intermediates such as R-S-X and R-S⁺(X)-R (X = OH, Cl, Br, NO). Decomposition of the peroxides, chloramines/chloramides, and bromamines/bromamides by low valent metal ions, superoxide radicals, or UV light can yield further radicals that may initiate further damage.^{100,107,108,300,302} Reaction of DOPA

formed from Tyr (either the free amino acid or on proteins), with trace metal ions such as Fe^{3+} or Cu^{2+} , can generate semi-quinone radical-anions and hence superoxide radicals (by electron transfer from the radical anion) and H_2O_2 by dismutation.^{109,386} Each of these processes may initiate further damage to the same protein, other proteins, or alternative biological targets.

Oxidation of protein side chains can result in unfolding and conformational changes with these having consequential effects on biological function.³⁸⁷ Oxidation of surface-exposed residues may have more limited effects than oxidation of buried residues, as many of the products of oxidation are more polar than the parent (cf. species in Table 7). This may be counter balanced by a slower rate of oxidation for access reasons, when the oxidant is present in the bulk aqueous phase. There are, however, some notable exceptions, including the decarboxylation of Asp/Glu residues¹⁰⁸ and deamination of Lys residues^{100,388} induced by hydroperoxide decomposition and chloramine decomposition, respectively.

Oxidation of aromatic and Met residues can also result in the incorporation of polar or charged groups (e.g., hydroxyl-, peroxy-, nitro-, chloro-, and bromo-groups, among others, cf. data in Table 8), which will preferentially localize on external, solvent-accessible locations potentially leading to protein unfolding.²⁷⁵ In the case of Met, it has been shown that solvent accessible residues are more readily oxidized than buried species,^{389,390} but oxidation of exposed residues does not appear to have marked effects on the conformation of most proteins,³⁹⁰ unless this residue is within an enzyme active site or in a binding pocket (e.g., in α_1 -proteinase inhibitor³⁹¹). Met sulfoxide is more polar than Met and can have marked effects on conformation.³⁹² Free energy calculations for the transfer of a residue from an α -helix inside a membrane to the aqueous phase indicate that Met and Phe side chains have the highest transfer free energy values,³⁹³ and the formation of oxidation products on these residues would therefore be expected to be a major driving force for changes in protein structure. Oxidation of only one of the eight Met residues (Met385) in α_1 -proteinase inhibitor results in the loss of the inhibition of elastase by this species. Similarly, oxidation of one of the vicinal (Met146 or Met147) residues in the C-terminal domain of

calmodulin has been shown to give rise to a large (30-fold) decrease in Ca^{2+} affinity.³⁹⁴

Not all oxidative events are, however, deleterious, and oxidation may result in a gain of function. Thus, oxidation of the Met-1 residue of ubiquitin to the sulfoxide results in a 50% increase in reactivity,³⁹⁵ and similar oxidation of Met residues in the native fifth component of human complement results in the conversion of this protein into its active form that binds component C6.^{396,397} Similarly, oxidation of a critical Cys residue is known to activate latent matrix metalloproteinases (the “cysteine switch” mechanism), with this process conserved across virtually the entire enzyme family.²⁷²

Oxidation of protein side chains has been proposed as a marker for protein degradation by cellular machinery.^{398,399} It has been proposed that oxidative modification results in enhanced turnover,^{400,401} although there is also evidence for decreased turnover with heavily modified material proteins.^{402–406} The cellular accumulation of heavily damaged, poorly degraded materials has been associated with lipofuscin accumulation and a wide range of human pathologies.^{407–411} In this respect, it is of interest to note that a number of protein oxidation products, particularly hydroperoxides, appear to be potent inhibitors of the proteolytic systems that are designed to remove damaged proteins. Thus, amino acid, peptide, and protein hydroperoxides have been shown to inhibit thiol-dependent lysosomal cathepsin enzymes⁴¹² and also the activity of the 26S proteasome.⁴¹³ These two systems constitute two of the major pathways by which cells remove modified/oxidized proteins and the impairment of their activity by the very molecules that they are supposed to remove may initiate a vicious cycle of protein damage and incomplete removal.^{412,413}

9 REPAIR OF PROTEIN DAMAGE

Although the prevention of protein oxidation is of immense industrial and biological importance, there are relatively little kinetic data available on the reaction of protein-derived radicals with antioxidants. This is probably due, at least in part, to the difficulties in generating known yields of specific radicals on proteins in the absence of other competing species. Some data have been obtained on the repair of amino acid radicals at neutral pH by Trolox C (a water-soluble vitamin E analog),⁴¹⁴

ascorbate,¹⁵¹ and GSH.⁴¹⁵ These data have been reviewed in Ref. 150.

With regard to repair of Trp-derived radicals, it has been shown that the Trp radical-cation reacts more rapidly than the neutral indolyl radical suggesting that repair can occur by electron transfer.⁴¹⁴ Repair of Trp-derived radicals on lysozyme by Trolox C has also been examined and shown to be a fast reaction ($k = 2\text{--}5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).⁴¹⁴ The observation that repair of Trp radicals occurs with a rate constant similar to that for the free amino acid supports the hypothesis that at least some repair reactions are efficient and can occur over large distances. In contrast, vitamin E present in sodium dodecyl sulphate (SDS) micelles, although it can repair free Trp-derived radicals, cannot rapidly repair the same species when present in lysozyme.⁴¹⁶

Trolox C has also been shown to repair Tyr phenoxyl radicals in a number of proteins,^{202–206} and α -tocopherol has been demonstrated to repair Tyr phenoxyl radicals in lysozyme.⁴¹⁶ Other phenolic compounds (e.g., *n*-propyl gallate and sesamol) and vitamin C act in a similar manner.^{416,417} Trolox C, vitamins C and E, and thiols have been shown to react with protein and peptide peroxy and alkoxy radicals.^{148,200,201} These latter reactions are not, however, “repair” reactions, as the peptide remains as an oxidized species (either alcohols or hydroperoxides), although these reactions would be expected to inhibit chain reactions within a protein by exporting the radical into bulk solution.

Cys, *N*-Ac-Cys, and GSH can react with Tyr phenoxyl radicals on proteins, although this is reversible, and repair can only be effective if the thiyl radical is removed (e.g., via reaction with O₂ or thiol anions) before it reacts further.⁴¹⁸ Uric acid can also repair both Trp indolyl radicals and Tyr phenoxyl radicals in lysozyme when the protein is denatured (i.e., in the presence of SDS).⁴¹⁶ The modest difference between the rate constants for repair of the free Trp indolyl radical and the same species in lysozyme again suggests the occurrence of electron transfer processes. Bilirubin (and other molecules) that bind strongly to HSA or BSA appears to protect against damage, but it is unclear whether this is due to repair of radicals formed on the protein or by providing an alternative target for the attacking species.^{419,420}

The majority of protein damage does not appear to be repaired by cells, and the major fate of

oxidized proteins is catabolism. The only exceptions appear to be the repair of some oxidized Cys products and reduction of hydroperoxides and Met sulfoxide. Cystine and mixed disulfides can be readily reduced back to the corresponding thiols by multiple disulfide reductases/isomerases (e.g., glutaredoxins, thioredoxin, and protein disulfide isomerases). Similarly, the formation of nitrosocysteine (RSNO) and the sulfenic acid (RS-OH) can be readily reversed by biological reductants (both low-molecular-mass and enzymatic), particularly by thiol-dependent systems, although ascorbate can also play a role.^{421–427} Reduction of some Cys sulfenic acid residues also occurs via the action of sulfiredoxin enzymes, although this activity appears (currently) to be highly specialized and limited to reduction of the sulfenic acid forms of some peroxiredoxins by mitochondrial enzymes.^{428–430}

Amino acid, peptide, and protein hydroperoxides do not appear to be metabolized by many “traditional” antioxidant enzymes, with no reaction detected with many peroxidases, pseudoperoxidases, or catalase.^{431,432} Recent studies have, however, shown that these materials can be readily reduced by some members of the peroxiredoxin family with the corresponding formation of alcohols⁴³³ and possibly by glutathione peroxidase-4 (Davies, unpublished data). Reduction of these hydroperoxides can also occur with low-molecular-mass thiols (e.g., GSH) and ascorbate, although the rates of these reactions are highly variable and in some cases very slow.^{10,431,432,434} The formation of alcohols from these materials is not strictly a repair process; however, it is likely to limit any subsequent reactions of these hydroperoxides that might exacerbate oxidation.

Met sulfoxide is reduced by a family of Msr enzymes. These enzymes are highly specialized and stereospecific, with some of the Msr proteins specific for free Met sulfoxide and some handling only protein/peptide Met sulfoxide.^{435–442} These Msr proteins are predominantly intracellular and there appears to be little extracellular activity.⁴⁴³

A considerable number of studies have searched for evidence of other “repair” systems in cells and biological fluid. Many of these studies have been complicated by the occurrence of metabolic/catabolic processes that can also remove the damaged materials. As such, there is limited evidence for any major alternative routes of repair (as opposed to removal) of many of the

oxidation products listed in Tables 7 and 8, although this is an active field of research. Some evidence has been presented for the dechlorination of 3-chlorotyrosine,⁴⁴⁴ and the reduction of 3-nitrotyrosine to 3-aminotyrosine and/or the parent amino acid,^{445,446} but the biological significance of these reactions is yet to be fully established.

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Electron Transfer in Peptides and Proteins

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1 INTRODUCTION

Directed and controlled electron transfer (ET) reactions through proteins are vital for all living organisms for energy conversion and metabolic processes.¹ During photosynthesis, ET reactions play a crucial role, utilizing the energy of light for the production of O₂ and adenosine-5'-triphosphate (ATP), the energy storage molecule of cells.^{2,3} In addition, photosynthesis produces the so-called reducing equivalents, which allow the conversion of CO₂ into carbohydrates, the source of biomaterials on earth. Protein complexes, embedded in the chloroplast membrane, guide the ET processes, which are coupled with proton translocation through the membrane (Figure 1).⁴

In Catabolic processes of carbohydrates NADH (nicotinamide adenine dinucleotide) is synthesized, whose oxidation is the starting reaction of aerobic respiration. As in photosynthesis, the protein complexes of the respiratory chain through which ET occurs are also embedded into cell membranes, and again proton transfer takes place as a consequence of ET, driving the synthesis of ATP (Figure 2).⁵

Thus, long-distance ET through membrane-bound protein complexes occurs during energy conversion processes (photosynthesis and aerobic respiration). Long-distance ET is also known to take place in enzymatic reactions. An important example is the ribonucleotide reductase (RNR) that is essential for all higher organisms since this enzyme is needed to catalyze the conversion of ribonucleotides to deoxyribonucleotides, the building blocks of DNA

(see Section 7). In these enzymes, ET occurs over a distance of 35 Å from the generation site of a tyrosyl radical to the site where a cysteinyl radical triggers the conversion of ribonucleotide to deoxyribonucleotide (Figure 3).⁶

These examples show that ET through proteins is fundamental for all living organisms and that these reactions can occur over long distances.⁷ In most cases, these processes occur in multistep reactions. As an example, respiration needs 15 ET steps to take electrons from NADH, deposit them in O₂, and generate the electrochemical proton gradient that drives the ATP synthesis.⁸ Each single step can be described by the Marcus theory discussed below.

2 SINGLE-STEP ELECTRON TRANSFER

Marcus developed a theory for ET between an electron donor (D) and an electron acceptor (A) that are in close contact with each other.⁹ The physical parameters defining the ET rates are the driving force $-\Delta G^0$, and the reorganization energy λ , which is needed for the nuclear rearrangement during ET. An additional parameter, the electronic coupling matrix element H_{AB} , was introduced into the Marcus theory, which describes the probability that an electron tunnels through the potential barrier between D and A.^{10,11} These three parameters are summarized in the expression for ET rates given in (1) with the Planck constant (h), the temperature (T), and the Boltzmann constant (k_B):

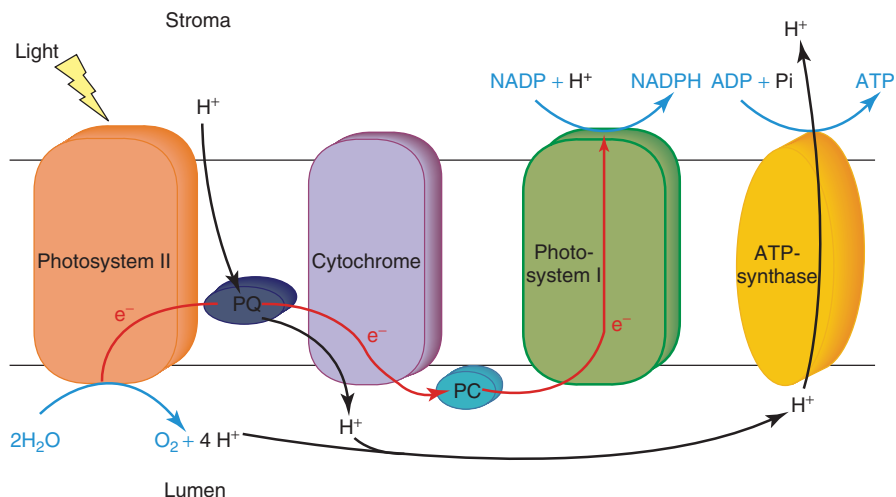


Figure 1 Simplified depiction of the light-dependent reactions of the photosynthesis. Electron and proton flow due to the conversion of water into molecular oxygen and protons are shown, which lead to the production of NADPH and ATP. PQ, plastoquinone; PC, plastocyanine; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP; ADP, adenosine-5'-diphosphate; ATP, adenosine-5'-triphosphate.

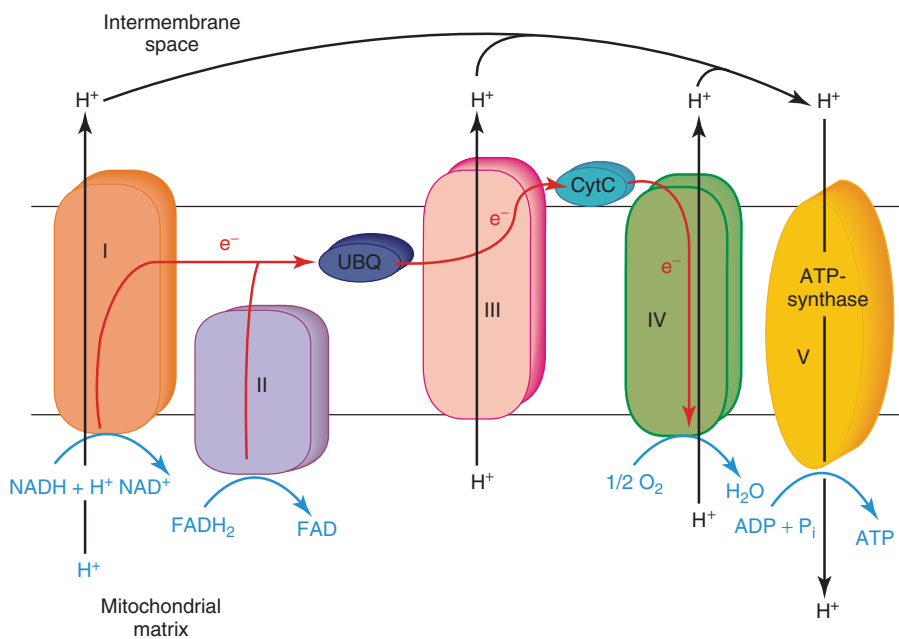


Figure 2 Simplified depiction of the aerobic respiration where the reducing potential of NADH and FADH₂ is converted to ATP through an electron transport chain with oxygen as terminal electron acceptor. ADP, adenosine-5'-diphosphate; ATP, adenosine-5'-triphosphate; CytC, cytochrome c; FAD, flavin adenine dinucleotide; FADH₂, reduced form of FAD; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP; UBQ, ubiquinone.

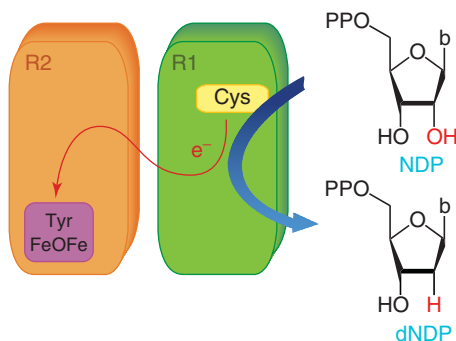


Figure 3 Simplified depiction of the ribonucleotide reductase, which transforms ribonucleotide diphosphates (NDP) to deoxyribonucleotide diphosphates (dNDP) and therefore plays a fundamental role in DNA replication and repair. The active cysteine radical located in the α^2 -subunit (shown in green) is generated by an ET cascade over a distance of 35 Å by a diferric tyrosine radical cofactor.

$$k_{\text{ET}} = \frac{\sqrt{\frac{4\pi^3}{h^2 \lambda k_B T} H_{\text{AB}}^2}}{e^{\frac{(\Delta G^0 + \lambda)^2}{4 \lambda k_B T}}} \quad (1)$$

The reaction profile of a typical ET reaction, where the donor D is separated from the acceptor A by a bridge B is shown in Figure 4. The nuclear coordinates of the reactant and product states are described using classical harmonic oscillators. In this classical model, ET only occurs when the reactant and the product state have the same energy, since the principle of energy conservation has to be satisfied, and when they also have the same nuclear configuration according to the Franck–Condon principle. The only position fulfilling both conditions is the intersection point of the two parabolas.

The rate of ET between D and A also depends on their distance, and it is the electronic coupling matrix element H_{AB} that introduces the distance dependence on ET theory. The splitting at the intersection point is equal to $2H_{\text{AB}}$ (Figure 4). This strength of the electronic coupling between D and A, that is, the overlap between their orbitals, decays exponentially with the donor–acceptor separation as expressed in (2). The exponential factor β is a measure for the ability of the separating bridge (B) to mediate electronic coupling (superexchange), r represents the donor to acceptor distance, r_0 the close contact distance, and k_0 the ET rate for close

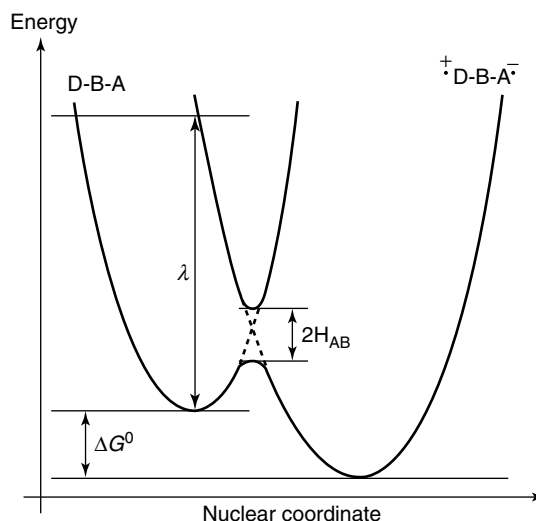


Figure 4 Intersecting parabolic potential energy surfaces are used to represent classical reactant and product harmonic oscillators for an ET reaction with the Gibbs free energy $\Delta G^0 < 0$. The parabolas at the left and right represent the reactant (D–B–A) and the product states, respectively. The figure shows the electronic coupling matrix element H_{AB} , which introduces the distance dependence on ET as well as the reorganization energy λ . This is the energy required to move along the product potential surface as the nuclear geometry is distorted from the average product configuration to the average reactant configuration.

contact:

$$k_{\text{ET}} \propto \frac{k_0}{e^{\beta(r-r_0)}} \quad (2)$$

In peptides, these separating bridges are the amino acids intervening D and A. The character of the bridge B exhibits a strong influence on the ET rate. In order to determine the strength of the electronic coupling, the orbitals of D, A, and B had to be mixed. A simple model was introduced by McConnell using n identical bridge units.¹² In this model, the coupling element H_{AB} is a function of the coupling between the redox sites (D and A) and the bridge B, the coupling between the bridge elements B_n as well as the energy gap between D and B (Figure 5).

Since peptides and proteins are built by up to 20 different amino acids, the McConnell model is too simple to explain the details of ET through these biomolecules. In order to gain a deeper understanding, Gray and Winkler¹³ measured the ET rates of several proteins. Using metalloproteins

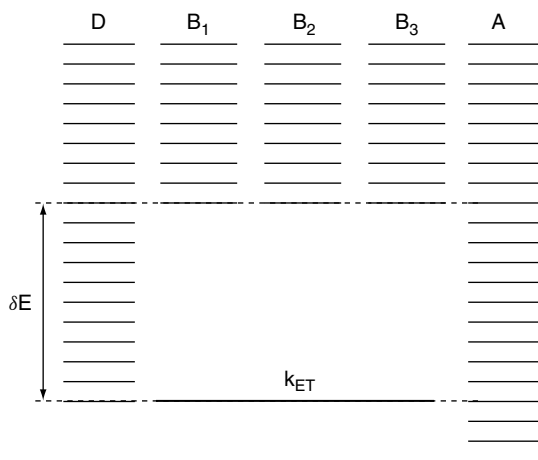


Figure 5 Energy diagram for superexchange ET between donor D and acceptor A across a bridge of n identical units B_n . The bridge orbitals are involved in the electronic coupling between the donor and acceptor leading to a lower potential barrier and therefore facilitate the ET. The rate depends on the coupling between the redox sites and the bridge, the coupling between the bridge elements, and the energy gap between the orbital donating the electron and the reduced bridge states δE .

with copper (azurin) or iron (cytochrome) cofactors, they attached ruthenium complexes to specific histidine residues at defined distances from the cofactors. Figure 6 shows the results of an azurin series.¹⁴ The measured ET rates fitted well with the exponential distance dependence of (2). From the

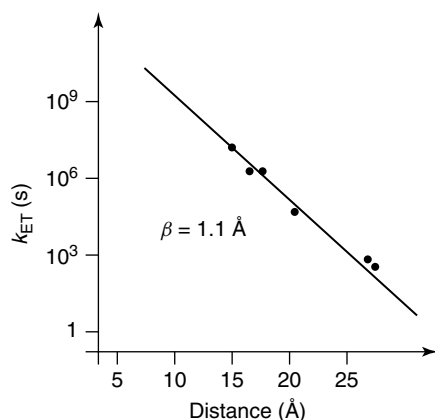


Figure 6 Distance dependence of the ET rate (k_{ET}) in modified azurins (arsenate reductase) with Ru complexes attached to six different positions on the surface of the metalloprotein. The ET rates from the metal cofactor (copper) to the oxidized ruthenium complex were measured by absorption spectroscopy using the flash-quench technique.

slope, a β -value of 1.1 Å^{-1} resulted for the peptides adopting a β -sheet.

For several other peptides, ET rate data could not be explained by the distances between D and A alone, and in some proteins, ET rates for similar D to A distances differed by several orders of magnitude. Gray and Winkler therefore concluded that a structural analysis of the peptide matrix is necessary in order to understand ET processes. Beratan *et al.*¹⁵ developed a model that links protein structures to their ET properties. According to their model, the electronic coupling depends on the specific bridging connections between D and A (covalent bonds, H-bridges, and Coulomb bonds). These interactions make different pathways for ET through peptides possible. For each pathway, the coupling strength can be calculated as a function of all possible bonding contacts that correspond to β -values of at least 1.0 Å^{-1} and nonbonding contacts of about 2.0 Å^{-1} . If the protein is very flexible, fast conformational averaging might occur and the matrix exhibits an average β -value.

A different approach was suggested by Dutton in his “uniform barrier” model, which assumes a uniform behavior of all bridging units.¹⁶ He derived a β -value of 1.4 Å^{-1} from studies on the bacterial reaction center as well as on synthetic peptides. In a refined version, the atomic packing is also taken into account. Anyhow, in the case of ET reactions in peptides and proteins, β -values larger than 1.0 Å^{-1} lead to such a strong distance dependency that single-step ET over more than 14 Å (Dutton)¹⁶ or 20 Å (Gray and Winkler)¹³ cannot occur under biological conditions. Nevertheless, long-distance ET in proteins exists, and it is today a well-accepted theory that, in analogy to DNA, multistep reactions (hopping) can make long-distance ET possible in peptides and proteins as well.

3 HOPPING

3.1 General Aspects

The hopping model of ET through biopolymers was first developed for DNA in order to explain the observation that ET in double-stranded DNA can occur over very long distances ($>100 \text{ Å}$). According to this model, a positive charge, induced into guanine (G), can migrate through double-stranded

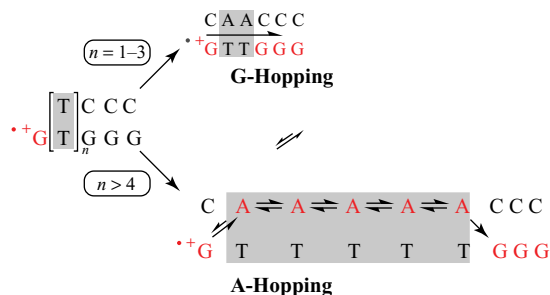


Figure 7 ET between guanine (G) bases separated by n A·T base pairs. For short distances ($n = 1-3$) superexchange between the guanine bases was observed, a process referred to as G-hopping. However, for long distances ($n > 4$), adenines were acting as additional stepping stones, a mechanism known as A-hopping. The DNA double strands with $n = 2$ and 5 are shown as example for each case and the nucleotides shown in red indicate the stepping stones of the ET process.

DNA in a multistep reaction using the other Gs as stepping stones at which the charge has a distinct lifetime (Figure 7).¹⁷ As a consequence, one long ET reaction is divided into several short and therefore much faster ET steps. The stepping stones act as electron donor in the first step and as electron acceptor in the subsequent reaction. Furthermore, if the distance between the Gs is so long that the ET rate becomes slow, the intervening adenines (A) can also become stepping stones (Figure 7), as the endothermic oxidation of the neighboring A is faster than the thermoneutral oxidation of a distant G.¹⁸

Each single reaction step follows (1), but the overall process cannot be described by (2). The ET rate for the hopping reaction is much less distance dependent than the superexchange process. If the hopping steps k_n are of the same rate, and if all steps (n = number of steps) are reversible, the overall ET rate k_{ET} decreases with n^2 , as shown in (3).^{17,19,20} In many cases, one of the hopping steps becomes the rate-determining step:

$$k_{ET} \propto \frac{k_n}{n^2} \quad (3)$$

If hopping explains long-distance ET through peptides and proteins, the question remains, which of the 20 natural amino acids in peptides can play a similar role as the nucleic acids in DNA and what are the conditions for a mechanistic change from a single-step reaction as in **1** (Figure 8a) to a hopping process as in **2** (Figure 8b).²¹ In order to find an

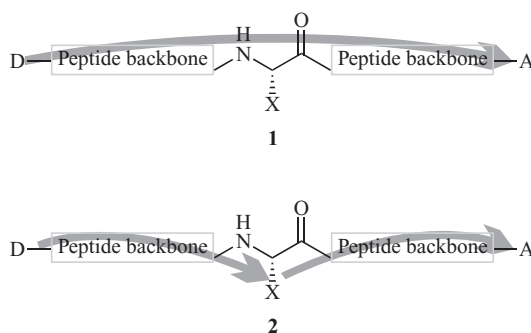


Figure 8 Possible ET pathways through peptides **1** and **2**. In **1**, ET occurs via a single-step reaction if there is no redox-active side chain at position X between the donor (D) and acceptor (A). In contrast to this, ET may occur via a two-step hopping mechanism if there is an amino acid with a redox-active side chain at position X between D and A (peptide **2**).

answer, we have carried out laser experiments with a model peptide. The goal was to detect all reactive intermediates and to determine the rates of the ET reaction steps.

3.2 Peptide Assay

As model peptide, nonapeptide **3** turned out to be a suitable assay for the study of ET processes through peptides (Figure 9).²¹ It consists of tyrosine, which functions as an electron donor (D), a dialkoxyphenylalanine, which can be used to generate the electron acceptor (A), and a third amino acid with side chain

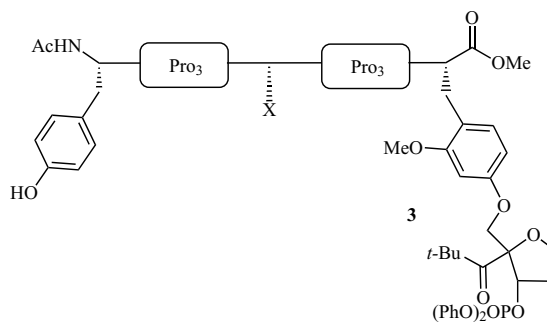


Figure 9 Peptide assay **3** for the investigation of intramolecular ET, with an electron donor (Tyr) at the N-terminal end, a dialkoxyphenylalanine that can be transformed into an electron acceptor at the C-terminal end, and a side chain X that might act as a relay station.

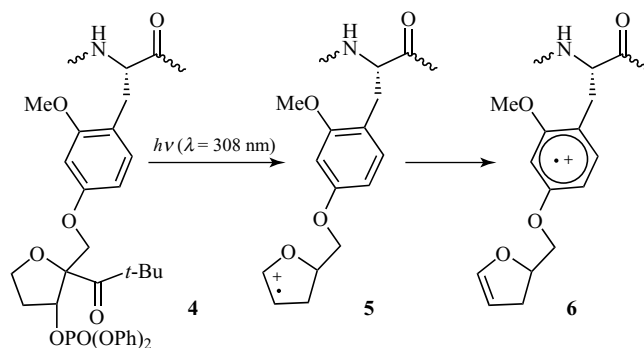


Figure 10 Generation of the radical cation (**6**), which acts as electron acceptor (A) in our model peptides, by laser flash photolysis of **4**.

X that might act as stepping stone for a hopping process.²² The latter is often referred to as relay amino acid or relay station. These three amino acids are separated from each other by rigid bridges consisting of three prolines.

A laser flash was used to generate a radical cation in the side chain of the dialkoxyphenylalanine, which then functions as an electron acceptor (A) during the ET reaction. The formation of this radical cation is shown in Figure 10. Photoexcitation of **4** by an excimer laser at 308 nm initiates a Norrish type I reaction that after β -elimination leads to intermediate **5**, which yields the electron acceptor **6** (A).²¹

Model peptide **3** fulfills all prerequisites for a successful investigation of ET through peptides. The electron donor tyrosine provides a sufficient driving force because deprotonation of the hydroxyl group leads to a nonreversible trapping of the charge. The overall ET process is exothermic by 0.37 V since the redox potentials of tyrosine, used as electron donor, and dialkoxyphenylalanine, whose radical cation is the electron acceptor, are 0.93 and 1.30 V, respectively. The electron acceptor can be generated selectively at a specific position in the peptide, and the UV/Vis spectra of the electron acceptor ($\lambda_{\text{max}} = 450$ nm) and the tyrosyl radical ($\lambda_{\text{max}} = 410$ nm) differ from each other so that they can be detected simultaneously. In order to minimize the influence of the peptide conformation on the ET rate, rigid peptide bridges were chosen. With two triproline spacers, a separation of donor (D) and acceptor (A) of about 20 Å was achieved due to their PPII (polyprolineII) helical structure.^{22–24} These proline sequences mediate ET but proline itself does not function as relay amino acid since its side chain

cannot be easily oxidized. Our peptide assay provides the opportunity to place different amino acids between donor and acceptor as indicated in Figure 9 (variation of side chain X) in order to answer the question which amino acids can act as relay stations. The functionality of this model system was then tested with trimethoxyphenylalanine as possible relay amino acid.²¹ Its redox potential of 1.30 V is low enough to act as relay station, and its absorption maximum ($\lambda_{\text{max}} = 550$ nm) allows the simultaneous detection of all three different reactive intermediates that are generated during the ET reaction, as shown in Figure 11. The radical cation of the electron acceptor in **7** yields the radical cation of the trimethoxyphenylalanine **8** in the first ET step. A second ET step leads to the formation of tyrosyl radical **9** (Figure 11).

The peptide assay **3** (X = trimethoxyphenylalanine) was irradiated by a laser flash, and the transient absorption spectra were recorded after a defined time delay. The spectrum obtained 40 ns after the laser flash (Figure 12, black curve) is a superposition of the absorption spectra of all three reactive intermediates. It is therefore possible to observe all three generated intermediates at the same time (Figure 12, colored curves). Taking into account their different extinction coefficients, it is furthermore possible to estimate their relative concentrations.

This demonstrates not only the quality of this assay for the investigation of ET processes in peptides, it furthermore provides a direct proof of the action of trimethoxyphenylalanine as relay station in a two-step hopping process, since 10% of its radical cation were detected 40 ns after the laser

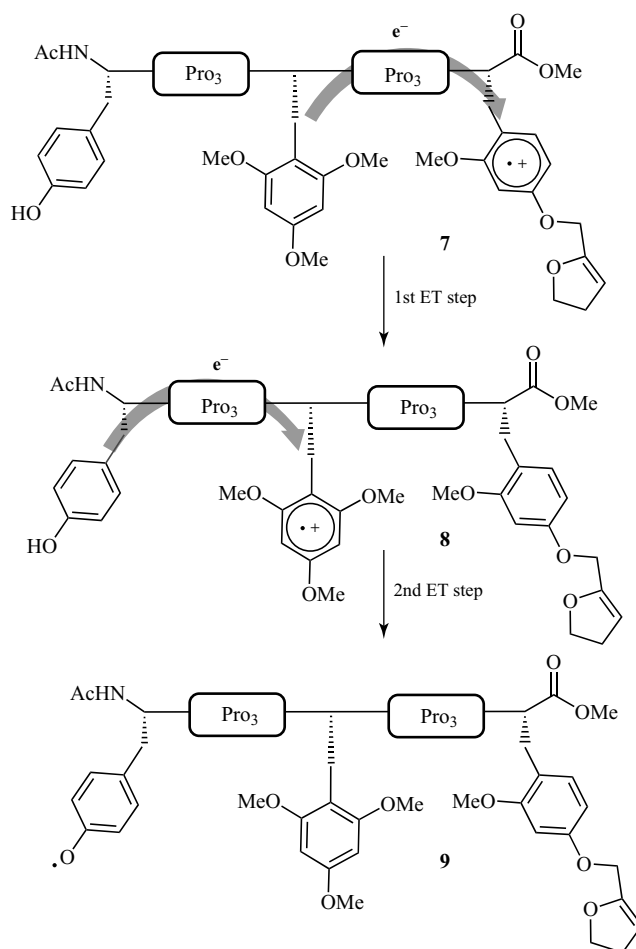


Figure 11 After generating the radical cation **7** by laser flash photolysis (LFP), ET through our model peptide takes place in a two-step hopping mechanism with trimethoxyphenylalanine as relay station (**7** → **8**) and tyrosine as electron donor (**8** → **9**). The deprotonation of tyrosine makes the overall ET reaction irreversible.

flash. Measurements between 40 and 500 ns lead to rate constants for the two hopping steps of $3.3 \times 10^6 \text{ s}^{-1}$ (first step) and $3.0 \times 10^7 \text{ s}^{-1}$ (second step).²⁵ This 10-fold rate difference is another proof for the applicability of this peptide assay, as the first step is thermoneutral but the second step is exothermic by 0.37 V. According to the Marcus theory, this change in the reaction enthalpy should lead to a rate increase (see Section 2).

Comparison with a peptide where the relay amino acid trimethoxyphenylalanine was exchanged by alanine ($X = \text{CH}_3$) demonstrated that in assay **3**, the two-step hopping reaction is at least one order of magnitude faster than single-step ET.²¹ The oxidation potential of alanine is so high that it

cannot act as relay station, and ET occurs in a superexchange one-step reaction over a long distance. By variation of the side chain X in peptide assay **3**, the behavior of other amino acids in ET processes could be studied, as presented below.

4 TRYPTOPHAN, TYROSINE, AND HISTIDINE AS RELAY AMINO ACID

So far, mainly the aromatic amino acids tyrosine (Tyr) and tryptophan (Trp) have been discussed to act as relay amino acids since the oxidation potentials of their side chains (0.93 V for Tyr and

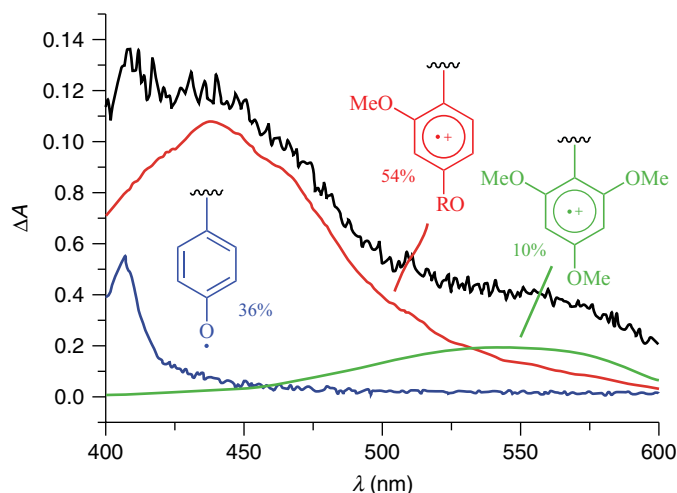


Figure 12 Transient absorption spectrum of peptide assay **3** 40 ns after the laser flash (black line). The absorption spectra of the transient intermediates are shown in blue **9** (tyrosyl radical, $\lambda_{\text{max}} = 410$ nm), green **8** (2,4,6-trimethoxyphenylalanine radical, $\lambda_{\text{max}} = 550$ nm), and red **7** (dialkoxyphenylalanine radical, $\lambda_{\text{max}} = 450$ nm). They are fitted to estimate the amounts of transients generated by laser flash photolysis of **3**.

1.03 V for Trp at pH 7)²⁶ are small enough to become easily involved in naturally occurring redox processes (see **Oxidative Damage to Proteins**).^{6,27,28} The results of ET experiments with several proteins, for instance, photolyase, RNR, or azurin, can best be understood if tryptophan acts as a relay amino acid in the hopping process. Brettel and Byrdin²⁸ have suggested that the activation of the DNA repair enzyme photolyase uses three tryptophan molecules in an ET hopping sequence. Stubbe *et al.*⁶ have studied tryptophan as relay amino acid in the ET process that generates the cysteinyl radical in RNR, which is a vital enzyme for the DNA synthesis (see Section 7). Gray and Winkler²⁷ have explained the fast oxidation of Cu(I) during ET through azurin by electron hopping, assuming tryptophan as a relay amino acid. These examples demonstrate that tryptophan is an appropriate relay amino acid. Experiments with our peptide assay **10** where tryptophan is centered between donor and acceptor show that tryptophan is an efficient electron donor but the next step, which is the electron abstraction from tyrosine, is rather slow.^{29,30} The reason is that under our reaction conditions (pH 7 buffer, $\text{CH}_3\text{CN}/\text{H}_2\text{O} = 3 : 1$ as solvent) the oxidized tryptophan becomes deprotonated, which reduces the oxidation potential of the reactive intermediate (stepping stone). The next ET step has to occur in a proton-coupled electron transfer (PCET)

reaction (Figure 13), a term introduced by Huynh and Meyer in 1981.³¹

In peptide **10**, tryptophan is a poor relay amino acid for the hopping process **10** → **11** → **12** because of the proton transfer from the tryptophan radical cation to the solvent. Nevertheless, tryptophan might act as an effective relay station for ET processes if the proton remains bound to the peptide so that it can be transferred back to the tryptophanyl radical during the next hopping step. The two-step ET process is thus coupled with a proton shuttle. In RNR, whose ET pathway has been discussed in more detail in Section 7, the amino acid Asp²³⁷ being in close contact to Trp⁴⁸ makes this proton shuttle possible (Figure 14).⁶ These two examples already demonstrate the importance of PCET processes, recently reviewed in a special *Chemical Reviews* issue.³²

In the DNA photolyase, three tryptophans are believed to facilitate long-range ET. Before catalysis the enzyme needs to reduce a flavin cofactor ($\text{FADH}^\bullet$) to its active form (FADH^-). This process occurs by photoactivation of $\text{FADH}^\bullet$ and subsequent ET over 15 Å with three highly conserved tryptophan residues (Trp³⁸², Trp³⁵⁹, and Trp³⁰⁶) on the pathway. The different redox potentials of the tryptophanyl radical and its radical cation are important for the efficiency of the photoactivation of this enzyme. At the end of the pathway, a deprotonation

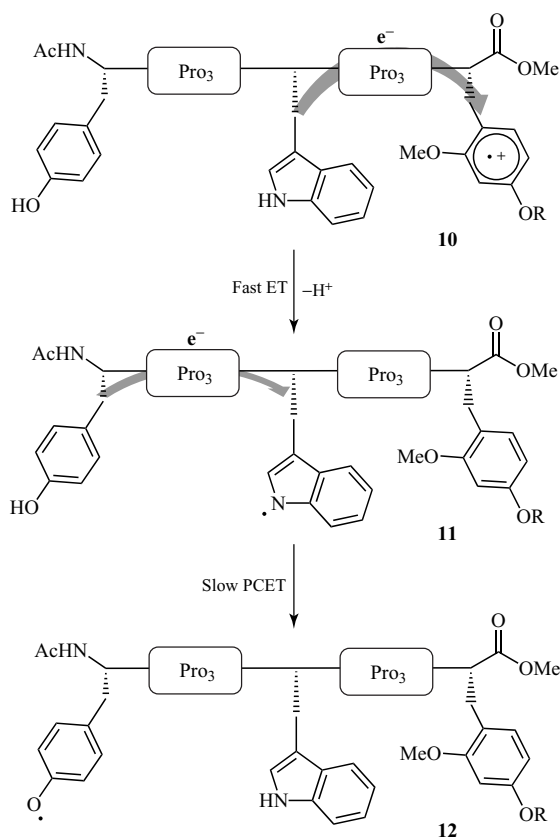


Figure 13 PCET for tryptophan as stepping stone in peptide **10**. After the first ET step, the deprotonation of the oxidized tryptophan reduces its oxidation potential and therefore slows down the second ET step (**11** → **12**), making tryptophan a rather weak relay amino acid in our peptide assay.

step prevents back ET, allowing the catalytic cycle to take place (Figure 15).²⁸ This pathway was first postulated by Aubert *et al.*,³³ but the ET could not be monitored by transient absorption since the ET between identical residues does not change the net absorption. However, polarized light was used in order to construct transient anisotropy spectra due to the different orientation of the tryptophan residues. These studies demonstrate that the ET occurs quickly so that the only oxidized tryptophan residue observed is the terminal one (Trp³⁰⁶). For a mutant in which the terminal Trp was substituted by the redox-inactive phenylalanine, the Trp³⁵⁹ radical was observed, giving strong evidence for the proposed ET pathway.²⁸

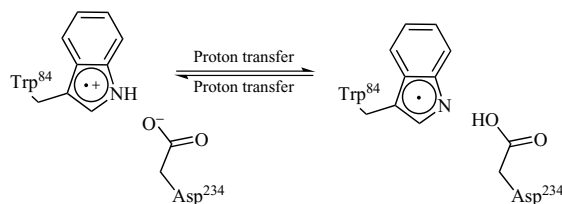


Figure 14 Tryptophan can only act as efficient stepping stone in ET processes if after deprotonation the proton stays in the proximity of the tryptophan residue. In ribonucleotide reductase, the ET is coupled with a proton shuttle between tryptophan (Trp⁴⁸) and aspartic acid (Asp²³⁷) allowing ET with tryptophan as a stepping stone.

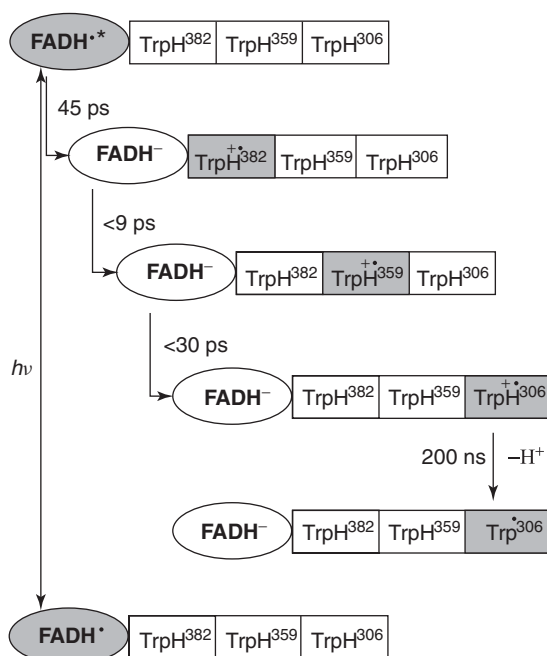
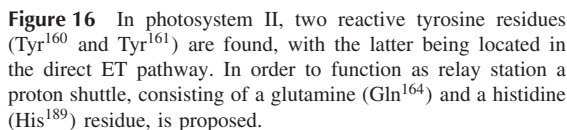


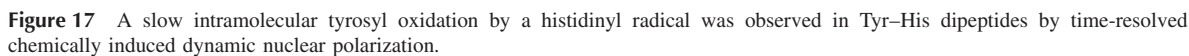
Figure 15 In DNA photolyase, a photoactivated flavine (FADH•*) has to be converted into its active form (FADH⁻). This is achieved by ET over three highly conserved tryptophan residues (Trp³⁸², Trp³⁵⁹, and Trp³⁰⁶) followed by a deprotonation of the last tryptophan to make the overall ET irreversible.

Similar to tryptophan, tyrosine can also act as a relay amino acid in ET reactions. Prominent examples are found in photosystem II (PSII) and in RNR. Since the tyrosine radical cation is a strong acid (pK_a approx. -2), deprotonation occurs during ET, which decreases the oxidation potential of the intermediate and slows down the subsequent hopping step. As discussed above for tryptophan,



The last remaining redox-active aromatic amino acid (histidine) is by its redox potential of 1.17 V,³⁷ also a conceivable relay amino acid. Unfortunately, the UV/Vis spectrum of histidine is very weak, and due to the deprotonation of the histidiny radical cation, the subsequent hopping step is again slowed down. Nevertheless, in our model assay **3** (X = imidazole), the electron donor tyrosine was oxidized with histidine acting as a relay amino acid, but the efficiency of this ET process was rather weak.²⁹ This is in accordance with the low ET rate of intramolecular tyrosine oxidation by the histidiny radical (Figure 17), as observed by Morozova and Yurkovskaya³⁸ for the dipeptides (Tyr-His and His-Tyr) by time-resolved chemically induced dynamic nuclear polarization.

Sulfur is essential for all organisms from microbes to the human being, where sulfur-containing amino acids are known to be part of biological ET processes.³⁹ The cysteinyl radical, for example, is the reactive species formed by an ET cascade as the initial step in all three classes of RNRs (see Section 7).^{6,40} Sulfur is also an essential part of the human defense mechanism against oxidative damage caused by reactive oxygen species (ROS), which are considered to be one of the reasons for aging⁴¹ and neurological disorders such as Alzheimer's or Parkinson's disease (see **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**).^{42,43} Experiments with our model peptide **3** (Figure 9), where we situated the sulfur-containing amino acids between the electron donor and acceptor, showed that both cysteine and methionine can function as real stepping stones in ET reactions.



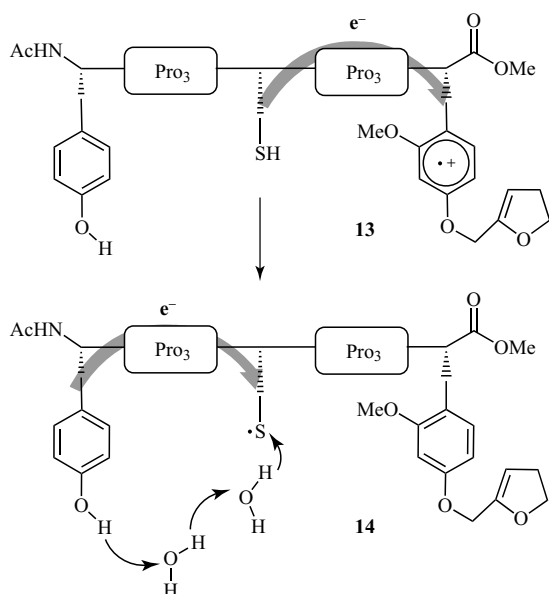


Figure 18 Cysteine was expected to be a poor relay station due to its deprotonation during oxidation, which should slow down the subsequent hopping step. However, water-mediated PCET between the cysteinyl radical and tyrosine enables sufficient ET in peptides.

Cysteine, whose oxidation potential of 0.92 V should be suitable for our system, was nevertheless expected to be a poor relay station due to its deprotonation during oxidation. However, our experiments showed a surprisingly efficient ET transfer with 15% of tyrosyl radical having been formed already after 40 ns. We have explained this by a water-mediated PCET as illustrated in Figure 18.^{29,30} In the first step, an electron is transferred from cysteine to the dimethoxyphenylalanine radical cation (**13** → **14**) followed by deprotonation yielding the thiyl radical. In a subsequent reaction, this thiyl radical is reduced by tyrosine in a water-mediated PCET reaction. This mechanism is supported by a deuterium isotope effect of about 2. In contrast to tryptophan or histidine, where the water-mediated PCET was not very effective in our assay (see Section 4), water could enable proton shuttling with cysteine as a relay amino acid because cysteine is more hydrophilic than the aromatic side chains, and there are more reaction pathways for a successful proton transfer than that in the heterocyclic amino acids.

Water molecules as mediators are also discussed in natural systems. Two prominent examples are

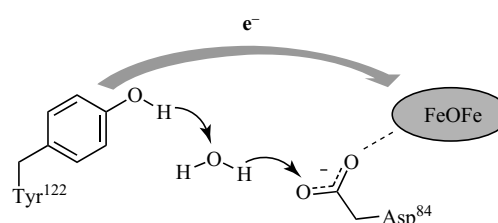


Figure 19 Water molecules play an important role in ET processes in natural systems. In ribonucleotide reductase, an electron is transferred from tyrosine (Tyr¹²²) to a diferric cofactor. Simultaneously, a water-mediated proton transfer has to take place as well.

RNR and cytochrome *P450*. In RNR, the formation of the tyrosyl radical, which induces the ET pathway (see Section 7), is a process during which an electron and a proton have to be transferred from tyrosine to a diferric cofactor. Quantum chemical calculations suggest a bridging water molecule between the diiron complex and tyrosine since the computed barrier without the water molecule is far too high.⁴⁴ A possible transition state proposed by Siegbahn is shown in Figure 19, which allows both proton and electron transfer. This leads to a computed barrier of 10 kcal mol⁻¹ for the tyrosyl radical formation, proposing a rapid transfer in the order of microseconds.⁴⁵

The biosynthesis of staurosporine, a natural alkaloid with a strong inhibitory activity on protein kinase or DNA topoisomerase I, involves the aryl–aryl coupling of two chromopyrrolic acids (CPAs → K252c), which is catalyzed by the cytochrome *P450* enzyme StaP (Figure 20a). Nagano and coworkers suggested a water-mediated PCET process.^{46,47} The proton transfer during oxidation of CPA shown in Figure 20b is made possible via the hydrogen-bonding network involving two molecules of water and a histidine residue (His²⁵⁰). Also, the aromatization steps following the C–C coupling are mediated by these two water molecules. In addition, the study of a mutant in which the histidine residue in the hydrogen bonding network is substituted by a phenylalanine reveals that the water diad seems to be the minimal requisite for enzymatic activity. The water molecules can therefore be regarded as biological catalysts.

Even more surprising than the proof of cysteine being a relay amino acid are our results^{29,30} indicating that methionine can also function as a stepping stone in ET processes, although the high redox

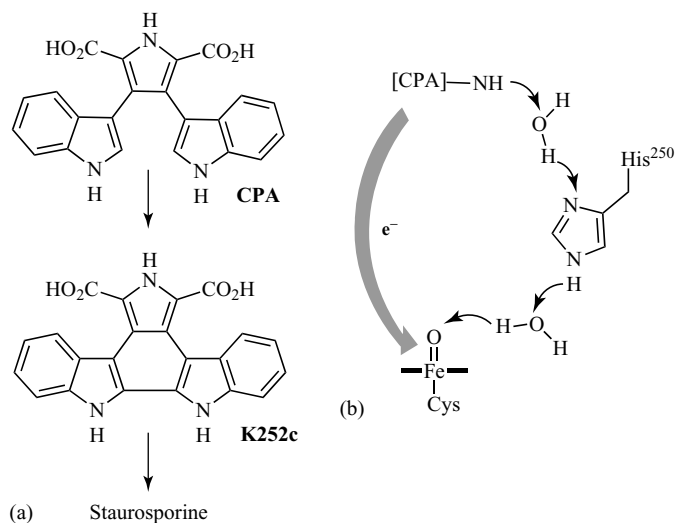


Figure 20 PCET during the biosynthesis of staurosporine. (a) The biosynthesis of staurosporine includes an aryl–aryl coupling reaction of two chromopyrrolic acids (CPAs) yielding the indolocarbazole scaffold (K252c). (b) The activation of CPA by PCET involves two molecules of water.

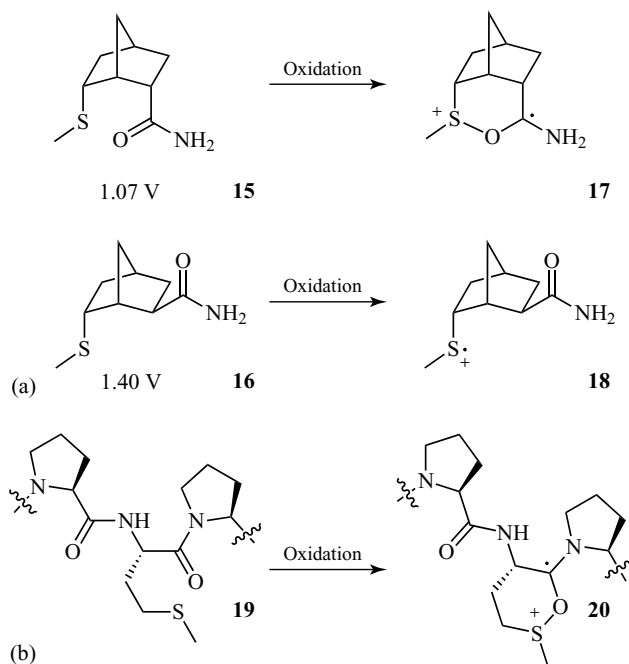


Figure 21 Neighboring amide participation lowers the redox potential of thioethers due to the formation of a stabilized radical. (a) The redox potential of the norbornene derivatives **15** and **16** differs by 0.33 V since for the endo derivative **15**, the formation of a captodative stabilized radical cation **17** is possible. For the exo compound **16**, the resulting radical cation **18** cannot be stabilized by a neighboring amide function, resulting in a higher redox potential. (b) Neighbor group participation **20** is also possible in our peptide assay, as shown for the fragment **19**, reducing the redox potential of methionine which makes it a stepping stone in ET reactions.

potential of thioethers (e.g., dimethylsulfide: 1.66 V vs normal hydrogen electrode)⁴⁸ should make the first ET step endergonic. This result can be explained by a neighboring group effect of the adjacent amide function that lowers the redox potential of methionine so that it can act as a stepping stone in our assay. The influence of neighboring amides on the redox potential has, for example, been demonstrated by the norbornene systems **15** and **16** (Figure 21a), in which the amide group at endo position (**15**) reduces the redox potential by 0.33 V compared to **16**, where the amide function is situated at the exo position. The effect is explained by the formation of a captodative stabilized radical cation (**17**), which cannot be generated during the oxidation of the exo compound (**16** → **18**) (see **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**).^{49,50} The formation of a similar stabilized radical cation (**20**) should also be possible in the case of our model peptide (**19**) (Figure 21b). An analog situation is also discussed for other peptides making methionine a target of oxidative stress,⁵¹ since it is one of the most easily oxidized residues by ROS (reactive oxygen species).⁵² For methionine, the damage due to ROS is reversible as the methionine sulfoxide formed can be enzymatically reversed to methionine by methionine sulfoxide reductase.⁵³ Therefore, methionine residues have been considered as protecting system against ROS.⁵⁴ In contrast to the oxidation to methionine sulfoxide, the one-electron oxidation forming the methionine radical cation is discussed as an important parameter in the pathogenesis of Alzheimer's disease. It was found that Met³⁵ in the β -amyloid peptide is critical for generating oxidative stress by initiating metal ion-dependent production of ROS.^{51,55} Molecular modeling results predict a neighbor group participation of isoleucine (Ile³¹) for this Met³⁵ residue.⁵⁶ Recently, a sulfimide bond, the nitrogen analog of a sulfoxide, was identified in collagen IV.⁵⁷ This bond formation can be explained by an oxidative cross-linking between methionine and an adjoining hydroxylysine.

Besides the two naturally occurring sulfur-containing amino acids, it was also possible to study ET in our peptide assay **3** with a cystine model containing the characteristic disulfide bridge (X = CH₂SSCH₃). The cystine model turned out to be an effective stepping stone in ET reactions as well, as it was expected from the redox potentials of cystine (1.25 V).⁵⁸

These results show that in addition to the redox-active aromatic amino acids tryptophan, tyrosine, and histidine, sulfur-containing aliphatic amino acids should also be taken into account as possible relay stations in ET reactions when ET in proteins/enzymes is discussed.

6 INFLUENCES OF THE PEPTIDE BACKBONE

6.1 Dipole Moment

Isied and coworkers have recently published theoretical studies on the influence of the peptide conformation on ET rates,^{59,60} predicting that the peptide conformation strongly influences the electronic coupling matrix element H_{AB} of (1). They calculated H_{AB} -values for 576 different peptide conformations and used these values in order to create a Ramachandran-like plot. It could be shown that the largest H_{AB} -values are found in H-bonded helical peptide conformations, including the α -, γ -, and 3_{10} -helices. In addition, the distances between donor and acceptor turned out not to be the only critical parameter influencing ET rates, but specific torsional peptide angles play a major role as well. With their calculations, the authors concluded that rate differences as high as eight orders of magnitude can be achieved for peptides with the same primary but different secondary structures. Along with different conformations comes a change in the overall dipole moment. In their theoretical studies, Isied and coworkers have also described an influence of the dipole moment on ET rates. Therefore, a rate difference between opposing directions of the ET should be observed if the peptide has an overall dipole moment along its backbone. Depending on the solvent, they predicted ratios of ET rates in opposing directions of approximately 8.5 for the α -helix and 1.1 for a PPII-helix.

First experiments investigating the influence of dipole moments on ET rates were carried out with α -helical peptides by Fox *et al.*^{61,62} The α -helix is a right-handed helix stabilized by hydrogen bonds between the amino acids i and $i + 4$.⁶³ With all the carbonyl groups pointing in the direction of the C-terminus, the α -helix shows a large overall dipole moment with its negative end at the C-terminus and its positive end at the

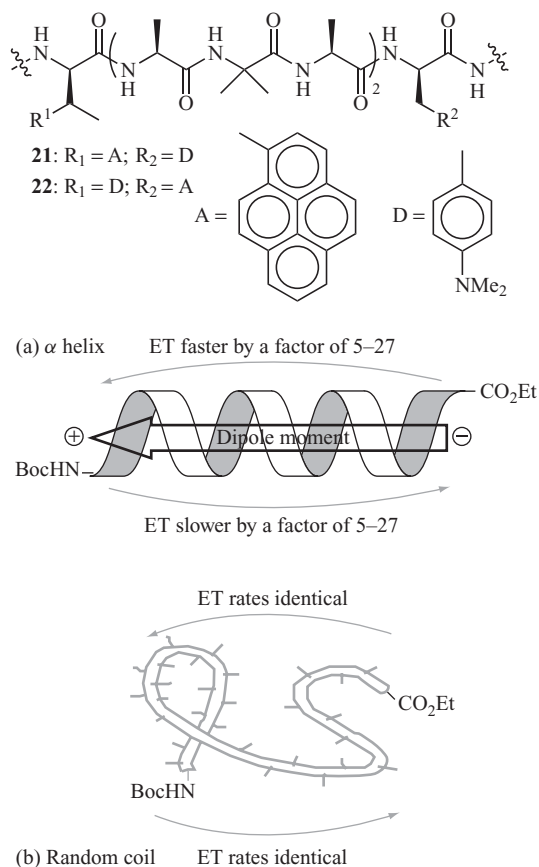


Figure 22 Peptides **21** and **22** used by Fox *et al.* show the influence of the dipole moment on ET rates. (a) If the peptides exist in a α -helical conformation, there is a dependence of the ET rates on the ET direction caused by the overall dipole moment. (b) If the α -helix is denaturized and the peptide adopts a random coil conformation, no difference in the ET rates in dependence of the ET direction was observed.

N-terminus, each amino acid contributing approximately 5.0 D.⁵⁹ Fox *et al.* synthesized α -helical peptides consisting of 14 amino acids with Ala-Aib (Aib = α -aminoisobutyric acid) repeating units and an electron acceptor/electron donor pair within a distance of 10 Å (Figure 22). In laser experiments, they studied ET in both directions along the peptide backbone and reported that depending on the solvent, the rates in the direction C $\rightarrow$ N (**21**) were 5–27 times faster than those in the opposite direction (**22**). In order to investigate whether this effect is really due to the dipole moment, the helix conformations of these peptides were denaturized. With the resulting random coils, the ET measurements

were repeated and were found to be identical in both directions along the denaturized peptide backbone. These results show the major influence a conformation and its overall dipole moment can have on ET rates.

Similar results have also been reported by several groups for α -helical peptides, which are self-assembled on gold surfaces. For instance, Sek *et al.*⁶⁴ used polyalanine to form self-assembled monolayers (SAMs) on gold surfaces and found that ET from the C- to the N-terminus was faster by a factor of 1.4 than that in the opposite direction. Kimura and coworkers synthesized α -helices consisting of Ala-Aib repeating units to form SAMs on gold surfaces, with which they could also show that the dipole moment has a major influence on the ET.^{65–67}

Experiments with 3_{10} -helical peptides were carried out by Gatto *et al.*⁶⁸ These helices are right-handed as well, but the alignment of the carbonyl groups is not as perfect as that of α -helices, resulting in a lower overall dipole moment (4.6 D per residue). In this study, oligopeptides with α -disubstituted amino acids, pyrene as electron donor, and azulene as electron acceptor were synthesized and the ET rates in opposite directions through the peptides were measured, resulting in a ratio of approximately 1.7. This factor is significantly lower than the one found by Fox *et al.* for α -helices, but although the reaction conditions are not directly comparable, the authors suggest that this is due to the lower overall dipole moment of the 3_{10} -helix. Similar effects were observed with α - and 3_{10} -helices, self-assembled on gold surfaces.⁶⁹

We investigated the influence of the dipole moment on ET reactions through PPII-helical peptides.^{25,29} In a PPII-helix, the amide bonds are in trans-conformation, resulting in a left-handed helix, which is not stabilized by hydrogen bonds and which has a weak dipole moment with its negative end at the N-terminus and the positive end at the C-terminus, with each amino acid contributing approximately 1.5 D.^{23,59} In order to investigate the influence of the dipole moment on ET through PPII-helices, we used our model peptide **7** and compared its ET rates with those of assay **23**, where ET occurs in the opposite direction (Figure 23). It was observed that ET from N- to C-terminus is 2.5 times faster than that in the opposite direction, indicating that the dipole moments in PPII and α -helices are opposite to each other.²⁵

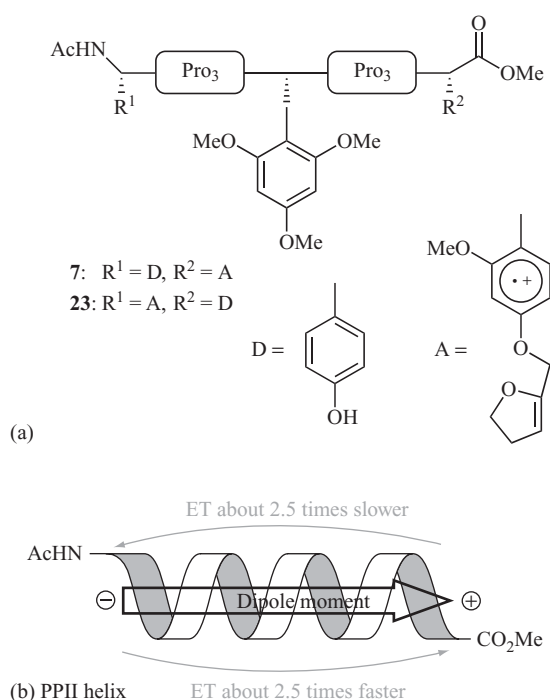


Figure 23 Influence of the dipole moment in PPII-helical peptides. (a) Our model peptide was used to investigate the influence of the dipole moment on intramolecular ET, by comparing the ET rates in opposing directions. (b) In a PPII-helix, the overall dipole moment has its negative end at the N-terminus and its positive end at the C-terminus. We measured a difference in ET rates of a factor of about 2.5 for the ET reactions in opposing directions.

6.2 Charges

Because dipole moments influence ET rates in peptides, charges (e.g., ammonium or carboxylate ions) should play an even larger role. However, to our knowledge, no other studies than ours have been reported so far.²⁵ The same type of model peptides (**7a,b** and **23a,b**) that were already employed to determine the influence of the dipole moment (see Section 6.1) are now used to investigate the charge effect on the ET rates, with the only difference that the N-termini are protonated instead of acetylated. The rates of the charged peptides were then compared with those of the uncharged peptides (Figure 24).

From experiments with peptide **7** (ET from N $\rightarrow$ C, Figure 24a) it could be concluded that the charge

only influenced the neighboring ET rate, which was slowed down by a factor of four. The ET reaction between the relay and the C-terminal amino acid, which is the distal hopping step, was left rather unaffected (within the experimental error). For peptide **23** (ET in the direction C $\rightarrow$ N, Figure 24b), a rate acceleration by approximately one order of magnitude was found. This influence of the ammonium ion on the adjacent hopping step can be explained by a change in the Coulomb repulsion. In the neutral peptide **23a**, the Coulomb energy remains unchanged as the charge is shifted. Contrary to this, in peptide **23b** (Figure 24b), two positive charges are in close proximity before the ET reaction and far from each other after the hopping step. If one assumes the distance between the charges before the ET step to be 3 Å (determined by calculations), a Coulomb repulsion of about 3.0 kcal mol⁻¹ can be calculated, making the ET in the charged peptide more exergonic than the analogous ET step in the neutral peptide.²⁵ By applying the Marcus theory for the case that $|\Delta G^0/\lambda|$ is small, which is the case in our system since the redox potentials of the trimethoxyphenylalanine and the dialkoxyphenyl side chain are nearly identical, a change in the Coulomb energy of approximately 3.0 kcal mol⁻¹ corresponds to an activation free energy difference of about 1.5 kcal mol⁻¹. Employing the Gibbs equation, one can calculate that this difference in activation free energy leads to a rate difference by a factor of about 10 (at 25 °C), which is in excellent agreement with our measurement.²⁵ These results clearly show that charges significantly affect ET rates in peptides. With the experiments described above, we only investigated the influence of a positive charge. However, preliminary experiments with negatively charged peptides (carboxylate instead of methyl ester) as well as zwitterionic species showed that negative charges also affect ET rates. A possible future investigation in this field is to determine the influence of charged side chains since there are five natural amino acids with acidic/basic side chains (lysine, arginine, histidine, aspartic acid, and glutamic acid), where charges could be easily introduced by controlling the pH. Another interesting topic would be to find out whether it is possible to switch the direction of ET reactions. This question might be addressed with our model system by installing two

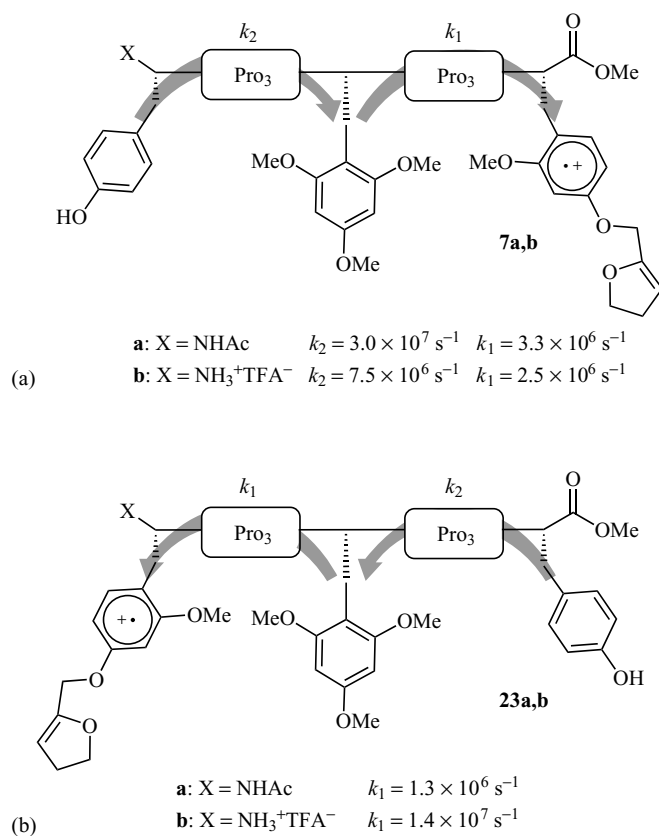


Figure 24 Influence of charges on intramolecular ET rates through our model peptides. (a) Comparison of the ET rates for a protected, uncharged (**7a**) and an unprotected, charged (**7b**) peptide with ET proceeding from the N- to the C-terminus. (b) Comparison of the ET rates for a protected, uncharged (**23a**) and an unprotected, charged (**23b**) peptide with ET proceeding from the C- to the N-terminus. In this case, only the rate constants k_1 for the first hopping step could be measured. $\text{TFA}^- = \text{CF}_3\text{COO}^-$.

aromatic amino acids with different redox potentials on both termini and the injection system centered in the middle of the peptide. An example for this approach is shown in Figure 25. By having tyrosine at the N-terminus, trimethoxyphenylalanine at the C-terminus and the radical cation between one expects tyrosine to be the electron donor in the neutral peptide **24a** due to its lower redox potential compared to trimethoxyphenylalanine. By introducing a positive charge at the N-terminus and/or a negative charge at the C-terminus (**24b**), it would be interesting to see whether this leads to trimethoxyphenylalanine becoming the electron donor, thereby inverting the ET direction.

Experiments of this kind might give an insight into whether nature uses basic and/or acidic amino acids to control ET rates or even ET directions in proteins.

6.3 Amides as Possible Stepping Stones

Recently, it has been suggested that amide bonds might act as stepping stones in long-range ET through peptides. Already in 1996, it was reported that excess ET from a nonbonding carboxylate orbital to a π^* orbital of the amide group was observed for dipeptides and that this transition might play an important role in ET through peptide backbones.⁷⁰ In 2004, Isied *et al.* have published work on Ru(II)/Ru(III) containing peptide complexes (**25**), where they varied the number of prolines (n) between 0 and 9, therefore enlarging the distance between donor and acceptor from 8.7 to 32 Å (Figure 26).⁷¹ With $n = 0$ –4, they could observe a strong distance dependence, which is consistent with a superexchange mechanism,

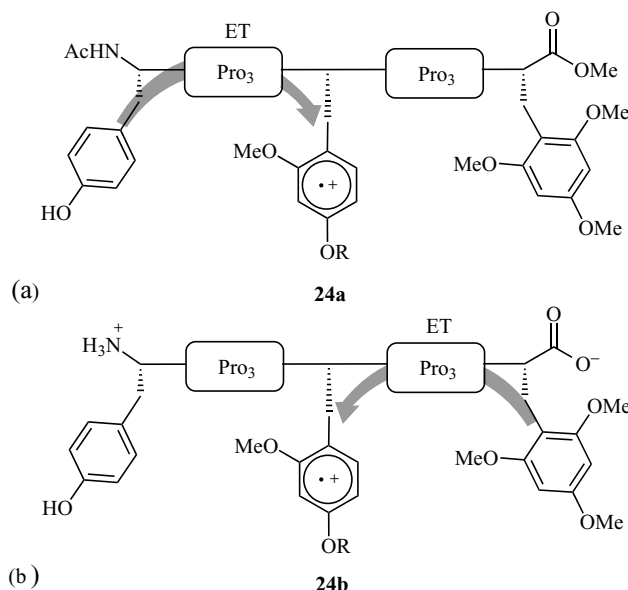


Figure 25 Switching the ET direction in peptides with a radical cation surrounded by different redox-active amino acids. (a) In the neutral peptide **24a**, the ET should proceed in the direction N $\rightarrow$ C due to the different redox potentials of tyrosine and trimethoxyphenylalanine. (b) In the zwitterionic species **24b**, a change in the ET direction should be observed due to the effects of charges on ET rates.

but for longer peptide bridges ($n = 5-9$), only a weak distance dependence was found that could be explained by a switch from the superexchange to the hopping mechanism.

For the measurements of fast ET rates, photochemical, and for the determination of slow ET rates, radiolytical methods were used. Since the reaction enthalpies ΔG^0 and the reorganization energies λ are different under these two different reaction conditions, the observed ET rates had to be corrected according to the Marcus theory.⁷¹ It should be noted that in these experiments, excess ET occurs. Under these reductive conditions, the amide groups can act as stepping stones if the distance between electron donor and acceptor is so long that the superexchange becomes very slow.

Kimura and coworkers used peptides with an Ala-Aib repeating unit for their electrochemical investigations of ET through α -helices.^{72,73} They synthesized 8-, 16-, 32-, 48-, and 64-mer peptides, ranging from 30 to 110 Å in length, self-assembled them on gold surfaces, and studied ET through the helices. Since they found only a weak distance dependence of ET rates with elongation of the peptide chain, they proposed a hopping mechanism, which uses the amide groups of the peptide

backbone as stepping stones. They suggested that the electron is first transferred from the N-terminal amide to the gold surface, generating the amide radical cation. The electron hole then hops among the amide groups to the C-terminal end, where the amide radical cation is reduced by the electron donor ferrocene (Figure 27). The oxidation potential of the amide bonds was measured to be 0.93 V versus Ag/AgCl in these α -helical peptides, whereas the oxidation potential for isolated peptide bonds⁷⁴ is known to be 1.95–2.10 V versus Ag/AgCl. This unexpected low value was explained either by stabilization of the amide radical cation by neighboring amide groups, by delocalization over a few amide groups, or by three-electron bond formation.

The suggestion that amide groups, when situated in an α -helix, can act as relay stations for ET under oxidative conditions is also supported by calculations carried out by Cukier and coworkers, who published *ab initio* calculations showing that the C-terminus of an α -helix could act as a relay element.⁷⁵ They used α -helical polyglycines and calculated vertical ionization potentials (IP_vs) in dependence of the helix length, and compared their findings with the IPs of known relay amino acids.

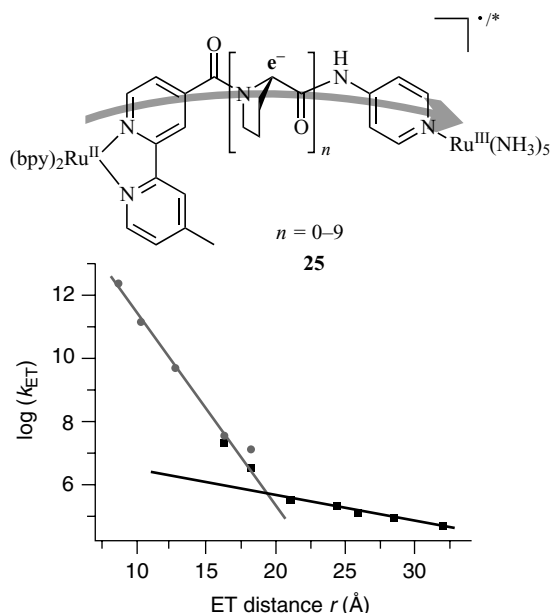


Figure 26 Isied *et al.* found a change in the mechanism of ET processes through peptides of different lengths (25). The fast rates were determined by photochemical (circles) and the slow rates by radiolytical methods (squares). The observed rates were corrected according to the Marcus theory. For short distances (r) superexchange ET and for long distances hopping using the amide bonds as stepping stones occur. Bpy = 4-carboxyl-4'-methyl-2,2'-bipyridine.

For Gly_n with $n = 4-15$, they found IP_v values ranging from 8.13 to 6.74 eV, and the inspection of spin densities showed that the electron hole is predominantly located in the region of the

C-terminus. The IP of tryptophan (a known relay amino acid, see Section 4), is 7.49 eV, implying that on a certain helix length ($n > 9$), the C-terminal amide could be a more preferential stepping stone than tryptophan. In order to further investigate this hypothesis, Cukier and coworkers replaced the second N-terminal glycine by tryptophan and calculated the spin densities in dependence of the helix length. For shorter helices ($n \leq 5$), the hole preferred the tryptophan, whereas for longer helices ($n > 8$), the hole was always found at the C-terminal end. In the case of medium-length sequences ($n = 6-8$), no clear preference could be observed. These calculations clearly suggest that α -helical peptides may use their C-terminal amino acid as a relay station even in the absence of an aromatic or sulfur-containing side chain, and they point out the importance of considering peptide bonds as possible relay stations. Schlag *et al.*^{76,77} concluded from their investigations on electron hole migration across polypeptide chains that ET takes place via a hopping mechanism. However, they stress the importance of the peptide conformation in these hopping processes. Quantum mechanical calculations have shown that the hopping of the charge is strongly connected to the alignment of the CO groups. Therefore, in their opinion, efficient ET only takes place in very few conformations, which are not the ones typically found for peptides. Since mechanical rotation of the peptide chain along the Ramachandran plot proceeds very fast, Schlag *et al.* suggested that the first step of the ET process are the dihedral motions between neighboring amino acids followed by the hopping reaction in a second step.

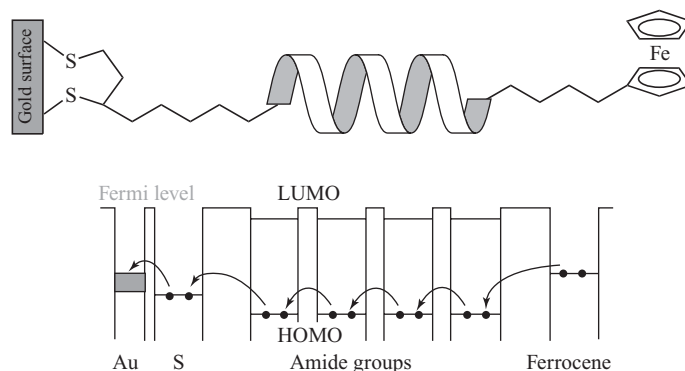


Figure 27 Kimura and coworkers found only a weak distance dependence on ET processes through α -helical peptides with ferrocene as electron donor, which are self-assembled on gold. They explain this phenomenon by proposing a hopping mechanism, which uses the amide bonds as stepping stones.

Despite these strong indications that amides might act as relay stations in certain peptides, this suggestion is still controversially discussed in the literature, and several publications stating the opposite opinion can be found. For instance, Polo *et al.*⁷⁸ carried out experiments with poly-Aib structures, using either *p*-cyanobenzamide or phthalimide radical anions as electron donor and a peroxide as electron acceptor. They synthesized peptides with different numbers of Aib units, confirmed that all these peptides form 3₁₀-helices, and carried out electrochemical investigations in order to answer the question whether the ET proceeds via hopping or superexchange. They concluded that in their case, ET takes place via a superexchange mechanism and that the hydrogen bonds of a 3₁₀-helix play an important role in the ET reaction. Dey *et al.*⁷⁹ addressed the question by carrying out ET measurements with peptide films on gold surfaces. They prepared a series of collagen mimics with proline–hydroxyproline–glycine repeating units, a ferrocene at the N-terminus and a thiol-functionalized cysteine at the C-terminus. The peptides, which show a strong tendency to form collagen-like triple helices, were then immobilized on gold surfaces and electrochemical measurements were carried out. In their experiments, a weak distance dependence of the ET was observed, which is usually taken as an indication that ET proceeds via a hopping mechanism. However, the authors interpret this observation as result of a tunneling with a low β -value due to increased coupling through hydrogen bonds. They further argue that it has been reported that ET through H-bonded helical peptide films is strongly influenced by the dynamics of the peptide, and they suggested that a dynamically modulated tunneling mechanism takes place in their collagen mimics. The role of amides as stepping stones in ET processes through peptides is therefore still a highly discussed topic with a lot of ongoing research in various groups (see **Oxidative Damage to Proteins**).

7 THE RNR AS PARADIGM FOR ET IN BIOLOGICAL SYSTEMS

The enzyme RNR transforms nucleotides to deoxyribonucleotides and therefore serves as a link between the RNA and DNA world (see also Figure 3).⁶ It exists in three different forms, all of them using a thiyl radical of a cysteine side chain

for the activation of the ribose moiety. The major difference between them is the way this radical is generated leading to the division in three different classes according to this initialization step.⁸⁰ We will discuss class I RNRs since this enzyme class has become the paradigm for long-range ET in biological systems.⁶ The active cysteine radical in the α^2 -subunit is generated from cysteine (Cys⁴³⁹) that donates an electron to a tyrosyl radical (Tyr¹²²) in the β^2 -subunit over 35 Å. On our human scale, an average-sized human being of 1.70 m height would have to run about 1050 km or 25 marathons in order to achieve the same performance as a 4.6×10^{-15} m small electron that travels over 35 Å. This distance corresponds to a timescale of hours to years for the ET assuming single-step tunneling. Since a single turnover of the RNR only needs about 200 ms, the ET between the two amino acids must be at least that fast.⁸¹ An electron relay mechanism was first proposed by Uhlin and Eklund,⁸² which is based on a docking model of the two subunits as well as the conservation of amino acid residues in the primary sequence alignment, leading to a distance of about 35 Å between the donor and acceptor. This long distance between the two residues is further supported by pulsed electron–electron double resonance spectroscopy.⁸³ A putative PCET pathway for the electron transport from the Tyr¹²² radical to Cys⁴³⁹ is shown in Figure 28, which is based on results of Stubbe *et al.*^{6,84} on site-directed mutagenesis, the incorporation of unnatural amino acids and spectroscopic examination of transient radical intermediates.

The electron hopping is initiated by the oxidation of Tyr¹²² by the diferric cofactor. Its assembly requires Fe(II) binding and the reduction of O₂ to H₂O and is suspected to be endorsed by Trp⁴⁸. Moreover, this tryptophan residue is a key player in the ET process since its replacement by a nonredox active amino acid led to a breakdown of the ET resulting in inactive mutants. Asp²³⁷ and His¹¹⁸, which are also conserved in all species, are hydrogen bonded to Trp⁴⁸. Asp²³⁷ is suspected to play a role as proton shuttle to Trp⁴⁸ (Figure 14). This hypothesis was strengthened by site-directed mutagenesis experiments, which showed that the replacement with another acidic side chain (glutamic acid) is tolerated, while the replacement with alanine or asparagine knocks out catalytic activity.⁸⁴ Tyr³⁵⁶ has been postulated to modulate ET between the two

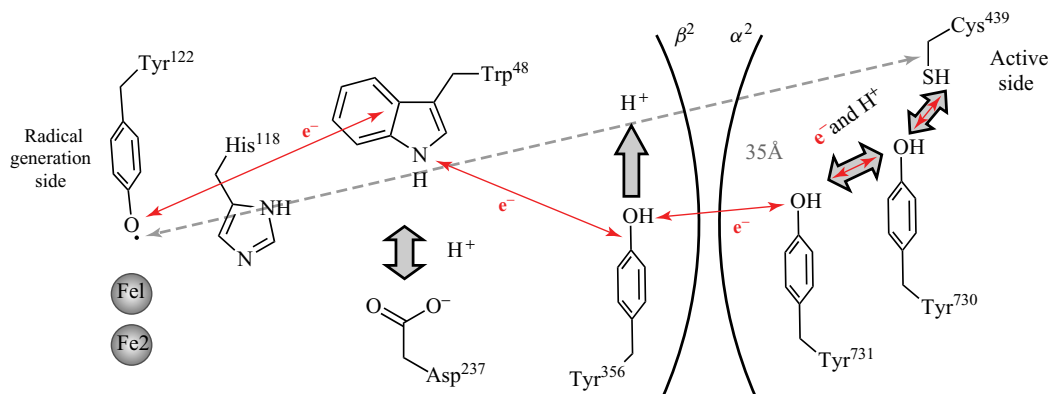


Figure 28 ET pathway and proton shuttles in ribonucleotide reductases class Ia. The generation of the active cysteine radical, which is responsible for the catalytic activity of this enzyme, is achieved by donation of an electron from Cys⁴³⁹ to a tyrosine radical (Tyr¹²²) over a distance of 35 Å. Along this pathway, the electron hops over several stepping stones, including a number of tyrosines as well as a tryptophan.

subunits of the enzyme, more precisely, between Trp⁴⁸ and Tyr⁷³¹. The exact location of this stepping stone is not specified since it has not yet been located in crystal structures. Nevertheless, its conservation together with experimental evidence based on mutagenesis studies and the incorporation of unnatural amino acids emphasize the role of Tyr³⁵⁶ as part of the ET pathway. It is suggested that on oxidation, the proton of Tyr³⁵⁶ is transferred directly

into the bulk solution. This is not the case for the last part of the pathway, from Tyr⁷³¹ over Tyr⁷³⁰ to Cys⁴³⁹, for which theoretical calculations⁴⁵ as well as mutations with redox-inactive phenylalanine predict a proton-dependent ET or a direct H-transfer. Furthermore, experiments with 3-aminotyrosine that served as thermodynamic trap showed the generation of the 3-aminotyrosine radical by X-band electron paramagnetic resonance spectroscopy.^{85,86}

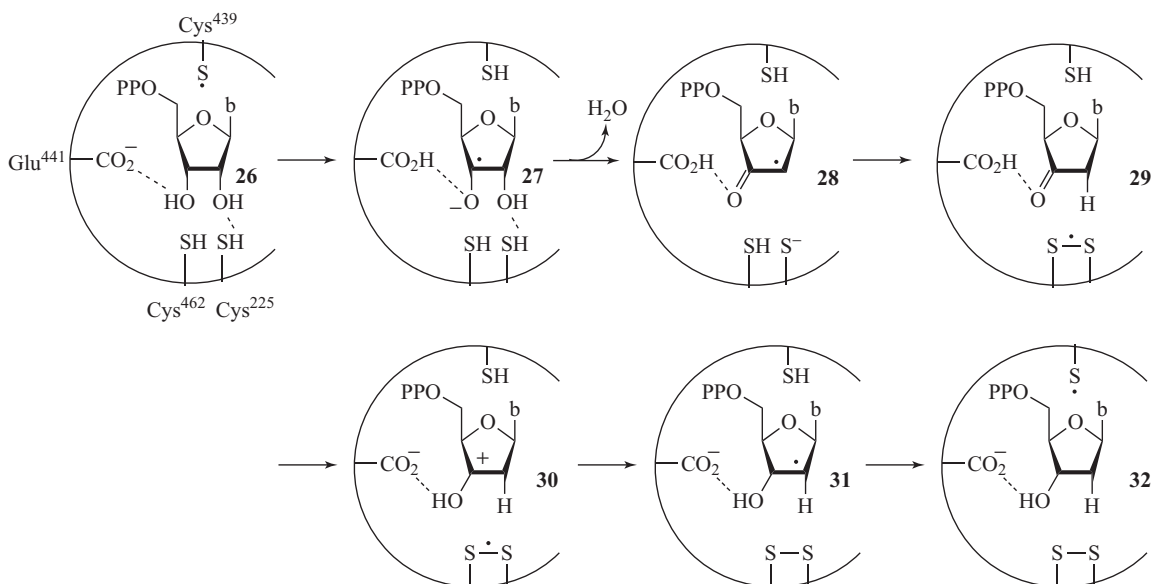


Figure 29 Schematic representation of the proposed mechanism for the transformation of ribonucleotides to deoxyribonucleotides in ribonucleotide reductases (26 → 32).

With the generation of the thiyl radical, the catalytic turnover for the transformation of ribonucleotides to deoxyribonucleotides is initiated at the active site.^{6,80} Besides the initiating Cys⁴³⁹, two additional cysteine residues (Cys⁴⁶² and Cys²²⁵) as well as a glutamic acid residue (Glu⁴⁴¹) are involved in catalysis (Figure 29). The Cys⁴³⁹ radical abstracts a hydrogen atom from the 3'-carbon of the ribose moiety **26** forming a substrate radical **27** in a general base catalyzed reaction.⁸⁷ Responsible for the general base catalysis is the glutamate residue, which is perfectly positioned for the deprotonation of the 3'-hydroxy group. Cleavage of the β -C–O bond in **27** yields radical **28** in a fast reaction step. Subsequent hydrogen abstraction from Cys⁴⁶² leads to ketone **29** and a disulfide radical anion. In the following subsequent reduction of **29** over its protonated form **30** to the α -hydroxyl radical **31**, glutamic acid acts as general acid catalyst, making the reduction of the carbonyl group by the disulfide radical anion thermodynamically feasible.⁸⁷ The final step then yields the desired deoxyribonucleotide **32** together with the regenerated Cys⁴³⁹ radical.

Recently, it was discovered that class Ib RNRs contain an active dimanganese(III)-tyrosine radical cofactor instead of the diferric-tyrosine radical cofactor present in class Ia RNRs.^{88,89} Both types have identical metal-binding sites. Since Mn(II) is bound more tightly than Fe(II) but cannot be converted to an active tyrosine radical containing form, the question arises, how correct metallation of metalloenzymes is ensured by the cell. The answer to this question is a topic of current discussion and experimental tests, and further elucidation are needed in order to understand the metal selectivity of class Ia and Ib RNRs *in vivo*.⁹⁰

8 ELECTRONIC MATERIALS

With the goal of minimizing the size of electronic devices, several research groups now focus on organic molecules to substitute the classical semiconductors (Si, Ge, GaAs, etc.).⁹¹ The most important advantages of organic molecules over these classical semiconductors for applications ranging from biomedical equipment and sensors to TV systems are the lower current and power operation, the cheaper and simpler fabrication as well as their mechanical flexibility. Therefore, in recent years,

a number of research groups started working on biomolecules (DNA and peptides/proteins) as electronic devices, investigating ET through single molecules rather than the bulk conduction of organic polymers, where the common theories focus on charge migration between neighboring polymers. The aim of this research is not directed toward the development of more flexible TV screens, but the main focus lies in the field of medicine (e.g., biosensors), of molecular electronics and nano-electromechanical systems (NEMS) as well as in the search for conductive nanowires.

In 2005, Yemini *et al.*⁹² developed peptide nanotube-based electrodes, which could be successfully employed as amperometric biosensors. It was found earlier that the diphenylalanine core of the β -amyloid polypeptide can self-assemble to form tubular structures. These self-assembled peptides were then immobilized on gold electrodes, and the electrochemical properties were investigated with regard to the detection of NADH and glucose. The analysis of NADH provides the opportunity to analyze ethanol, whereas the glucose detection is needed for the diagnosis of diabetes as well as in food industry. It could be shown by amperometric response measurements that this system is indeed a promising biosensor.

Rinaldi *et al.*⁹³ used the electron-transfer protein azurin in order to produce biomolecular rectifiers. On a Si/SiO₂ substrate, two gold nanoelectrodes were interconnected, with a gap of 50–100 nm that contained a monolayer of immobilized copper-containing azurins. The resulting rectifiers were then tested by measuring *I*–*V* (current–voltage) curves and were found to operate at room temperature and in the presence of air and to exhibit a rectification ratio of 500 at 10 V. The replacement of the copper ions by zinc as well as devices without any metal ions showed that copper seems to be responsible for the ET, as a drop in the current flux was detected in the zinc-containing proteins and no conductance could be found in the metal-free device. Since the authors also observed a sensitivity of this rectifier to the atmosphere composition, they suggest that its suitability as a biosensor might also be exploited.

In 2004, Kimura and coworkers developed a molecular photodiode, which can switch the photocurrent direction (Figure 30).⁶⁵ They synthesized α -helical peptides with L- or D-leucine/Aib repeating

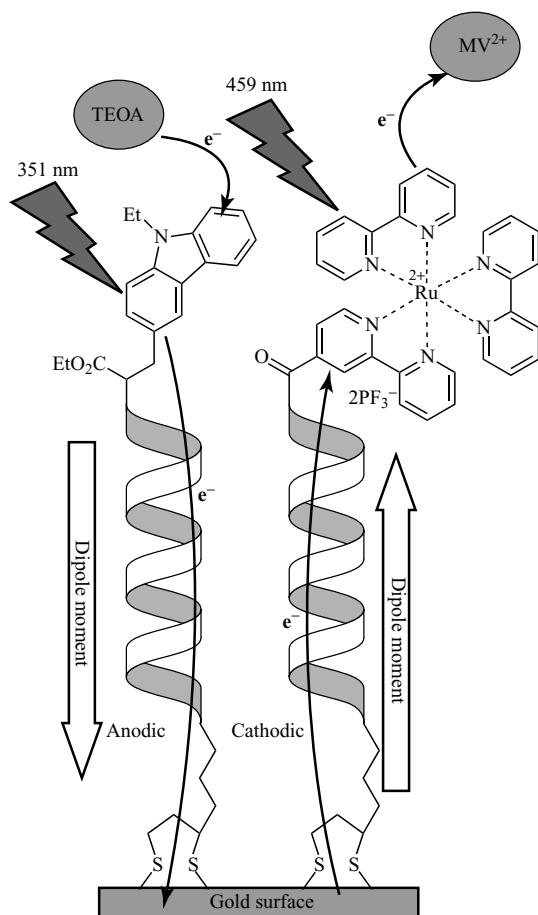


Figure 30 Kimura *et al.* developed a photoswitchable diode by coassembling α -helical peptides with opposing dipole moments and two different photosensitive groups on a gold surface. On excitation with different wavelengths (351 or 459 nm), a photocurrent in opposing directions, which is explained by the direction of the overall dipole moment, could be observed.

units, with one of them carrying a photosensitive group at the C- and a disulfide group at the N-terminus and the second one having a different photosensitive group at the N- and a disulfide group at the C-terminus. These peptides were then coassembled on a gold surface via an Au–S linkage, resulting in monolayers, containing peptides with opposite dipole moments. On excitation of the two different photosensitizers, which were addressed independently of each other (the one at 351 nm and the other at 459 nm), a photocurrent in opposite directions could be observed. Therefore, Kimura *et al.* developed a photodiode whose photocurrent

direction can be switched by changing the wavelength of the irradiating light.

Research in this area of SAMs has also been carried out by several groups, including Kraatz, Zhou and coworkers⁹⁴ and Strong and Moore,⁹⁵ with self-assembled peptides on gold surfaces. They investigated ET with regard to applications in molecular electronics, sensors, and catalysis. It should be noted that in all these experiments, α -helical peptides were used. This already shows that the conductance of peptides is highly dependent on several factors, including their secondary structure, and thus also their amino acid sequence, as well as pH, overall length, and the amount of water present, indicating the importance of protons in these processes.⁹¹

Apart from using SAMs, research with single molecules has also been carried out. However, investigating the ET properties of single biomolecules is far more complicated than studying the same phenomenon with SAMs. First of all, methods for the connection of a single molecule to the electrodes as well as suitable characterization methods have to be developed.⁹⁶ Furthermore, it is desirable to study biomolecules in their natural conformations. Therefore, it is required to expose the molecules to solvents and to control the pH of the surrounding medium.⁹⁷ Tao and coworkers have carried out investigations with simple peptides, consisting of one to three amino acids and different numbers of amine and/or carboxyl groups.⁹⁸ All these peptides contained thiol-functionalized termini in order to covalently attach them to gold electrodes (Figure 31). The attachment of a single molecule to the gold electrodes was achieved by repeatedly moving the gold electrode in and out of contact with a gold substrate in a diluted solution of the peptide. The control of the molecular junctions was done using a piezoelectric transducer. In accordance with other studies, it was shown that the ET through these single peptides proceeds via a tunneling mechanism with decay constants β varying between 0.7 and 0.9 Å.^{96,97,99} The three different devices were then tested for their pH dependence by recording conductance histograms at different pH values (pH 1.5, 7.4, and 13.0). The strong pH dependence found in these systems was explained by deprotonation/protonation of the amine/carboxyl groups, which influences the tunneling barrier for electrons and therefore increases the conductance at low pH values.

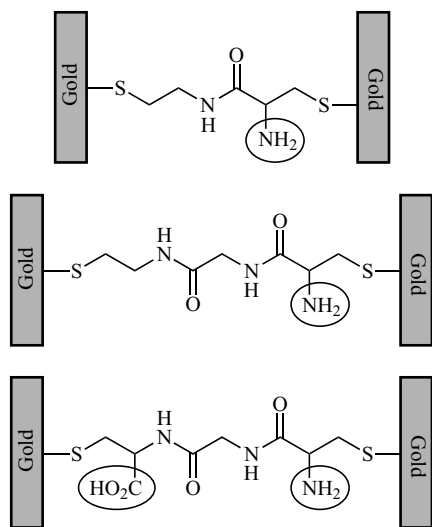


Figure 31 Tao and coworkers investigated the pH dependence of ET through single molecules. They attached peptides of different lengths and/or different numbers of acidic and basic groups to gold electrodes and measured the ET at different pH values.

Apart from the influence of the pH value, a change in conductance has also been reported on the binding of metal ions. Tao and coworkers synthesized peptides of different lengths, containing cysteamine, cysteine, and glycine and then covalently attached single molecules to gold electrodes and measured I - V curves of these peptides with and without the presence of metal ions (Cu^{2+} , Ni^{2+} , Zn^{2+} , K^+ , and Na^+).¹⁰⁰ For Cu^{2+} and Ni^{2+} , they found a large dependence of the conductance on binding to the metal ions. The exact value depended on the length and sequence of the peptide as well as on the metal ion which was used for complexation. An increase in conductance up to a factor of 320 was observed for the sequence cysteamine–diglycine–cysteine complexed to Cu^{2+} . The increased conductance is explained by two factors. First, the complexation of the metal ion to the deprotonated peptide affects the charge distribution and therefore the tunneling barrier. However, this effect was found not to be large enough to explain the large increase in conductance. The authors explain this significant change by an altered conformation as well as by electrons being transported through the chelate bonds instead of the peptide backbone. The findings described in this publication not only give rise to molecular wires with

higher conductance values, but they also suggest a method to study molecular recognition processes on a single-molecule basis, since the change in conductance depends on the complexed metal ion.

9 CONCLUSION

ET in peptides and proteins is a hot topic of ongoing research. A breakthrough for the understanding of long-distance ET is the discovery of the hopping mechanism, which describes long-range ET by several short and therefore fast ET steps. This charge diffusion between relay stations dramatically reduces the influence of the overall distance on the ET rate. Amino acids with low redox potentials can act as stepping stones, and recent experiments have revealed that not only aromatic but also sulfur-containing aliphatic amino acids function as relay stations. The reactive intermediates in these ET reactions are radicals and radical cations.

It remains to be seen whether amide bonds of peptides are also stepping stones under certain conditions. Another area for further research is the influence of dipole moments on ET rates and the significance of charges or Lewis acids for these processes. ET is often coupled with a proton shift, which is used by nature to monitor enzymatic reactions. Future work will also reveal whether certain natural or unnatural peptides can be applied as electronic materials.

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Radical Enzymes

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1 INTRODUCTION

The term *radical enzyme* describes those enzymes that catalyze reactions in which species with an odd number of electrons participate. Such species were classically described as free radicals,¹ but this is confusing because of the two meanings of the word free, although the definition originally applied to radicals was in the sense of a free, that is, nonbonded, electron. In enzymes, radicals cannot be free, in the sense of not being shackled, because they are usually bound to the protein.² The mode of binding is either as a component of a polypeptide chain as with glycyl and tyrosyl radicals or as a reactive intermediate, which is anchored to an enzyme by noncovalent interactions.

It seems paradoxical that some enzymes with their multitude of functional groups are able to survive in the presence of radicals, which are renowned for their high reactivity and consequent short lifetime. However, this overlooks the possibility that enzymes restrict the movement of radicals and therefore their ability to attack distant and even neighboring groups within the protein. Furthermore, dimerization is impeded by encapsulation of the radical. However, the reactions of radicals with some external agents, notably the small diradical dioxygen, cannot be avoided with otherwise long-lived radicals, for example, glycyl radicals in a special class of radical enzymes. With radicals that are

intermediates in catalytic pathways, their short lifetimes and low concentrations enable capture by dioxygen to be minimized.

Two classes of radical enzymes have emerged: one in which radicals are generated and consumed, for example, biotin synthase, and the other in which the radicals are recycled, for example, coenzyme B₁₂-dependent mutases. With biotin synthase, *S*-adenosylmethionine (SAM) serves as precursor of the 5'-deoxyadenosyl (adenosyl) radical, which irreversibly abstracts a hydrogen atom from dethiobiotin³ to afford 5'-deoxyadenosine and a substrate-derived radical that reacts with a sulfur of the [2Fe–2S] cluster. Conversely, with the coenzyme B₁₂-dependent mutases, the 5'-deoxyadenosyl radical also abstracts a hydrogen atom from a substrate molecule to give the methyl group of 5'-deoxyadenosine and a substrate-derived radical. However, after rearrangement of the substrate radical to a product-related radical, this becomes a product molecule by regaining a hydrogen atom from 5'-deoxyadenosine, thus regenerating the 5'-deoxyadenosyl radical.

This article succeeds earlier reviews, which focused on radical enzymes in anaerobic organisms.⁴ As in these reviews, we will primarily discuss enzymatic reactions via intermediate radicals. We will also refer to processes with one-electron transfers, when these are essential to the catalytic

reaction, for example, for 2-hydroxyacyl-CoA dehydratases and benzoyl-CoA reductase (BCR).

1.1 The Primary Radicals of Biology

A recent review classified biologically relevant radicals as reactive oxygen, nitrogen, sulfur, and carbon species.⁵ The reactive oxygen species (ROS) include the radicals superoxide ($\text{O}_2^{\cdot-}$), hydroxyl ($\cdot\text{OH}$), and carbonate ($\cdot\text{OCO}_2^-$), while nitric oxide ($\cdot\text{NO}$) is the principal reactive nitrogen species. These radicals are discussed elsewhere and are not covered here (see **Oxidative Damage to Proteins**). Thiyl radicals ($\text{RS}^\cdot$) are generated when thiols act as scavengers of other radical species (e.g., ROS) and are also active species in some of the radical enzymes described below. In this article, the focus is on carbon radicals that are integral to the mechanisms of certain enzymes. These radicals are either derived from a cofactor (e.g., coenzyme B_{12} , the precursor of the 5'-deoxyadenosyl radical) or substrate molecule (e.g., glutamate, the precursor of the 4-glutamyl radical) or exist within a polypeptide chain (glycyl radical). Such radicals may be relatively long-lived by virtue of their encapsulation within enzymes and can be characterized by electron paramagnetic resonance (EPR) and electron nuclear double resonance spectroscopy (ENDOR). Carbon radicals formed as a consequence of oxidative damage to proteins are not discussed here. The iron-oxy radical species used by *P450* mono-oxygenases (CYP450s) and the intermediate carbon radicals in CYP450 oxidations are detailed elsewhere. Single-electron transfer processes as found in photosynthesis and respiration, as well as mechanisms protecting against ROS, for example, Refs 6 and 7, are not covered here.

1.2 Mechanisms of Radical Enzymes and Generation of Radicals

The principal steps in the catalytic pathways of radical enzymes leading from substrate to product are (i) generation of an initiating radical either from a suitable molecule (e.g., 5'-deoxyadenosylcobalamin (adenosylcobalamin, coenzyme B_{12}), SAM) or from a relatively stable storage radical (e.g., glycyl radical); (ii) reaction of this radical with a substrate molecule to give a substrate-derived radical; (iii) transformation of the substrate-derived radical

into the product-related radical; and (iv) conversion of the product-related radical into a product molecule, which may regenerate and hence recycle the initiating radical. In most of the SAM radical enzymes, however, the 5'-deoxyadenosyl radical is not regenerated. This is because it abstracts a hydrogen atom either from the substrate directly or from a protein's conserved glycine residue, which is converted into an active radical enzyme. 5'-Deoxyadenosine is released and the product survives either as a radical (e.g., with glycyl-radical enzymes) or is converted into a nonradical species. We can distinguish primary "SAM radical enzymes" from secondary "glycyl-radical enzymes," which are active without SAM.

The generation of radicals can be achieved by homolysis of a σ -bond, which necessarily produces two radicals. When coenzyme B_{12} is bound to an enzyme partner, addition of substrate triggers homolysis of the weak Co–C σ -bond (bond dissociation energy $\sim 130 \text{ kJ mol}^{-1}$) and affords cob(II)alamin and the 5'-deoxyadenosyl radical. This bond homolysis is accelerated by approximately 10^{12} -fold as a consequence of contributions from binding energy and conformational change.⁸ One-electron transfer from ferredoxin or flavodoxin to SAM effects homolytic fission of its S–CH₂ bond to give methionine and the 5'-deoxyadenosyl radical. Barker⁹ called SAM the "poor man's adenosylcobalamin" because of the structural simplicity of SAM compared to coenzyme B_{12} . This epithet was inverted by Perry A. Frey to "rich man's adenosylcobalamin," so as to express the multitasking of SAM.¹⁰

An alternative mode of generation of a radical is by reductive one-electron transfer. This may occur to a carbonyl group of a coenzyme A (CoA) thiol ester or to an amide (e.g., thymidine) with formation of a nucleophilic ketyl radical. The energy for these processes, where necessary, derives either from adenosine triphosphate (ATP) hydrolysis or from light, respectively. Acyl-CoA dehydrogenases and 4-hydroxybutyryl-CoA dehydratase may form ephemeral ketyl radicals by deprotonation—one-electron oxidation—deprotonation. Finally, the "pseudo radical enzymes" pyruvate:ferredoxin oxidoreductase and methyl-CoM reductase can effect two-electron cleavage of a C–C or C–H bond, which is followed by stepwise one-electron oxidation or reduction.

There are only a few SAM-dependent enzymes in which SAM is recycled after each turnover, with the most extensively studied example being lysine-2,3-aminomutase.¹¹ Although the formation of active ribonucleotide reductase (RNR), class I, is irreversible, the tyrosyl radical is recycled after each turnover of substrate to product. With coenzyme B₁₂-dependent enzymes, the coenzyme's Co(III)–C σ -bond acts as a storage entity for the active 5'-deoxyadenosyl radical and cob(II)alamin. Glycyl-radical enzymes store the glycyl radical, which reacts with a cysteine thiol to give the active thiyl radical. In 2-hydroxyacyl-CoA dehydratases, storage is via a β -[4Fe–4S]⁺ cluster, while the active form is an α -[4Fe–4S]⁺ cluster. Finally, 4-hydroxybutyryl-CoA dehydratase uses flavin adenine dinucleotide (FAD) with [4Fe–4S]²⁺ for storage, while the active species are FAD semiquinone, [4Fe–4S]^{2+/1+}, and possibly a substrate-based radical.

2 SPECIFIC RADICAL ENZYMES

2.1 Ribonucleotide Reductases

The conversion of ribonucleotides to 2'-deoxyribonucleotides, the monomers required for the construction of DNA, is catalyzed by radical enzymes called *RNRs*, of which there are three distinct kinds (classes I, II, and III) depending on the host organism.

Class I enzymes, which are further subdivided into Ia, Ib, and Ic, are found in aerobic organisms such as *Escherichia coli* (class Ia) and are widely distributed among eubacteria, eukaryotes, bacteriophages, and viruses.^{12,13} Inhibitors of some of these

enzymes are potential chemotherapeutic agents.¹⁴ Human RNR belongs to class I, specifically the subclass Ia. The catalytic activity of RNR depends on the combination of a tyrosine residue with either a di-iron-oxo species (class Ia) or a di-manganese-oxo entity (class Ib). Class Ic enzymes, for example, the RNR from *Chlamydia trachomatis*, contain an Fe(III)–(O)₂–Mn(IV) unit. For each subclass, there is an array of tyrosines (Figure 1) that act as radical carriers (see **Electron Transfer in Peptides and Proteins**). Ultimately, one particular tyrosine oxy radical abstracts a hydrogen atom from a conserved cysteine leading to a cysteine thiyl radical responsible for activating ribose for reduction (Figure 1).

Class II enzymes are used by some algae, archaeobacteria, and eubacteria (e.g., *Lactobacillus leichmannii*) that are anaerobic by nature but can survive when exposed to dioxygen. These enzymes harness the adenosyl radical from coenzyme B₁₂ and it is this species which is used to generate a thiyl radical from an active site cysteine.¹⁶ As with the class I enzymes, the derived thiyl radical initiates the reduction of ribose.

Class III enzymes are strictly anaerobic and exemplified by some archaeobacteria and eubacteria. They employ a relay system, whereby the adenosyl radical from SAM, rather than coenzyme B₁₂, abstracts a hydrogen atom from a conserved glycine in the protein's polypeptide chain. The resulting glycyl radical, in turn, converts an active site cysteine into a thiyl radical.¹⁷

Despite the remarkable diversity among RNRs with respect to their radical-generating machinery, although all converge on an intermediate cysteine thiyl radical, they pursue a common mechanism for the critical steps of the catalytic pathway, that is, the abstraction of the 3'-hydrogen atom

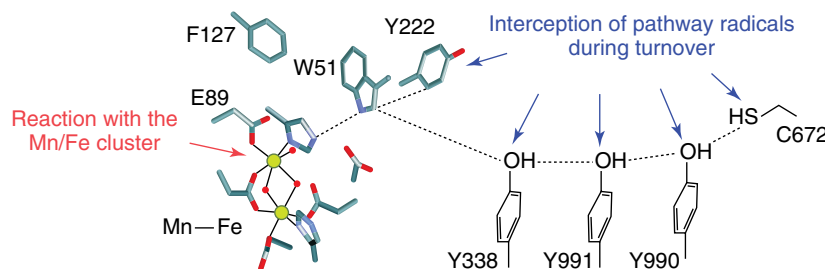


Figure 1 Pathway for proton-coupled electron transfer in *Chlamydia trachomatis*. [(we thank Dr., J. M. Bollinger for a copy of this illustration). Reproduced from Ref. 15. © American Chemical Society, 2010.]

of ribose coupled to reductive elimination of the 2'-hydroxyl group (see **Theoretical Studies of Radical Enzymes**).

2.1.1 The Radical-Generating Machinery of RNRs

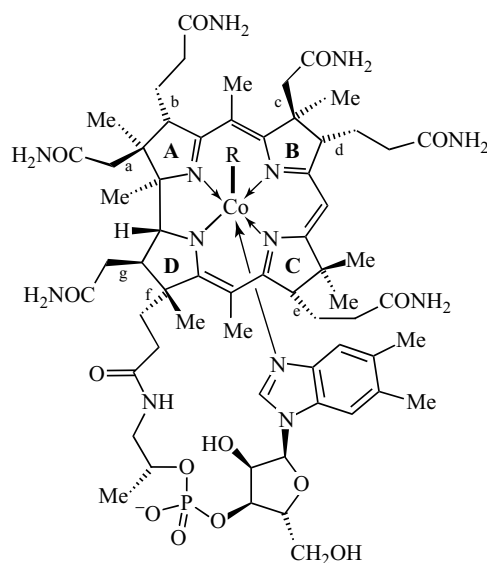
Structural biology and spectroscopic techniques (primarily EPR and ENDOR) have provided a wealth of information on the active sites of all classes of RNR.

The *E. coli* class Ia enzyme is composed of subunits R1 and R2, also labeled α and β , respectively. The 1 : 1 complex ($\alpha_2\beta_2$) of the homodimeric subunits is believed to be the catalytically active form of this RNR with the nucleotide-reducing activity being located in α , while the di-iron-tyrosyl radical (Y122) cofactor resides in β .¹⁸ The identity of the oxygen species in the di-iron part has been controversial.^{18–20} This entity is formed by reaction between a Fe(II)–Fe(II) dimer and dioxygen generating a Fe(III)–Fe(IV) pair with additional oxygen ligands. Examination of this oxygenated di-iron species with 35-GHz pulsed ENDOR suggested the presence of a terminal hydroxide ligand bound to Fe(III) and one or two oxo bridges between the Fe centers.¹⁸ Communication between the α and

β sites could be via proton-coupled electron transfer over circa 35 Å assisted by intervening tyrosines and a tryptophan and leading to the formation of a thiyl radical by abstraction of a hydrogen atom from C439 by the tyrosyl radical. The *E. coli* RNR serves as a reference point for all RNRs, with the class II and III enzymes exhibiting a structurally similar protein to the α_2 subunit. However, the circuitous electron transfer with the *E. coli* RNR is not a feature of class II and III RNRs, which rely on the adenosyl radical as the focal point of the catalytic apparatus.

X-ray analysis of an RNR from *Corynebacterium ammoniagenes* identified the enzyme as belonging to class Ib with a manganese dimer bridged by an oxo/hydroxo group close to a tyrosine (Y115).²¹ The oxidation of the dimer was achieved with hydrogen peroxide derived by reduction of dioxygen with a flavoprotein.²² A theoretical study of the class Ic RNR from *C. trachomatis* identified the manganese center of the Fe(III)–(O)₂–Mn(IV) unit as that serving as oxidant.²³

A detailed examination of the class II RNR from *Thermotoga maritima* gave new insights into the role of coenzyme B₁₂.¹⁶ The binding of the cobalamin to the RNR active site guards the intermediate cysteinyl radical and substrate radical. A hydrogen bond between the substrate α -phosphate



In the structure alongside, R = 5'-deoxyadenosyl is coenzyme B₁₂ (also called 5'-deoxyadenosylcobalamin or simply adenosylcobalamin), whilst R = CN denotes cyanocobalamin (vitamin B₁₂). All cobalamins contain 5,6-dimethylbenzimidazole, which is the so-called 6th ligand to cobalt. Substances containing the corrin ligand, i.e. the planar 14 electron π -system embracing cobalt in the above structure, are also called corrinoids.

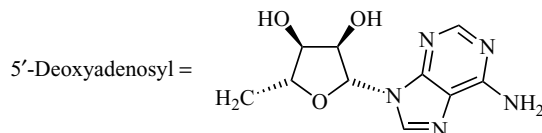
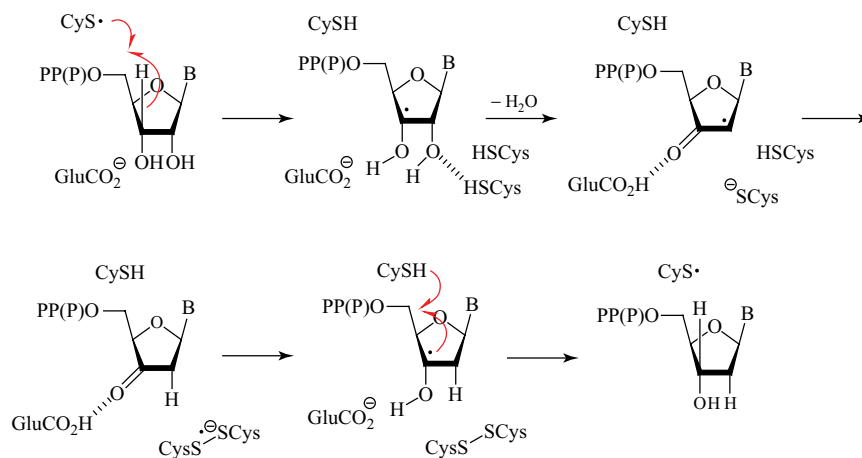


Figure 2 Structure of coenzyme B₁₂ and other cobalamins.



Scheme 1 Outline mechanism for *E. coli* RNR.

and *e*-propionamide of adenosylcobalamin (see lettering in Figure 2) locks the coenzyme in place. In addition, a conformational change in the ribose ring of adenosylcobalamin enables transfer of a hydrogen atom from ribose (H-3') to the cysteine thiyl radical.

2.1.2 Mechanism of RNRs

The nonenzymatic reductive cleavage of a secondary alcohol to an alkane requires conversion of the hydroxyl group to a better leaving group (e.g., sulfonate ester) and reduction with a powerful hydride-transfer agent (e.g., lithium aluminum hydride). An analogous pathway with RNR is implausible because there is no evidence of phosphorylation of the 2'-hydroxyl group and reducing cofactors such as NADH for the ribose reduction are not involved. However, the facile acid- or base-catalyzed elimination of a hydroxyl group *beta* to a carbon radical center has long been known and was originally suggested²⁴ as being relevant to the mode of action of diol dehydratase, the reaction pathway of which resembles that of RNR, thus justifying the soubriquet “eliminase” for both enzymes. Detailed knowledge of the protein, theoretical studies of putative reaction pathways, and the use of inhibitors have led to the mechanism shown in Scheme 1 for the RNR from *E. coli*.^{14,18,25,26}

The initial step is the abstraction of a hydrogen atom from C-3' of the ribose unit by a cysteine thiyl radical (from C439) to afford a substrate-derived C-3' radical. Concomitant with partial deprotonation

of the 3'-hydroxyl group by E441, elimination of the 2'-hydroxyl group facilitated by partial protonation by C225 affords an enoxy radical; compare the mechanisms of diol dehydratase (Section 2.2.3) and the 2-hydroxyacyl dehydratases (Section 2.4). Sequential reductions utilizing cysteine residues (C225 and C462), which generate a transient disulfide radical anion,²⁷ lead to deoxyribose with a radical center at C-3'. This is quenched by transfer of hydrogen atom from C439, which generates 2'-deoxyribose and the starting C439 thiyl radical. For recent discussions on specific aspects of Scheme 1, see Refs 28 and 29.

Similar mechanisms apply to all other RNRs with an additional caveat for the coenzyme B₁₂-dependent RNR. The acidity of a cysteine thiol ($pK_a \approx 8$) results in exchange of hydrogen between this thiol group, the 5'-methylene group of coenzyme B₁₂, and water.³⁰ Furthermore, incubation of this RNR with adenosylcobalamin containing one deuterium atom at C-5' (*R/S* ratio = 3 : 1) gave an *R/S* ratio of 1, indicating that the cobalt–carbon σ -bond is homolyzed to a 5'-deoxyadenosyl radical and cob(II)alamin reversibly, thus enabling rotation about the C-4'/C-5' bond.

2.2 Coenzyme B₁₂-Dependent Enzymes

2.2.1 Introduction

Coenzyme B₁₂ (Figure 2) operates with two types of radical enzymes, the “base-on” (see

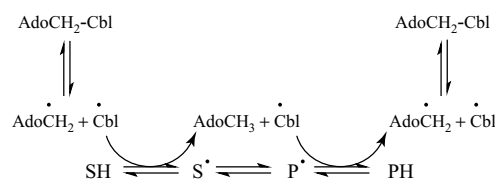
footnote *c* of Table 1 for the definitions of “base-on” and “base-off, his-on”) eliminases (e.g., propane-1,2-diol dehydratase)³¹ and the “base-off, his-on” mutases,³² with the latter group being subdivided into carbon skeleton mutases (e.g., glutamate mutase)³³ and amino mutases (e.g., β -lysine-5,6-aminomutase,³⁴ see Table 1 for a summary). Some authors refer to classes I, II, and III of coenzyme B₁₂-dependent radical enzymes. The carbon skeleton mutases are placed in class I, the eliminases in class II, and the amino mutases in class III, but this classification seems illogical and conveys no sense of the enzyme’s purpose. Coenzyme B₁₂’s radical enzymes are found mainly in anaerobic bacteria, except for methylmalonyl-CoA mutase, which mediates the oxidation of propionate in animals (but not insects) and syntrophic bacteria as well as the formation of propionate in propionibacteria.³⁵ Recently discovered CO₂ fixation pathways use the carboxylation of propionyl-CoA to methylmalonyl-CoA with a subsequent rearrangement to succinyl-CoA.^{36,37} Furthermore, the reductive carboxylation of crotonyl-CoA yields (*S*)-ethylmalonyl-CoA, which is epimerized and rearranged by a novel mutase to (*S*)-3-methylsuccinyl-CoA.³⁸

Since the discovery of the first B₁₂-dependent radical enzymes some five decades ago,^{39,40} their study has passed through several phases in the quest for mechanistic understanding at atomic precision. In the early phase (up to the 1980s), most of the catalytic reactions were defined and experimental and theoretical model systems were developed, some of which have survived the test of time.⁴¹ In the middle phase, the first crystal structures emerged for methylmalonyl-CoA mutase⁴² and diol dehydratase,⁴³ high level calculations made a further impact^{44,45} and mechanisms were refined. Finally, post 2000, the field matured with crystal structures being available for all the eliminases, the carbon skeleton mutase glutamate mutase⁴⁶ and for β -lysine aminomutase.³⁴ The detailed study of isotope and tunneling effects^{47,48} and the further application of theoretical calculations⁴⁹ have provided ever more detailed mechanistic insights. Many books and reviews have traced the evolution of the subject.^{50–55}

2.2.2 Overview of Mechanisms

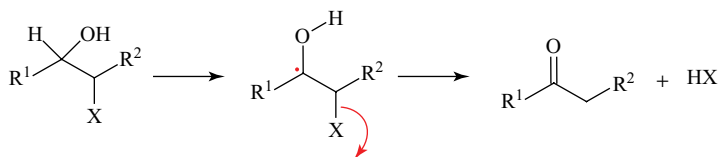
The fundamental philosophy for all coenzyme B₁₂-dependent reactions is that homolytic fission of the coenzyme’s Co–C σ -bond is a prelude to the conversion of substrate to product. Although this Co–C bond is relatively weak (bond dissociation energy circa 130 kJ mol^{–1}) and the coenzyme is rather stable in water at 30 °C ($\tau_{1/2}$ 1.9 years),⁵³ it is assumed that the binding to the enzyme partner and the arrival of a substrate molecule initiates cleavage of the Co–C bond. The mechanistic basis for this proposal is that the cob(II)alamin–5′-deoxyadenosyl radical pair enables some specific tighter binding interactions. One such interaction is a possible hydrogen bond between the 3′-oxygen of ribose and H-19 of the corrin. This was suggested by calculations that indicated that the 3′-oxygen approaches H-19 within 3.5 Å and that the resulting stabilization amounts to 30 kJ mol^{–1}.⁵⁶ Other evidence for beneficial postcleavage interactions has come from a careful examination of the coenzyme B₁₂-binding site in ethanolamine ammonia lyase (EAL).^{57,58}

After the formation of cob(II)alamin and the 5′-deoxyadenosyl radical, hydrogen atom abstraction by the adenosyl radical from a substrate molecule (SH) generates 5′-deoxyadenosine and a substrate-derived radical (S′), which is converted into a product-related radical (P′) and hence product (PH) (Scheme 2). Abstraction of a hydrogen atom from relatively inert substrate carbon centers indicates that radicals participate in the coenzyme B₁₂-dependent enzymatic reactions. Most convincingly, freeze-quench techniques and EPR spectroscopy, aided by the use of isotopically labeled substrates (e.g., ²H and ¹³C), have detected radical species for diol dehydratase,⁵⁹ EAL,^{60,61} 2-methyleneglutarate mutase,⁶² methylmalonyl-CoA mutase,⁶³ glutamate mutase,⁶⁴ lysine-5,6-mutase,⁶⁵ and ornithine mutase.⁶⁶



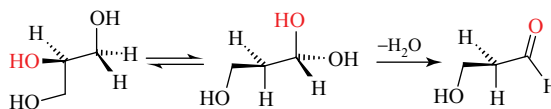
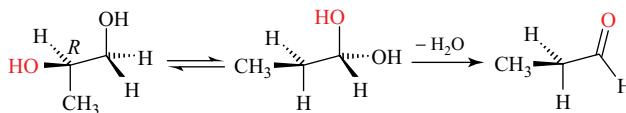
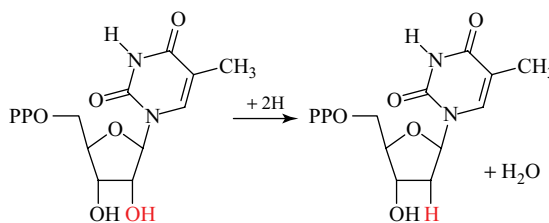
Scheme 2 Minimal mechanism for coenzyme B₁₂-dependent enzymatic reactions (AdoCH₂-Cbl = adenosylcobalamin).

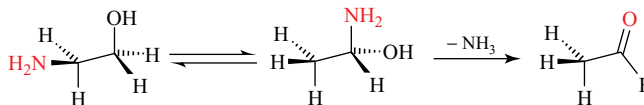
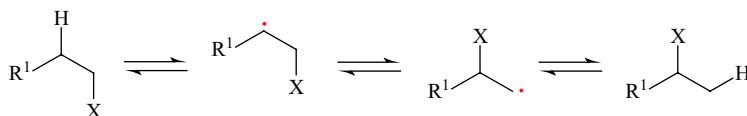
Table 1 Classification of radical enzymes^a depending on coenzyme B₁₂.^b

 Eliminases (“base-on”)^c


Substrate-derived radical

 Irreversible reactions that eliminate water (X = OH) or ammonia (X = NH₂); X is shown in red below

 1. Glycerol dehydratase
(enterobacteria and clostridia)

 2. Propane-1,2-diol dehydratase
(*Klebsiella oxytoca*)

 3. Ribonucleotide reductases
(*Lactobacillus leichmannii*)

 (PP = diphosphate; the reduction requires NADPH + H⁺ and generates NADP⁺ + H₂O in addition to the deoxynucleotide)

 4. Ethanolamine ammonia lyase
(clostridia)

 Mutases (“base-off, his-on”)^c

 Intermediate
methylene radical

 Reversible molecular rearrangements (the migrating group X, shown in red, is an sp² or sp³ carbon-centered group in the carbon-skeleton mutases and NH₂ in the amino mutases)

(continued overleaf)

Table 1 (continued)

Carbon-skeleton mutases	
5. Glutamate mutase (<i>Clostridium cochlearium</i>)	
6. 2-Methylene-glutarate mutase (<i>Eubacterium barkeri</i>)	
7. Methylmalonyl-CoA mutase (bacteria, humans)	
8. Isobutyryl-CoA mutase (<i>Streptomyces cinnamonensis</i>)	
Amino mutases	
9. β -Lysine-5,6-aminomutase (<i>Clostridium subterminale</i> and <i>Fusobacterium nucleatum</i>)	
10. Ornithine-4,5-aminomutase (<i>Clostridium sticklandii</i>)	

^aThe natural or typical substrate + product are given.

^bSee Figure 2.

^cThe term *base-on* means that N-1 of the 5,6-dimethylbenzimidazole ligand (Figure 2) remains attached to cobalt; “base-off, his-on” signifies that the 5,6-dimethylbenzimidazole ligand is substituted by a histidine residue from the partner enzyme.

The complex signals observed were ascribed to cob(II)alamin interacting with an organic radical at a distance of 6–11 Å.

For the reversible reactions given in Table 1 (all mutases), substrate and product are synonymous

in principle, as reversion to substrate can occur via hydrogen atom removal from the so-called product to give the product-related radical, which reverts to the substrate-related radical. However, a distinction can be made (Table 1) on the

basis of the physiological direction of the reaction. For example, methylmalonyl-CoA mutase accepts (*R*)-methylmalonyl-CoA from the degradation of certain amino acids and converts it into succinyl-CoA, which enters the Krebs cycle. Whatever the direction of reaction catalyzed by the mutases, the role of 5'-deoxyadenosine is to trap the intermediate radicals (S' and P') with regeneration of the 5'-deoxyadenosyl radical.

An alternative to the concept of a stabilized cob(II)alamin-5'-deoxyadenosyl radical pair is that the homolysis of the Co–C bond is coupled to hydrogen atom abstraction from substrate.^{57,67} In this way, the formation of the essentially nonstabilized primary adenosyl radical is avoided, but only in some cases, by direct formation of a stabilized radical. For all the mutases provided in Table 1, at least one of the radicals is itself a primary organic radical and therefore no major energetic benefit from a concerted pathway is apparent.

Following the rupture of the coenzyme's Co–C bond and formation of a substrate-derived radical (or, alternatively, a product-related radical for the reversible reactions), the next challenge is to formulate satisfactory mechanisms for the interconversion of S' and P'. The precise mechanism of this process has been debated since the 1970s. For each of the enzymes provided in Table 1, the mechanism is influenced by the nature of the migrating group and the substituents in the vicinity of the radical centers. And for each group, be it eliminase, carbon-skeleton mutase, or amino mutase, there is a close correspondence of mechanism as discussed below.

The reactions catalyzed by the eliminases are all replicated by enzymes that are either dependent on SAM or a glycyl radical but are coenzyme B₁₂ independent (see below). In contrast, coenzyme B₁₂-independent mutases are unknown.³²

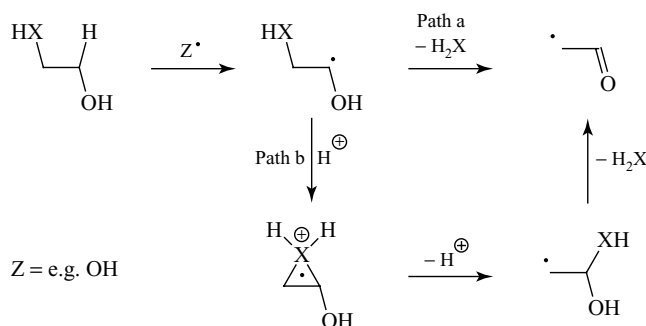
2.2.3 Eliminases

It was recognized early on that there were nonenzymatic precedents for the eliminases,²⁴ and in some respects, for the mutases (see the following section).⁶⁸ Chemical studies of 1,2-dihydroxyalkyl radicals and 2-amino-1-hydroxyalkyl radicals in the 1970s had shown the propensity of these species under acidic or basic conditions to eliminate water or ammonia, respectively, with the

formation in each case of a 2-oxoalkyl radical (Scheme 3). The authors of these studies were unaware of their possible relevance to the coenzyme B₁₂-dependent eliminases, which was pointed out with the introduction of a critical question: is there a bridged intermediate or transition state that enables conversion of a 1,2-dihydroxyalkyl radical or 2-amino-1-hydroxyalkyl radical into a 2,2-dihydroxyalkyl radical or 2-amino-2-hydroxyalkyl radical and hence a 2-oxoalkyl radical (Scheme 3).^{24,68} The “bridging” mechanism contrasts with the alternative and obvious fragmentation pathway whereby the 2-oxoalkyl radical is formed directly by elimination of water or ammonia. Since this initial period of conjecture, numerous studies have tried to unravel every possible nuance of the pathway.

The idea of a bridged species arose for diol dehydratase and glycerol dehydratase because of the startling discovery that hydroxyl at C-2 of propane-1,2-diol and glycerol migrates to C-1.^{69,70} This conclusion, based on evidence with ¹⁸O-labeled substrates, can only be accommodated by the fragmentation pathway if there is a recombination step giving an intermediate 2,2-dihydroxyalkyl radical. Irrespective of whether the 2,2-dihydroxyalkyl radical arises by the bridging or fragmentation-recombination route, why does the enzyme take the circuitous path rather than be satisfied with the 2-oxoalkyl radical initially derived from direct elimination? The mechanism proposed for RNR (Section 2.1, Scheme 1) includes a 1,2-dihydroxyalkyl radical that is supposed to undergo elimination of water to afford a 3-oxoalk-2-yl radical (ribose numbering), the radical center of which is quenched with formation of a 2-deoxy-3-oxoriboside. The reason for the formation of a 2,2-dihydroxyalkyl radical rather than a 2-oxoalkyl radical is that only the former is energetically primed to retrieve a hydrogen atom from 5'-deoxyadenosine.^{71,72} The analogous step with RNR requires the abstraction of a hydrogen from a cysteine thiol, which is circa 40 kJ mol^{−1} easier than abstraction from the methyl group of 5'-deoxyadenosine⁷⁴ and can be accomplished by the 3-oxoalk-2-yl radical.

The most advanced current mechanism for diol dehydratase and glycerol dehydratase provides a rather complete account of the roles of enzyme and coenzyme. Crystal structure analyses have confirmed that after fission of the Co–C bond of



Scheme 3 Alternative pathways for the decomposition of 1,2-dihydroxyalkyl radicals and 2-amino-1-hydroxyalkyl radicals derived from a 1,2-diol ($X = O$) and 2-amino-alcohol ($X = NH$): path (a) involves direct elimination of water or ammonia and path (b) proceeds via an intermediate bridged species.

coenzyme B_{12} , cob(II)alamin is at a distance of circa $10 \text{ \AA}$ from substrate and is therefore a spectator of radical chemistry initiated by the adenosyl radical.⁴³ The activation of diol dehydratase by a monovalent cation such as K^+ or NH_4^+ has long been known. The first electron density maps with the coenzyme surrogate cyanocobalamin bound to diol dehydrase were interpreted as showing that propane-1,2-diol acted as bidentate ligand to the potassium ion. Recently, the use of adenylylpentylcobalamin as an analog of coenzyme B_{12} led to a surprising re-interpretation, whereby it is Ca^{2+} that binds the diol, whereas K^+ anchors the coenzyme (Figure 3). Diol dehydratase was now termed a *metalloenzyme* because it is inhibited by ethylenediaminetetraacetic acid (EDTA), which extracts the calcium ion.⁷³ The substrate diol is positioned to give up a hydrogen atom to the adenosyl radical (see Figure 3, which shows, in addition, the four amino acid residues hydrogen bonded to the diol). It was proposed that the resulting 1,2-dihydroxyprop-1-yl radical rearranges to the 1,1-dihydroxyprop-2-yl radical by an intramolecular migration of the 2-hydroxyl group via a bridged intermediate (cf. Scheme 4, which shows this process for the 1,2-dihydroxyethyl radical from ethane-1,2-diol).⁷² This “push–pull” mechanism involves “partial protonation” of the migrating 2-OH and “partial deprotonation” of the nonmigrating 1-OH group. “Partial protonation” describes the ability of hydrogen bonding by protein functional groups to confer significant acid–base catalysis.⁷² Several theoretical calculations have supported this route as an energetically viable pathway, whereas the alternative fragmentation-recombination is more

costly (see data for glycerol dehydratase acting on glycerol (see **Theoretical Studies of Radical Enzymes**)).⁷⁵ Note that diol dehydratase is unusual in that both enantiomers of propane-1,2-diol react at similar rates. In Figure 3, the (*S*)-enantiomer is shown and it is the pro-*S* hydrogen that is removed. With the (*R*)-enantiomer, the pro-*R* hydrogen is removed.⁷⁶

EAL performs a similar reaction on vicinal aminoalcohols to that of diol and glycerol dehydratase on vicinol diols: the conversion of ethanolamine (2-aminoethanol) to ethanal and ammonia, and propanolamine (2-amino-1-propanol) to propanal and ammonia. A similar bridging pathway was proposed based on theoretical calculations.^{24,61,68,77} There is extensive spectroscopic evidence (EPR) for the proposed substrate-derived radical, that is, 2-amino-1-hydroxyethyl or 2-amino-1-hydroxyprop-1-yl.^{61,78} The crystal structure of EAL from *E. coli* containing a coenzyme B_{12} analog (cyanocobalamin or adenylylpentylcobalamin) showed a trimer of an $(\alpha\beta)_2$ dimer with a cobalamin molecule bound at the boundary of the α and β subunits.⁵⁸ The mode of binding of substrate 2-amino-1-propanol was via an array of hydrogen bonds similar to those observed with diol and glycerol dehydratase for their substrates. A critical issue is the protonation state of the substrate amino group, but this was not clearly resolved. Given that the ionization state of ethanolamine or propanolamine at physiological pH is the protonated species, it would be surprising if this were not the case for bound substrate, especially as a protonated substrate-derived radical is required for conversion to the product-related

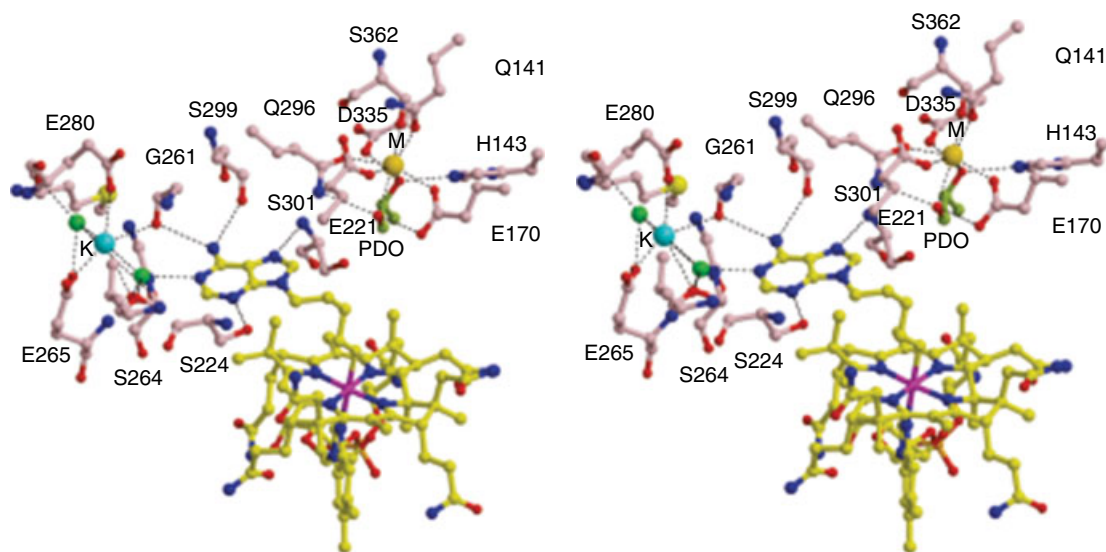
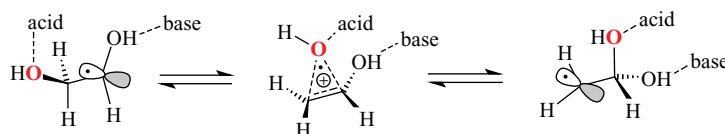


Figure 3 Stereopicture of the active site of diol dehydratase showing both the Ca^{2+} and K^+ ions. [(reproduced by permission of Professor T. Toraya). Reproduced from Ref. 73. © American Chemical Society, 2010.]



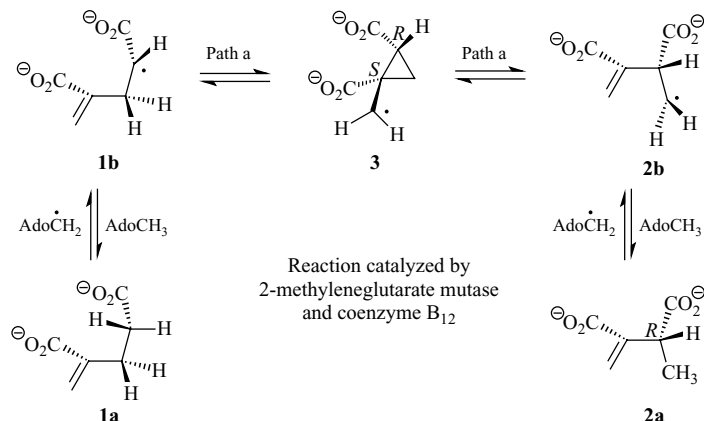
Scheme 4 “Push–pull” mechanism for diol dehydratase with substrate ethane-1,2-diol.

radical. The detailed mechanism given by Shibata *et al.*⁵⁸ assumes a protonated substrate amino group arising from interactions with the side-chain groups of the neighboring residues Glu α 287, Asp α 362, and Gln α 162. All intermediates are shown as being anchored by an interaction between their hydroxyl group and a protonated arginine (Arg α 160), which takes the place of the metal ion in diol and glycerol dehydratase.

2.2.4 Carbon-Skeleton Mutases

The rearrangement of carbon skeletons catalyzed by coenzyme B_{12} -dependent carbon-skeleton mutases is an equilibratory process in which the less branched component dominates at equilibrium (Table 1). With the exception of glutamate mutase, the migrating groups all contain a $\text{C}=\text{C}$ or $\text{C}=\text{O}$ group that enables the rearrangement to be achieved via a bridged (cyclopropane)

intermediate (cf. the eliminases), as shown in Scheme 5 for 2-methyleneglutarate mutase equilibrating with (*R*)-3-methylitaconate.^{62,79} The mechanism shown is consistent with the observation that 2-methyleneglutarate mutase catalyzes the equilibration of (*E*)- and (*Z*)-2-(monodeuteromethylene)-3-methylsuccinate with the concomitant formation of (*E*)- and (*Z*)-2-(monodeuteromethylene)glutarate. The equilibration probably occurs via an intermediate 1-deuteromethylene-cyclopropane-1,2-dicarboxylate radical in which there is a low barrier to rotation around the σ -bond connecting the deuteromethylene radical-bearing group to the cyclopropane framework.⁷² This mechanism is also consistent with model studies, which showed the conversion of di-*t*-butyl 1-bromomethylene-cyclopropane-1,2-dicarboxylate, di-*t*-butyl 2-(methylene)-3-bromomethylsuccinate, and di-*t*-butyl 2-bromo-4-methyleneglutarate to di-*t*-butyl 4-methyleneglutarate when treated with triphenyltin hydride.⁸⁰ In this

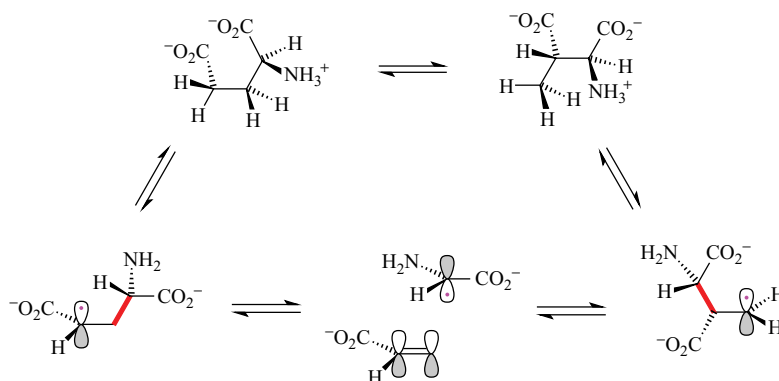


Scheme 5 Intermediate radicals (**1b**, **2b**, and **3**) in the 2-methyleneglutarate mutase reaction (**1a** = 2-methyleneglutarate; **2a** = 3-methylitaconate).

case, the initially formed radicals correspond to each of those proposed as intermediates in the enzymatic reaction. All evidently converge on the thermodynamically most stable radical, that is, the di-*t*-butyl 2-(methylene)glutarate-4-yl radical, which is quenched to afford di-*t*-butyl 2-methyleneglutarate. The lack of a crystal structure for 2-methyleneglutarate mutase has hindered further progress.

The crystal structure for methylmalonyl-CoA mutase⁴² supports a similar mechanism to that described for 2-methyleneglutarate mutase, that is, via a bridged intermediate, the formation of which is facilitated by “partial protonation” of carbonyl oxygen by His244.⁷² Similar mechanisms can be written for isobutyryl-CoA mutase and

ethylmalonyl-CoA mutase. However, the remaining member of this group, glutamate mutase, is different from the others. This enzyme catalyzes the coenzyme B₁₂-dependent equilibration of (*S*)-glutamate with (2*S*,3*S*)-3-methylaspartate (Scheme 6). Now a bridged intermediate analogous to those discussed for the other mutases is not permissible. The possibility was considered that pyridoxal phosphate or other suitable species could generate an intermediate imine by combining with the α -amino group of substrate/product, thus enabling a bridged mechanism analogous to that proposed for lysine 2,3-aminomutase (see Section 2.3.1).⁸¹ However, no such species has been detected. This led to the postulate of a “fragmentation-recombination” mechanism (Scheme 6),^{82a} which was sustained by a



Scheme 6 Fragmentation–recombination mechanism for the equilibration of (*S*)-glutamate with (2*S*,3*S*)-3-methylaspartate catalyzed by coenzyme B₁₂-dependent glutamate mutase showing intermediate radicals.

critical experiment⁸³ in which the working enzyme was quenched by addition of trifluoroacetic acid. The fragments acrylate and glycine were retrieved in comparable quantities (0.06 mol each per mol of enzyme) from the resulting mixture. In an EPR study, the 4-glutamyl radical was detected as the dominant radical species for a reaction mixture that was arrested by cooling in liquid nitrogen.⁶⁴

The experiments described do not settle the mechanistic question because of the relatively high calculated energy barriers ($\geq 60 \text{ kJ mol}^{-1}$) that interconnect the intermediate radicals: 4-glutamyl, glycyl (+acrylate) and 3-methyleneaspartate (Scheme 6).^{44,84} The central issue concerns the participation of the nonstabilized, primary aspartate 3-methyl radical. To account for the involvement of such radicals in the mutase-catalyzed reactions, it was proposed that cob(II)alamin acts as a “conductor” that partially stabilizes the intermediate methylene radicals.³² The nature of this stabilization, if present, is unclear. What is clear is a sharp distinction between eliminases and mutases with respect to the distance between substrate/product radicals and cob(II)alamin (circa 10 Å in eliminases and circa 6 Å in mutases).

The structure of the complex between *apo*-glutamate mutase (components E & S) and

coenzyme B_{12} + its inhibitor (2*S*,3*S*)-tartrate revealed that transfer of a H atom to the 5'-deoxyadenosyl radical is controlled by pseudorotation of the cofactor's ribose ring (Figure 4).⁸⁵ On the basis of calculations, it has been suggested that the 3'-oxygen of the ribose moiety approaches H-19 of the corrin ring within 3.5 Å. This leads to the formation of a hydrogen bond that stabilizes the cob(II)alamin–deoxyadenosyl radical pair arising from fission of the Co–C σ -bond.⁵⁶

2.2.5 Aminomutases

β -Lysine-5,6-aminomutase and D-ornithine-4,5-aminomutase both catalyze the reversible shift of a terminal amino group to the next carbon atom with the aid of pyridoxal-5'-phosphate in addition to coenzyme B_{12} : (3*S*)- β -lysine yields (3*S*,5*S*)-3,5-diaminohexanoate; the enzyme also acts on (2*R*)- α -lysine to form 2,5-diaminohexanoate.^{34,65,86–88} In a similar manner, (*R*)-ornithine gives (2*R*,4*S*)-2,4-diaminopentanoate.^{66,89,90} The mechanisms of these reactions are analogous to that proposed for SAM-dependent lysine-2,3-aminomutase (see Section 2.3.1). The question arises as to why the

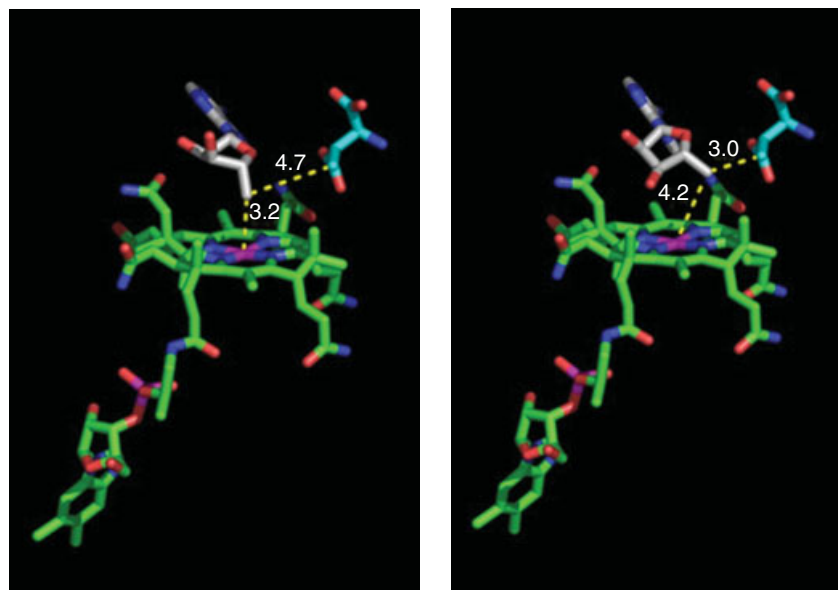


Figure 4 Pseudorotation of the cofactor's ribose ring controls the radical transfer in glutamate mutase. [Adapted from Ref. 85. © Wiley-VCH Verlag GmbH & Co. KGaA, 2001.]

shift of a terminal amino group requires coenzyme B₁₂, whereas that of an internal amino group is accomplished by SAM. It has been speculated that an isolated methylene radical that occurs during catalysis of lysine-5,6-aminomutase (Table 1, reaction 4), but not of lysine 2,3-aminomutase, needs to be stabilized by cob(II)alamin.³²

2.2.6 Reactivases

A remarkable feature of the eliminases and mutases is their relative stability in the presence of dioxygen. Although the coenzyme B₁₂-dependent glycerol dehydratase is also active under oxic conditions, the alternative glycyl-radical enzyme, which catalyzes the identical reaction, is rapidly cleaved at the glycyl-radical site when exposed to air. Coenzyme B₁₂-dependent enzymes have the advantage that the radical disappears by reformation of the Co–C σ -bond after each turnover. On the other hand, several coenzyme B₁₂-dependent enzymes, especially glycerol dehydratase and lysine-5,6-aminomutase, become inactivated during turnover. With glycerol as substrate, diol dehydratase from *Klebsiella oxytoca* survives only about 10⁴ turnovers, although with propane-1,2-diol its lifetime is 100 times longer.⁹¹ A chaperone-like reactivation factor has been detected, which in an ATP-dependent manner expels the inactive cob(II)alamin and replaces it by intact adenosylcobalamin.⁹² MeaB is an auxiliary protein that plays a crucial role in the assembly and protection of the coenzyme B₁₂-dependent methylmalonyl-CoA mutase. Impairments in the human homologue of MeaB, methylmalonic aciduria type A, lead to methylmalonic aciduria, an inborn error of metabolism.⁹³ Genes that probably code for related chaperones have been detected adjacent to the structural genes of glutamate mutase from *Clostridium cochlearium* (*glmL*)⁹⁴ and 2-methyleneglutarate mutase from *Eubacterium barkeri* (*mgmL*).⁹⁵

2.3 SAM Radical Enzymes

SAM radical enzymes, which generate the 5'-deoxyadenosyl radical and methionine by reductive cleavage of SAM, are often characterized by the sequence motif CX₃CX₂C, where C stands for

cysteine and X for any other of the 20 proteinogenic amino acids. Some of these enzymes contain the CX₂CX₄C motif and in one case CX₅CX₂C.⁹⁶ Amino acid sequences with these motifs have been found not only in genomes of anaerobes but also in aerobic bacteria, fungi, plants, animals, and even in humans. A bioinformatic survey published in 2002 revealed more than 600 different sequences of putative SAM radical enzymes in the database.⁹⁷ In 2008, the number already exceeded 2800¹¹ and, due to the ever increasing sequencing of genomes and metagenomes, the number will continue to rise. The number cited demonstrates the importance of SAM radical enzymes for life, but masks the fact that it comprises many enzymes that catalyze the same reaction but occur in different organisms. To date, there are about 40 different radical reactions known that are catalyzed by putative and characterized SAM radical enzymes.

All SAM radical enzymes need a low-potential one-electron donor, ferredoxin or flavodoxin (*E'* circa –500 mV), in order to reduce the [4Fe–4S]²⁺ cluster to the [4Fe–4S]¹⁺ state. Crystal structures of several SAM radical enzymes revealed that the three cysteines of the CX₃CX₂C motif coordinate three irons of the characteristic [4Fe–4S]²⁺ cluster. The fourth iron serves as binding site for SAM, which is coordinated by the amino, the carboxyl, and the sulfonium of the methionine moiety (Figure 5). On reduction of the [4Fe–4S]¹⁺ cluster, an inner shell electron transfer to the sulfonium center over a distance of 3.25 Å releases the 5'-deoxyadenosyl radical, whereby the sulfur of the methionine formed moves toward the iron by 0.63 Å.⁹⁸ Although the redox potential of trialkylsulfonium salts such as SAM has been estimated as –1.8 V, binding of SAM to the [4Fe–4S]²⁺ cluster together with the

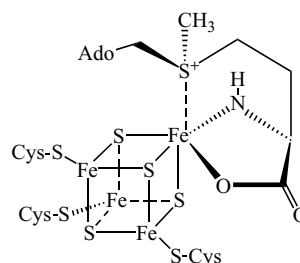


Figure 5 Mode of SAM binding to the fourth iron of the cluster. The Fe–S distance is 3.25 Å; AdoCH₂ = 5'-deoxyadenosyl.

substrate increases the potential by at least 800 mV. There are excellent reviews on this topic.^{11,99,100}

The thus formed 5'-deoxyadenosyl radical initiates catalysis, just like its identical twin from coenzyme B₁₂, generally by hydrogen atom abstraction from the substrate, even from strong C–H bonds such as the unactivated methyl group of dethio-biotin.³ Only compound I of cytochrome P450, an iron(IV)oxo or ferryl species with an additional radical delocalized over the porphyrin and thiolate ligands, has a similar oxidizing power.¹⁰¹ The 5'-deoxyadenosine formed is either irreversibly released as product or recycled to regenerate SAM. The generation of 5'-deoxyadenosine, that is, the consumption of one SAM in every turnover, is energetically very expensive for the cell because the 5'-deoxyadenosine is degraded and SAM has to be resynthesized de novo. Hence, for ATP-forming catabolism with high turnover, the cell can only afford reversible SAM radical enzymes. Nature tends to use irreversible SAM radical enzymes for the synthesis of molecules that are only required in small number by the cell. The more extensive characterization of SAM radical enzymes, however, may uncover further examples of the reversible type.

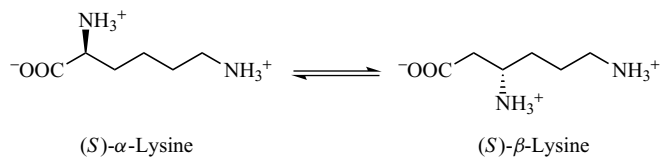
2.3.1 Recycling SAM Radical Enzymes

The first known SAM-dependent enzyme that did not catalyze methylation, but rather a rearrangement reminiscent of a coenzyme B₁₂-dependent reaction, was lysine-2,3-aminomutase from *Clostridium* SB4, later renamed *Clostridium subterminale*. The oxygen-sensitive aminomutase, which was discovered by Barker, mediates the equilibration of (*S*)- α -lysine with (*S*)- β -lysine (Scheme 7), the first step of lysine fermentation to ammonia, acetate, and butyrate.¹⁰² Surprisingly, the catalyst of the chemically similar second step in this fermentation has been characterized as coenzyme B₁₂-dependent β -lysine-5,6-aminomutase (see above). Both

aminomutases require pyridoxal-5'-phosphate as an additional cofactor and the amino group migrations occur without exchange of the hydrogens involved with the solvent. The function of SAM in lysine-2,3-aminomutase remained an enigma for 20 years until Perry A. Frey discovered hydrogen transfer from the 5'-methylene group of SAM to α - and β -lysine.¹⁰³ This important result immediately indicated the transient formation of the 5'-deoxyadenosyl radical, which supported Barker's view of SAM being a poor man's adenosylcobalamin,⁹ although in his papers Barker never contemplated radical intermediates.

Subsequent studies in Frey's laboratory using isotopically labeled lysines were indeed able to characterize by EPR spectroscopy the postulated intermediate β -lysine-2-yl radical bound to pyridoxal-5'-phosphate via a Schiff base. But neither the 5'-deoxyadenosyl radical nor the pyridoxal-5'-phosphate adduct of the α -lysine-3-yl radical or a radical based on pyridoxal-5'-phosphate itself could be detected under these conditions. If, however, the 4-methylene group of lysine was replaced by sulfur, then the pyridoxal-5'-phosphate adduct of the 4-thia- α -lysine-3-yl radical became the major species during steady state.¹⁰ The 5'-deoxyadenosyl radical is too high in energy and therefore its concentration is too low to be observed directly by EPR. This radical was "trapped" with an alternate coenzyme, the SAM analog 3',4'-anhydroadenosylmethionine with a double bond between ribosyl-C-3' and C-4'. The resultant allylic 3',4'-anhydro-5'-deoxyadenosyl radical is spin delocalized and thus present at a much higher concentration and detectable by EPR spectroscopy.

In the initial catalytic step of lysine-2,3-aminomutase, the 3*Re*-hydrogen atom is removed from the β -carbon of α -lysine bound via the amino group to pyridoxal-5'-phosphate. The resultant 5'-deoxyadenosine acts as a spectator during the consecutive rearrangement of



Scheme 7 Reaction catalyzed by lysine-2,3-aminomutase.

the α -lysine-3-yl radical to the β -lysine-2-yl radical, probably via an aza-cyclopropylcarbinyl radical.⁴¹ Finally, the 5'-deoxyadenosine donates one methyl hydrogen back to the β -lysine-2-yl radical to form the 2*Re*-hydrogen of the product (*S*)- β -lysine, resulting in an overall inversion of configuration at both chiral centers. The regenerated 5'-deoxyadenosyl radical is either ready for the next turnover or recombines with methionine coordinated to the [4Fe-4S] cluster to regenerate SAM.

The mechanism of the coenzyme B₁₂-dependent β -lysine-5,6-aminomutase closely resembles that of lysine-2,3-aminomutase and raises the question as to why two different cofactors are required for almost identical reactions in the same organism. The only difference is the reversible conversion of an unactivated methyl group into a methylene group by β -lysine-5,6-aminomutase, whereas with α -lysine-2,3-aminomutase, an unactivated methylene group is reversibly converted into a methine group. The energy difference for the more difficult removal of a hydrogen atom from a methyl group versus removal from a methylene group⁷⁴ is about 10 kJ mol⁻¹ possibly resulting in up to a 100-fold rate difference. It was recently proposed that the intermediate methylene radical in β -lysine-5,6-aminomutase is stabilized by interaction with cob(II)alamin, whereas this is not necessary for α -lysine-2,3-aminomutase.^{32,56,104,105}

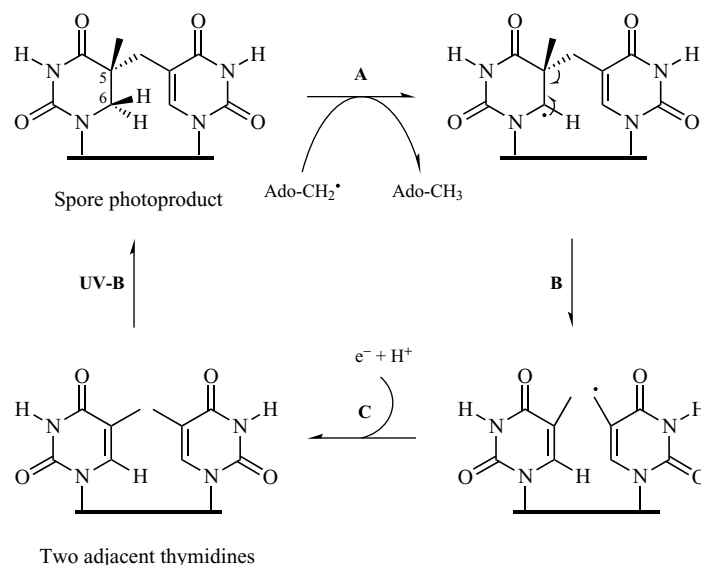
Bioinformatics has indicated the existence of many other SAM-dependent 2,3-aminomutases. The enzyme from *E. coli* acts on (*S*)- α -lysine, like that from *C. subterminale*, but the product is (*R*)- β -lysine, whereby the 3*Si*-H rather than 3*Re*-H is initially abstracted.¹⁰⁶ Expression of a gene from *Clostridium difficile* homologous to α -lysine-2,3-aminomutase and analysis of the protein indicated the production of a (*S*)-glutamate-2,3-aminomutase.¹⁰⁷ In the active site of this enzyme, asparagine 369 and lysine 332 replace the two aspartates (D293 and D330) of lysine-2,3-aminomutase that interact with the ϵ -amino group of lysine. Finally, there is a fourth enzyme of this group, arginine-2,3-aminomutase that catalyzes the reversible interconversion of (*S*)- α -arginine with (*S*)- β -arginine in *Streptomyces griseochromogenes*.¹⁰⁸

Spore photoproduct lyase, which occurs in endospore-forming bacteria such as the aerobic *Bacillus subtilis* and the anaerobe *Clostridium acetobutylicum* was long considered to be the only

recycling SAM radical enzyme other than the 2,3-aminomutases acting on amino acids. Recent experiments suggest, however, that this is not the case.¹⁰⁹ In contrast to lysine-2,3-aminomutase, which is involved in the energy metabolism of the strict anaerobe *C. subterminale* that requires a high turnover, spore photoproduct lyase has to repair DNA lesions that occasionally occur in bacteria germinated from spores. After repair, the two separated nucleotides fold back into the double helix and the enzyme moves along the DNA until it detects another lesion, which has to flip out from the helix. Hence, the organism does not need an enzyme with high turnover and can afford to spend one SAM for every DNA lesion.

As the name indicates, the spore photoproduct can only be formed by irradiation of packed dry DNA that occurs in spores. In the overall reaction, the methyl group of thymidine adds stereospecifically in a *syn*-geometry to the double bond of the neighboring thymidine to yield the dimeric (*5R*)-thymidine, probably via radical intermediates (Scheme 8). The repair mechanism is straightforward—just the reverse of the formation.^{110,111} Abstraction of the added hydrogen by the 5'-deoxyadenosyl radical derived from SAM yields a radical that fragments into thymidine and a thymidine radical. The latter is recycled by reaction with 5'-deoxyadenosine or is reduced by an unknown electron donor (Scheme 8), probably via a conserved cysteine residue.¹⁰⁹ Which of the C-6 hydrogen atoms is removed by the 5'-deoxyadenosyl radical remains to be established.

A very recently characterized reversible radical SAM enzyme is DesII that catalyzes the $\alpha\beta$ -elimination of ammonia from a 2-aminoethanol moiety in the biosynthesis of the sugar thymidine diphosphate (TDP)-D-desosamine.¹¹² In this pathway, the keto group at C-4 of TDP-6-deoxy-4-dehydro-D-glucose is converted to an amino group by pyridoxal-5'-phosphate-dependent amino transfer from glutamate. The 5'-deoxyadenosyl radical derived from SAM abstracts the hydrogen atom at C-3 causing the elimination of ammonia at C-4, possibly via a ketyl radical. The resulting product-related radical recycles SAM from 5'-deoxadenosine and methionine, leading to TDP-4,6-dideoxy-3-dehydro-D-glucose. If TDP-4-amino-4,6-dideoxy-D-[3-²H]glucose is used as substrate, after some turnovers, the 5'-methylene group of SAM contains two deuterium atoms,



Scheme 8 Radical mechanisms for formation and irreversible cleavage of the spore photoproduct. Steps A, B, and C are catalyzed by spore photoproduct lyase.

showing that SAM has been recycled. The enzyme DesII is remarkable in two ways. First, it shows how nature aided by an aminotransferase converts a keto to a methylene group adjacent to a hydroxyl group. Second, the reaction is almost identical to that mediated by the adenosylcobalamin-dependent EAL (Section 2.2.3).

2.3.2 Irreversible SAM Radical Enzymes

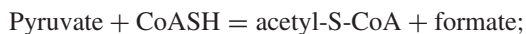
The large group of irreversible SAM radical enzymes comprises the activases of glycyl-radical enzymes, which together with their target enzymes deserve a separate study. Several crystal structures have been determined for these SAM radical enzymes, which pave the way to mechanistic proposals. The products of the reactions catalyzed by these enzymes are equal amounts of methionine, 5'-deoxyadenosine, and a substrate-derived radical that is converted into the product-related radical. An interesting yet unsolved question is the quenching of the latter radical. It could be removed either by oxidation or by reduction via proton-coupled electron transfers. The electron donors/acceptors could be ferredoxin or flavodoxin as required for radical formation. Many SAM radical enzymes have a second [4Fe-4S] cluster coordinated by other cysteine

residues of the protein, which could be involved in the electron transfer. The following paragraphs comprise specific SAM radical enzymes. They are grouped by their catalytic reactions and not with respect to their phylogenetic relationships.

In *glycyl-radical enzymes*, a conserved glycine (RVXG) near the C-terminus of one subunit of a large dimeric *apo*-enzyme ($2 \times \sim 80$ kDa) is irreversibly converted to a carbon-based radical through stereospecific α -hydrogen atom abstraction effected by the 5'-deoxyadenosyl radical derived from SAM. As discovered with pyruvate formate lyase, the relatively stable glycyl radical exhibits a characteristic EPR signal, resulting from coupling with the hydrogen that remains on the amino acid.^{113,114} Quantum mechanical calculations demonstrated that glycine gives the thermodynamically most stable radical as compared to the other proteinogenic amino acids (see **Radical Stability—Thermochemical Aspects**).¹¹⁵ The facile reaction of the radical with molecular oxygen inactivates the enzyme by cleavage of the polypeptide chain at the glycine residue. Hence, these enzymes can occur only in microorganisms that thrive anaerobically.

The structure of pyruvate formate lyase revealed an $(\alpha\beta)_{10}$ barrel. At the center of the barrel, the glycyl radical is located like the rotating knife of a Waring Blender.¹¹⁶ This architecture prevents the radical

from dimerizing and allows catalysis without side reactions.¹¹⁷ The 5'-deoxyadenosyl radical is generated by the action of the SAM-dependent pyruvate formate lyase activating enzyme, which contains the specific [4Fe-4S] cluster. The C-terminal domain with the glycine residue is turned inside out, thereby reaching the active site of the activating enzyme. Afterwards, the glycine radical domain flips back into the center of the lyase and catalysis can start.¹¹⁸ On addition of pyruvate, the radical is transferred to a cysteine residue, which is conserved in all glycine radical enzymes. Only in pyruvate formate lyase does the radical move to an adjacent cysteine that is specific for this type of enzyme. It has been proposed that the thiyl radical thus formed adds to the carbonyl group of pyruvate and the resulting adduct fragments into *S*-acetylcysteine and a formyl radical anion. The conserved cysteine residue donates a hydrogen atom to the formyl species yielding formate, while the thiyl radical is recycled. Finally, the acetyl moiety is transferred from cysteine-SH to CoASH.¹¹⁹



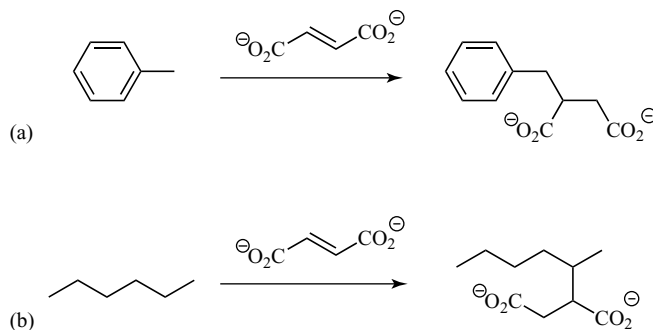
$$\Delta G^{\circ} = -16 \text{ kJ mol}^{-1}$$

The calculated free energy indicates that this reaction is reversible, though the equilibrium lies almost completely on the right side. In the direction of pyruvate synthesis, the thiyl radical has to abstract the hydrogen atom from formate, which is feasible because the resulting radical anion is spin delocalized.

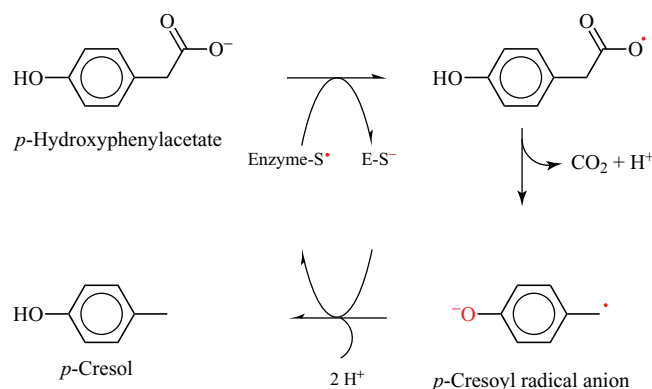
There are only six additional glycy radical enzymes known¹²⁰:

- The anaerobic or type III RNR,^{121,122} which is discussed in Section 2.1.
- 2-Oxobutyrate formate lyase, which is closely related to pyruvate formate lyase.¹²³
- Benzylsuccinate synthase, see Scheme 9a^{124–130}; a similar enzyme catalyzes the addition of fumarate to *m*-xylene.¹²⁹
- Presumably 2-(1-methylpentyl)succinate synthase, see Scheme 9b.¹³¹
- *p*-Hydroxyphenylacetate decarboxylase, see Scheme 10.^{132–134}
- Glycerol dehydratase. The functionally similar coenzyme B₁₂-dependent enzyme^{135,136} is discussed in Section 2.2.3.

The glycy radical enzymes benzylsuccinate synthase and 2-(1-methylpentyl)succinate synthase catalyze the addition of fumarate to the hydrocarbons toluene and hexane, respectively (Scheme 9). In this way, the hydrocarbon is converted into a water-soluble product that can be thioesterified with CoASH for the subsequent β -oxidation. The initial step in fumarate addition most likely proceeds via radicals derived from the hydrocarbons. Although the benzyl radical derived from toluene is spin delocalized, the only stabilization of the hex-2-yl radical is by hyperconjugation. Evidently, the thiyl radical of the enzyme abstracts a hydrogen atom from C-2 (calculated difference in bond dissociation energy, $\Delta\text{BDE} \approx 40 \text{ kJ mol}^{-1}$) rather than from C-1 of hexane ($\Delta\text{BDE} \approx 50 \text{ kJ mol}^{-1}$).⁷⁴ It is still difficult to understand how the thiyl radical can manage the energy difference of 40 kJ mol^{-1} . Furthermore, sulfate-reducing bacteria have recently been described that are able to degrade propane by addition of fumarate even to the methyl



Scheme 9 Initial steps of hydrocarbon degradation by addition to fumarate catalyzed by glycy radical enzymes: (a) degradation of toluene and (b) degradation of hexane.



Scheme 10 Proposed Kolbe-type mechanism for the decarboxylation of *p*-hydroxyphenylacetate catalyzed by a glycyl-radical enzyme.

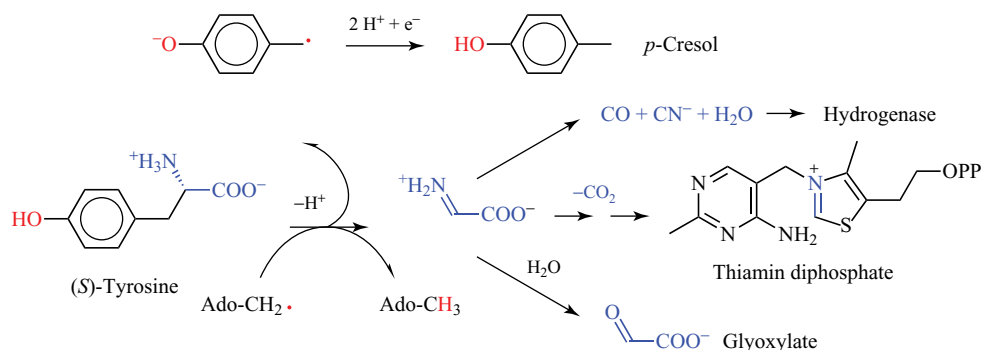
group as well as to the methylene.¹³⁷ There is, however, a remarkable difference within benzylsuccinate synthase and 2-(1-methylpentyl)succinate synthase. Using dideuterofumarate, the succinate moiety of benzylsuccinate retained both deuteriums (H. Wilkes, R. Rabus, J. Heider, and F. Widdel, personal communication), whereas in 2-(1-methylpentyl)succinate, the deuterium at the tertiary carbon was lost.¹³¹ Possibly this difference is caused by an epimerase, because the subsequent carbon-skeleton rearrangement of 2-(1-methylpentyl)succinyl-CoA to the malonyl-CoA derivative, 2-carboxy-4-methyloctanoyl-CoA,¹³¹ could require a different stereoconfiguration.

Direct decarboxylation of *p*-hydroxyphenylacetate would lead to a destabilized carbanion because of the electron-rich phenolic substituent. However, abstraction of the phenolic hydrogen atom by the thiyl radical of the enzyme would generate a stabilized phenoxyl radical that can decarboxylate due to the spin delocalized *p*-cresoyl radical anion that is formed.¹³² Interestingly, the fragmentation of tyrosine to dehydroglycine catalyzed by the SAM radical enzyme ThiH most likely leads to the same *p*-cresoyl radical anion (Scheme 11). Owing to the facile formation and stability of this radical, nature destroys a whole tyrosine molecule just to secure either CO and HCN for the maturation of the [FeFe]hydrogenase or a C=N unit for the synthesis of the thiazole ring of thiamin diphosphate (ThDP). Surprisingly, the crystal structure of the unactivated *p*-hydroxyphenylacetate decarboxylase with bound substrate revealed that the cysteine

converted to the catalytic thiyl radical is located close to the carboxyl moiety rather than near the phenolic hydroxyl group.^{138,139} As all structurally characterized unactivated glycyl-radical enzymes contain the substrate in the correct orientation, an alternative Kolbe-type mechanism has been proposed. Oxidation of the carboxylate by the nearby thiyl radical and deprotonation of the phenolic hydrogen by a glutamate residue triggers decarboxylation and the formation of the *p*-cresoyl radical anion (Scheme 10). ThiH, however, has no choice. In this reaction, the phenolic hydrogen has to be abstracted by the 5'-deoxyadenosyl radical.

The pathogenic anaerobic bacterium *C. difficile* produces *p*-cresol from tyrosine probably to suppress other bacteria in the human intestine. The decarboxylase is an octamer composed of four large subunits (4×100 kDa) that contain the active site glycine and cysteine as well as four small subunits (4×9.5 kDa), each of which comprises two [4Fe-4S] clusters. Probably, the clusters, which are essential for activity, reduce the glycyl radical to glycine to avoid suicide of the bacterium if the concentration of cresol rises to toxic values.^{133,134}

The activating SAM radical enzymes of *p*-hydroxyphenylacetate decarboxylase, glycerol dehydratase, and benzylsuccinate synthase contain two additional [4Fe-4S] clusters with unknown functions. This makes them distinct from the activases of pyruvate formate lyase and RNR, in which only the typical SAM cluster is present. While the 5'-deoxyadenosyl radical forms the glycyl-radical in *p*-hydroxyphenylacetate decarboxylase,¹³⁹ the activase of glycerol dehydratase appears to cleave SAM into 5'-methylthioadenosine and the



Scheme 11 Generation of dehydroglycine from tyrosine catalyzed by HydG leading to hydrogenase or by ThiH leading to thiamin diphosphate. If no acceptor is present, dehydroglycine hydrolyzes to glyoxylate.

2-aminobutyryl-4-yl radical that abstracts the hydrogen from a specific glycine residue.¹⁴⁰ The same fragmentation of SAM also occurs in the synthesis of wybutosine and diphthamide (Figure 7).

Activation of Sulfatases by Oxidation of an Alcohol to an Aldehyde

In biology, the most common electron acceptor for the oxidation of alcohols to aldehydes ($E^{\circ'} = -300 - 0 \text{ mV}$ against the hydrogen electrode at pH 7.0) is NAD^+ ($E^{\circ'} = -320 \text{ mV}$; under physiological conditions $E' = -270 \text{ mV}$). Therefore, in most cases, the equilibria for these oxidations lie on the side of the alcohol. To achieve complete oxidation of an alcohol to an aldehyde, aerobes employ the very strong oxidant molecular oxygen ($E^{\circ'} = +820 \text{ mV}$), whereas anaerobes use the 5'-deoxyadenosyl radical derived from SAM. This was shown for the maturation of the sulfatase AtsA by AtsB of *Klebsiella pneumoniae*¹⁴¹ and for the anaerobic sulfatase maturing enzyme (an SME) from *Clostridium perfringens*.¹⁴² In both of the enzymes, a specific serine or a cysteine residue is oxidized with one 5'-deoxyadenosyl radical to a 3-oxoalanine (formylglycine) residue. The reaction

probably proceeds via a ketyl or thioketyl radical, which after deprotonation at the oxygen or sulfur is further oxidized to the aldehyde or thioaldehyde. The latter is hydrolyzed to an aldehyde. The maturase contains two additional [4Fe-4S] clusters, which are probably involved in the electron transfer. In the sulfatase mechanism, the sulfate is transferred to the hydrated aldehyde, which expels the sulfate with regeneration of the aldehyde.

Fragmentations and Rearrangements by SAM Radical Enzymes

Coproporphyrinogen III oxidase from *E. coli* catalyzes the oxidative decarboxylation of two propionate side chains of coproporphyrinogen to vinyl side chains.¹⁴³ The 5'-deoxyadenosyl radical abstracts the β -Si-hydrogen of a propionate residue to generate a spin delocalized radical, which has been observed.¹⁴⁴ Decarboxylation of this fairly stable radical is probably initiated by an unknown electron acceptor. The second vinyl group is presumably formed in the same way, as the crystal structure shows two SAM molecules.¹⁴⁵

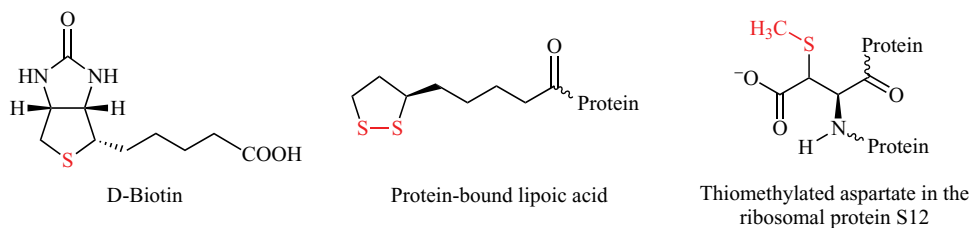


Figure 6 Examples of sulfur insertion by radical SAM enzymes.

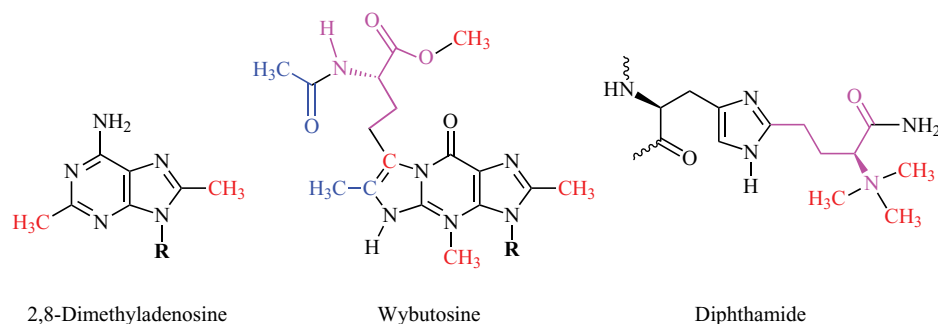


Figure 7 Modifications of 23S rRNA, tRNA, and elongation factor 2. The red carbons stem from SAM by N-, O-, or C-methylation; the pink structures originate from SAM by alternate cleavage. Acetyl-CoA is the most likely precursor of the blue moieties. R = 1-ribosyl.

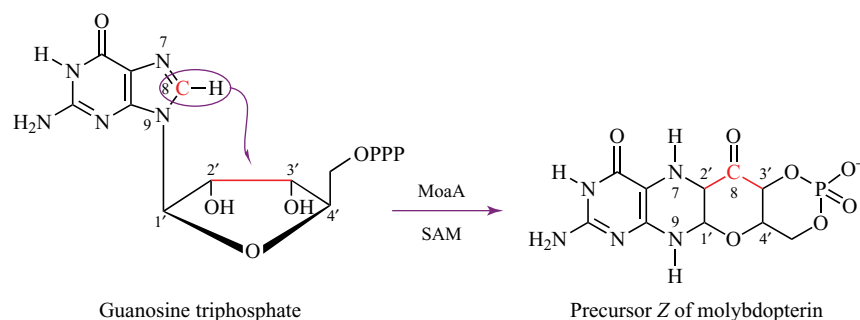
The extremely active [FeFe]hydrogenases catalyze the reduction of protons to molecular hydrogen by reduced ferredoxin or flavodoxin, whereas the less active [Fe]hydrogenases (see below) and [NiFe]hydrogenases are primarily involved in the uptake of hydrogen due to the higher redox potentials of their electron acceptors. [FeFe]hydrogenase comprises a [4Fe–4S] cluster connected via a cysteine to a two-iron active site that is bridged by a dithiolate ($\text{HS-CH}_2\text{-X-CH}_2\text{-SH}$; X = probably NH) and coordinated by three CO and two CN^- . Three enzymes, HydE, HydF, and HydG, are required for maturation of the hydrogenase. The radical SAM enzyme HydG probably catalyzes the abstraction of the phenolic hydrogen from tyrosine.^{146,147} The resulting tyrosyl radical fragments to the resonance stabilized *p*-cresoyl radical anion and dehydroglycine, which disintegrates into CO, HCN, and H_2O (Scheme 11). HydE is most likely involved in the radical SAM-dependent synthesis of the dithiolate cofactor and the whole active site of the hydrogenase is assembled on the scaffold HydF accompanied by guanosine triphosphate (GTP) hydrolysis.

An enzyme related to HydG is ThiH, which is responsible for the biosynthesis of the thiazole ring of ThDP, the physiological active form of vitamin B₁. ThDP is the cofactor for the metabolism of ketosugars and 2-oxoacids, for example, pyruvate. Like HydG, ThiH catalyzes the cleavage of tyrosine to the *p*-cresoyl radical and dehydroglycine, which acts as a building block of the thiazole ring. If dehydroglycine is not used for the consecutive step, it spontaneously hydrolyzes to ammonia and glyoxylate, which were identified (Scheme 11).¹⁴⁸ The reduction and protonation of the *p*-cresoyl

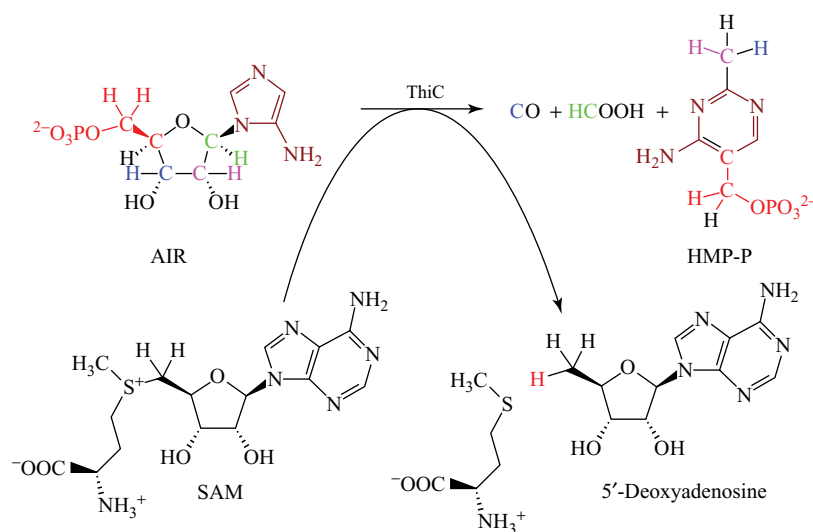
radical to *p*-cresol remains to be established. Interestingly, the dehydroglycine used by aerobic organisms for thiamin biosynthesis is obtained from glycine with oxygen as oxidant. Hence, the 5'-deoxyadenosyl radical derived from SAM can be regarded as “the oxygen of the anaerobes.”

Molybdopterin is the cofactor of many oxidases, for example, xanthine oxidase in mammalian milk. Its biosynthesis in *Staphylococcus aureus*¹⁴⁹ and most likely in all kingdoms of life including humans is catalyzed by MoaA and the accessory protein MoaC. The pathway starts with the fragmentation of the ribose C-2'–C-3' bond of GTP, followed by insertion of the C-8 methine group of the guanine ring (Scheme 12).¹⁵⁰ The enzyme contains, in addition to the N-terminal “SAM cluster,” a second C-terminal [4Fe–4S] cluster that binds GTP at the two imidazole nitrogens. The 5'-deoxyadenosyl radical abstracts a hydrogen atom either from C-2' or C-3' of the ribose. The product is called *precursor Z*, an oxygen-sensitive tetrahydropyranopterin that is further converted to the mature cofactor molybdopterin.

An even more complex fragmentation and rearrangement is the “radical dance” catalyzed by the single enzyme ThiC from the bacterium *Caulobacter crescentus*. Induced by one electron, it converts SAM and aminoimidazole ribonucleotide (AIR), an intermediate in the purine nucleotide biosynthesis pathway, to 5'-deoxyadenosine, CO, formate, and hydroxymethylpyrimidine phosphate, the other building block of ThDP (Scheme 13).¹⁵¹ Amazingly, only one SAM molecule is required for each turnover but it is used twice, as revealed by the incorporation of two deuterium atoms from the substrate into the 5-methyl group of 5'-deoxyadenosine,



Scheme 12 Radical SAM-dependent initial step in the biosynthesis of molybdopterin.



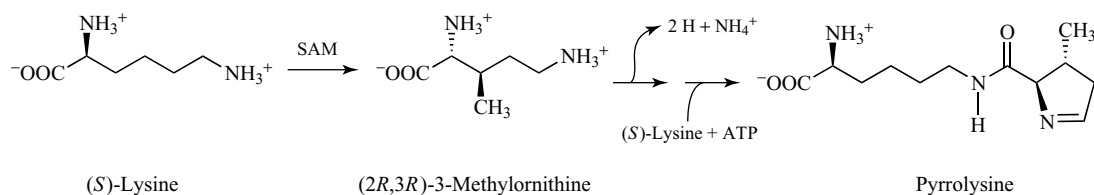
Scheme 13 Synthesis of the hydroxymethylpyrimidine phosphate (HMP-P) building block of thiamin diphosphate from 5-aminoimidazole nucleotide (AIR) catalyzed by the SAM radical enzyme ThiC. One red hydrogen and the bold black hydrogen of AIR end up in the 5'-methylene group of 5'-deoxyadenosine. The two bold black hydrogens in HMP-P come from the solvent water.

one from the 5'-carbon and the other from the 4'-carbon of AIR. The authors suggested that after the first H-abstraction, SAM is recycled, but it is then used irreversibly for the second abstraction. On incubation of ThiC with SAM and a reducing agent, a protein-based radical was also observed.¹⁵² Whether this radical is catalytically competent remains to be established.

The structure of ThiC also yielded surprises. Each subunit of the homodimeric enzyme is composed of a $(\beta\alpha)_8$ barrel with an extra domain, which contains the [4Fe-4S] cluster coordinated to a CX₂CX₄C motif.¹⁵³ The enzyme with the closest architecture is glutamate mutase from *C. cochlearium* (see above), which is composed of a $(\beta\alpha)_8$ barrel-containing

GlmE homodimer and to each subunit the coenzyme B₁₂-binding subunit GlmS is attached. Hence, in both the enzymes, the “radical reaction flask” is similar with only the radical-generating domains or subunits being different. The same situation is found in the three classes of RNRs (see above).

Very recently, yet another intriguing rearrangement was revealed. The SAM radical enzyme NosL from *Streptomyces actuosus* catalyzes the fragmentation of tryptophan and its recombination to 3-methyl-2-indolic acid, a building block of the antibiotic thiopeptide nosiheptide. Completely deuterated tryptophan only lost the deuterium at C-2 and the 5'-deoxyadenosine formed was not labeled. Hence, the fragmentation was most likely induced



Scheme 14 Synthesis of pyrrolysine, the 22nd proteinogenic amino acid.

by abstraction of the imino hydrogen that resulted in the removal of the glycyI moiety and recombination with the carboxylate, whereas the glycyI α -carbon was converted to ammonia and CO.¹⁵⁴

A reaction that closely resembles the carbon-skeleton rearrangement catalyzed by the coenzyme B₁₂-dependent glutamate mutase (Scheme 6) is involved in the biosynthesis of the 22nd proteinogenic amino acid pyrrolysine (Scheme 14). Archaeal methyltransferases contain in their amino acid sequence a specific L-lysine, to whose ϵ -amino group a methylated pyrroline carboxylate is attached via an amide linkage. The pyrroline is derived by oxidation of (2R,3R)-3-methylornithine, which is obtained from L-lysine by a carbon-skeleton rearrangement catalyzed by the SAM radical enzyme PylB.¹⁵⁵ The difference from the reaction catalyzed by the reversible glutamate mutase is inversion of configuration at the amino carbon and the irreversibility due to the consumption of most likely one SAM per turnover. One can assume that the 5'-deoxyadenosyl radical abstracts a hydrogen atom from C-4 of lysine and the resulting 4-lysyl radical fragments to a glycyI-radical and 4-amino-1-butene. Recombination by addition of the glycyI-radical at C-2 of 4-amino-1-butene, followed by one-electron reduction and protonation, would yield the branched carbon chain of (2R,3R)-3-methylornithine. An alternative pathway, in which the fragmentation occurs between C-4 and C-5,¹⁵⁶ appears very unlikely because the resulting 2-aminoethyl radical is not as stabilized as the glycyI radical.

Sulfur Insertion by SAM Radical Enzymes

The common theme of this topic is the abstraction of a hydrogen atom bound to carbon, followed by insertion of sulfur derived from a second iron-sulfur cluster of the SAM radical enzyme; for a review see Ref. 157. The most prominent enzyme of this group is biotin synthase from

E. coli. This enzyme catalyzes the formation a sulfur bridge between a methyl and a methylene group of its substrate dethiobiotin at the expense of two molecules of SAM, which are both converted to 5'-deoxyadenosine. The enzyme contains the standard radical SAM [4Fe-4S] cluster and an additional [2Fe-2S] cluster,¹⁵⁸ which donates the sulfur.³ Hence, the enzyme sacrifices itself during the turnover. But even in the presence of a sulfur source that regenerates the cluster, no more than one turnover could be observed. Recently, it has been shown that impurities and degradation products of SAM, especially adenosylhomocysteine (SAM without the methyl group) strongly inhibited the reaction. Using enzymatically synthesized pure SAM under strictly anaerobic conditions, many turnovers could be observed.¹⁵⁹ After its synthesis, biotin is attached to a specific lysine residue of an *apo*-carboxylase, in a reaction catalyzed by the ATP-dependent biotin ligase.

The synthesis of the lysine-bound lipoyl residues in 2-oxoacid-dehydrogenases occurs in a different order. First, octanoic acid is attached to a conserved lysine residue of the protein, and second, one sulfur atom is inserted at C-6 followed by the other sulfur at C-8, both catalyzed by LipA. Like biotin synthase, the whole process requires two molecules of SAM, and the sulfur originates from the additional [4Fe-4S] cluster.¹⁶⁰

The syntheses of thiomethyl groups by the radical SAM enzymes RimO from *T. maritima*, as well as MtaB and MiaB from *B. subtilis*, follow a similar scheme: hydrogen atom abstraction, sulfur insertion, and final methylation by a second SAM. RimO catalyzes methylthiolation at the methylene group of a specific aspartate residue in the S12 ribosomal protein.¹⁶¹ MtaB and MiaB are responsible for the final maturation of tRNA at already modified bases near the anticodon. They catalyze the introduction of thiomethyl groups into position 2 of *N*⁶-threonylcarbamoyladenosine and

*N*⁶-isopentenyladenosine.¹⁶² All three thiomethyl residues are essential for protein biosynthesis. A variant within the human gene CDKAL1 belonging to the eukaryotic MtaB subfamily is unable to catalyze thiomethylation, a genetic defect shown to predispose for type 2 diabetes.¹⁶³

C–C Bond Formation by SAM Radical Enzymes

The methyltransferases RlmN and Cfr catalyze methyl transfer to aromatic carbon atoms of an adenosine within a complex 23 S rRNA substrate to form the 2,8-dimethylated product.¹⁶⁴ The introduction of one methyl group requires two SAM molecules: one for radical formation and the second as methyl donor. In this way, the 5'-deoxyadenosyl radical derived from one SAM abstracts a *hydrogen atom from the methyl group* of the second SAM. This new radical adds to the adenosine carbon to be methylated. One-electron reduction and a hydride shift result in the formation of the methylated product and adenosylhomocysteine, in addition to methionine and 5'-deoxyadenosine.¹⁶⁵ A consecutive paper shows, however, that the second SAM methylates a conserved cysteine residue of the enzyme. The 5'-deoxyadenosyl radical then abstracts a hydrogen atom from this methyl group to afford a methylene radical that adds to the purine ring. In contrast to the hydride shift, the authors propose deprotonation/protonation steps and cleavage of the S–C bond by disulfide formation.¹⁶⁶

Recently, one enzyme has been discovered that cleaves SAM in a different manner to methyladenosine and a 3-amino-3-carboxypropyl radical.¹⁶⁷ The enzyme is involved in diphthamide biosynthesis in Archaea and Eukarya. The 3-amino-3-carboxypropyl radical adds at the carbon between the two imidazole nitrogens of a specific histidine residue of the elongation factor 2 required for protein biosynthesis. The crystal structure of the enzyme from *Pyrococcus horikoshii* revealed an [4Fe–4S] cluster coordinated by three cysteine residues, which do not show the CX₃CX₂C motif but are spread over the whole molecule. The adduct is further modified by three SAM-dependent methylations at the amino group and conversion of the carboxylate to an amide. Diphtheria toxin catalyzes the NAD⁺-dependent ADP ribosylation at N–H of the imidazole moiety, which arrests protein synthesis.

The combination of three different SAM-dependent C–C bond forming reactions

is found in the biosynthesis of wyosine derivatives: SAM-dependent addition of a C-2 unit, probably an acetyl group, to *N*¹-methylguanosine to yield the tricyclic 4-demethylwyosine. This is followed by C-methylation at C-6 and addition of the 3-amino-3-carboxypropyl radical derived from SAM at C-7. Finally, conversion to the methyl ester and N-acetylation leads to wybutosine in archaeal and eucaryal tRNAs.¹⁶⁸

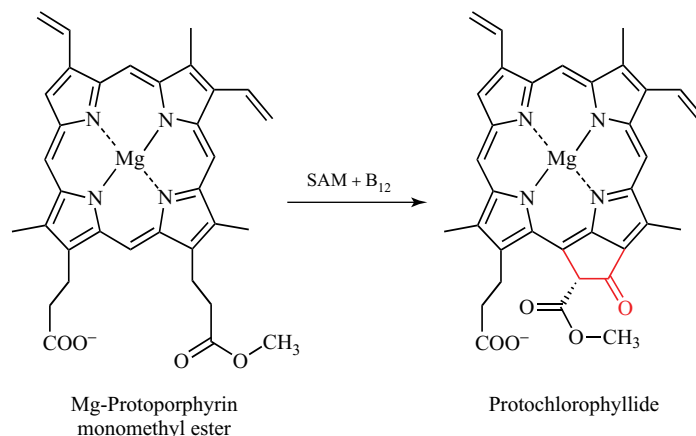
Unknown Reactions Catalyzed by the SAM Radical Enzymes NirJ, BchE, PqqE, HmdB (HcgA), NifB, and Viperin

NirJ is involved in the transformation of precorrin-2 into heme *d*₁, a cofactor of nitrite reductase also called cytochrome *cd*₁.¹⁶⁹ It was suggested that NirJ catalyzes the replacement of two propionate side chains by keto groups. The authors claimed to have detected the 5'-deoxyadenosyl radical by EPR merely on incubation of NirJ from *Paracoccus pantotrophus* with SAM and dithionite.

Under anaerobic conditions, BchE catalyzes the formation of the isocyclic ring of protochlorophyllide from magnesium-protoporphyrin monomethyl ester in the phototrophic bacterium *Rhodobacter capsulatus*, a step in bacteriochlorophyll biosynthesis. Surprisingly, the enzyme requires adenosylcobalamin besides SAM.¹⁷⁰ The reaction comprises the oxidation of a methylene group to a ketone and the removal of two hydrogen atoms for cyclization. Under aerobic conditions, the same reaction uses dioxygen (Scheme 15).

PqqE from *K. pneumoniae* catalyzes an early step in the formation of protein-bound pyrroloquinoline quinone (PQQ, Figure 8a) by condensation of a glutamate and a tyrosine side chain in the protein PpqD.¹⁷¹ Surprisingly, consecutive steps require molecular oxygen for hydroxylation reactions. PQQ is an oxidant with a more positive redox potential than NAD⁺. It is involved in, for example, the aerobic oxidation of ethanol in wine to acetic acid during vinegar production in *Acetobacter* species.

HmdB also named HcgA, is involved in the synthesis of the prosthetic group of the so-called [Fe]hydrogenase (HmdA) occurring in methanogenic Archaea (Figure 8). HmdA catalyzes the reduction of methenyl-tetrahydromethanopterin to methylene-tetrahydromethanopterin by molecular hydrogen. Biochemical characterization of the enzyme has revealed the presence of a unique active site metal cofactor, which consists of an



Scheme 15 Formation of the isocyclic ring in protochlorophyllide.

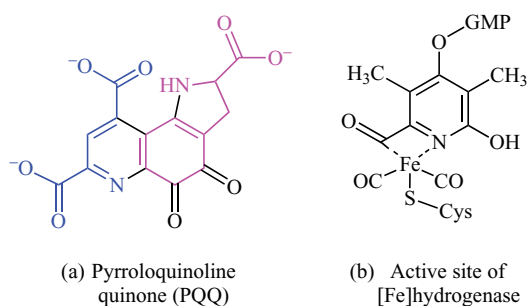


Figure 8 PQQ is formed by condensation of a glutamyl and a tyrosyl residue in a peptide. In [Fe]hydrogenase, the hydrogen probably binds to the open sixth coordination site of Fe. GMP, guanosine monophosphate.

iron ion ligated by two CO molecules, a cysteine side chain, a guanylyl pyridinol cofactor, and an unknown ligand suggested from crystallographic data to be the acyl side chain from the pyridinol (Figure 8b).¹⁷² Recently, it has been elucidated that HmdB is a radical SAM enzyme despite its unusual CX₅CX₂C motif.⁹⁶ HmdB could be involved in the formation of CO like HydG or ThiC as shown above or more likely in C-methylation of the pyridinol. It has been shown that one of the two methyl groups stems from methionine.¹⁷²

NifB is required for the biosynthesis of the MoFe cofactor of nitrogenase that catalyzes the reduction of dinitrogen to ammonia.^{173,174} NifB probably bridges two [4Fe–4S] clusters by inserting a sulfur atom along with the central atom, X = C, N, or O, thereby generating a FeS scaffold that is rearranged into a precursor, closely resembling the

core structure of the mature FeMoCo. Afterwards, Mo and homocitrate are added.

The interferon-induced antiviral protein viperin is a radical SAM enzyme that inhibits influenza A virus release from the plasma membrane of infected cells.¹⁷⁵ Viperin probably interacts with farnesyl diphosphate synthase, which affects the membrane fluidity.¹⁷⁶

2.4 Reactions Involving Ketyl Radicals

One-electron reduction of carbonyl groups, in ketones, thioesters, or amides, generates nucleophilic ketyl radicals. The extra electron is located in the 2p_z antibonding orbital of the carbonyl group and is stabilized by the electronegative oxygen atom.¹⁷⁷ The “Umpolung” or polarity inversion¹⁷⁸ of carbonyl groups in this way gives versatile intermediates with remarkable properties.⁵⁴ The nucleophilic character of ketyl radicals can be denoted by placing their negative charge at the carbon, which triggers elimination of an adjacent leaving group such as hydroxyl. This provides a useful method in synthetic chemistry for preparing ketones from α -hydroxyketones using one-electron donors such as Zn(0), Cr(II), and Sm(II) (see **Organic Synthesis Using Samarium Diiodide**). This reaction is thought to proceed via a ketyl radical that eliminates the hydroxyl to give an enoxy radical, which suffers one-electron reduction and protonation to yield the ketone.^{82b}

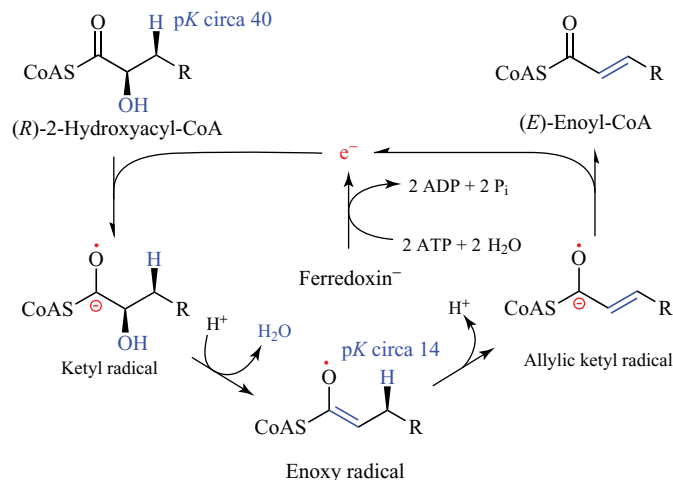
2.4.1 2-Hydroxyacyl-CoA Dehydratases

Several clostridia and fusobacteria thrive on the fermentation of amino acids to ammonia, CO₂, acetate, short-chain fatty acids, and H₂. Some of these fermentations occur pairwise, one amino acid acting as electron donor and the other as acceptor. These dismutations are called *Stickland reactions*,¹⁷⁹ but single amino acids such as alanine and leucine can disproportionate in a similar manner.³⁹ The acidic and basic amino acids are degraded by special pathways, in which radical enzymes are involved that have been described above, such as the SAM-dependent lysine-2,3-aminomutase and the coenzyme B₁₂-dependent enzymes methylmalonyl-CoA mutase (for aspartate), glutamate mutase, β -lysine-5,6-aminomutase, and ornithine-4,5-aminomutase (for arginine). Although the oxidative fermentation branches apparently resemble amino acid oxidations in aerobes, the irreversible NAD-dependent 2-oxoacid dehydrogenases are replaced by reversible 2-oxoacid ferredoxin oxidoreductases that comprise relatively stable radical intermediates in their catalytic pathways (see below). The reductions of 12 of the 20 proteinogenic amino acids to short-chain fatty acids are unique and exhibit a different type of radical chemistry. They proceed via their conversion to the corresponding (*R*)-2-hydroxy acids. This is followed by activation to (*R*)-2-hydroxyacyl-CoA, dehydration

to enoyl-CoA, reduction to saturated acyl-CoA, and excretion of the free fatty acid.^{54, 180–182}

The most interesting enzyme in this pathway is 2-hydroxyacyl-CoA dehydratase, whose substrate encounters the same problem as the parent amino acid, the activation of the β -hydrogen atom with a $pK_a \approx 40$. The reason for the conversion of the amino acids to the 2-hydroxy acids could be twofold. First, owing to their quite negative free energy change for hydrolysis, CoA-thioesters of α -amino acids are very unstable and tend to polymerize. In biology, the only known thioesters of α -amino acids are covalently bound to nonribosomal peptide synthetases, where polymerization is inhibited by structural separation.¹⁸³ Second, the elimination of a hydroxyl group adjacent to the electron withdrawing thioester via ketyl radicals may be easier than that of an amino group as demonstrated in the mechanistic proposal (Scheme 16).

This mechanism starts with a high-energy electron (E' circa -900 mV) that reduces the thioester carbonyl to a ketyl radical, which eliminates the adjacent hydroxyl group.⁸² It has been calculated that the pK_a of the β -proton of the resulting enoxy radical is 26 units lower as compared to that of the substrate.¹⁸⁴ After deprotonation, the allylic ketyl radical formed recycles its extra electron back to the enzyme and the product enoyl-CoA is released (Scheme 16). To date, four such unusual enzymes have been characterized which catalyze the following dehydrations.



Scheme 16 Proposed mechanism of 2-hydroxyacyl-CoA dehydratases. R = H, methyl, acetate, propionate, propyl, isopropyl, phenyl, *p*-hydroxyphenyl, or indolyl.

Lactyl-CoA dehydratase from *Clostridium pionicum* (Scheme 16, R = H) participates in the fermentation of α - and β -alanine, serine, cysteine, threonine, and methionine and catalyzes the *syn*-dehydration of (*R*)-lactyl-CoA to acryloyl-CoA ($K_{eq} = 0.02$) and of (*R*)-2-hydroxybutyryl-CoA to (*E*)-crotonyl-CoA.^{185–188}

2-Hydroxyglutaryl-CoA dehydratases from *Acidaminococcus fermentans* and *Clostridium symbiosum* (Scheme 16, R = CH₂-COO[−]) are involved in the fermentation of glutamate, glutamine, and histidine and catalyze the *syn*-dehydration of (*R*)-hydroxyglutaryl-CoA to (*E*)-glutaconyl-CoA ($K_{eq} = 57$).^{187,189–191}

2-Hydroxyisocaproyl-CoA dehydratase from *C. difficile* (Scheme 16, R = isopropyl) is required for the fermentation of leucine and catalyzes the dehydration of (*R*)-2-hydroxyisocaproyl-CoA to isocaprenoyl-CoA (4-methylhex-2-enoyl-CoA), most likely in a *syn*-geometry to yield the *E*-isomer ($K_{eq} = 1600$).^{187,192,193}

Phenyllactyl-CoA dehydratase from *Clostridium sporogenes* (Scheme 16, R = phenyl) is implicated in the fermentation of phenylalanine, tyrosine, and tryptophan and catalyzes the *syn*-dehydration of (*R*)-phenyllactyl-CoA to (*E*)-cinnamoyl-CoA [(*E*)-phenylacryloyl-CoA],^{194,195} of (*R*)-*p*-hydroxyphenyllactyl-CoA to *p*-hydroxycinnamoyl-CoA, and of (*R*)-3-indolelactyl-CoA to (*E*)-indoleacryloyl-CoA (H. Li, A. Parthasarathy, and W. Buckel, unpublished data).

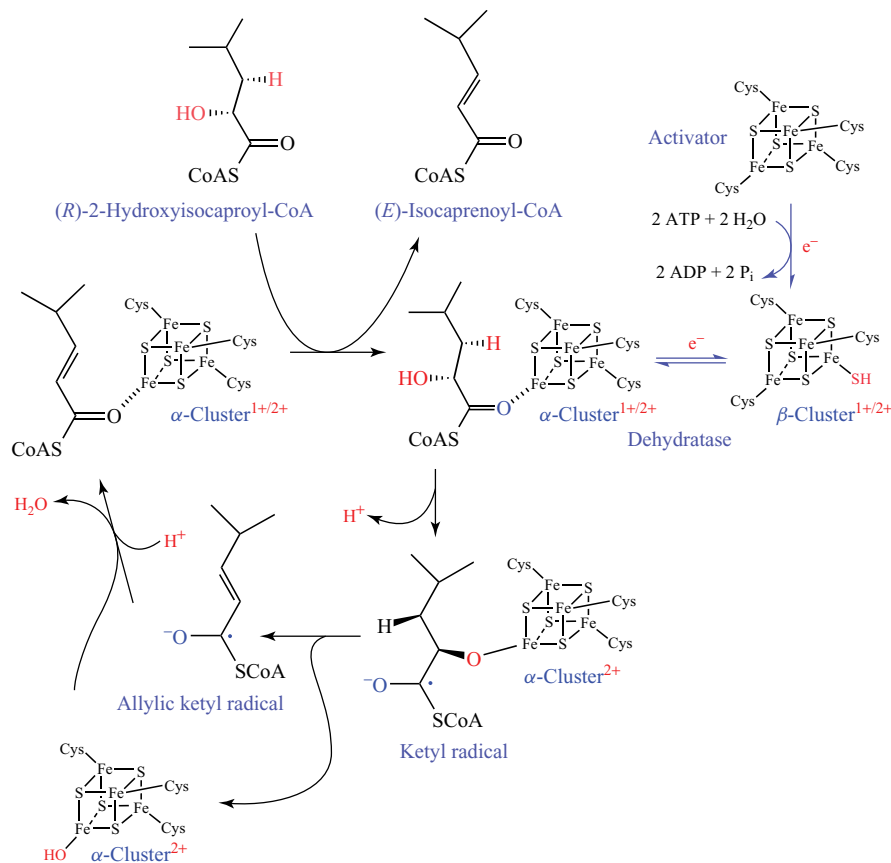
All these dehydratases consist of two extremely oxygen-sensitive proteins: a homodimeric activator or “archer”¹⁹⁶ containing one [4Fe-4S] cluster between the two subunits and the actual heterodimeric dehydratase with two [4Fe-4S] clusters, one in each subunit.^{182,197,198} The crystal structure of the activator protein of 2-hydroxyglutaryl-CoA dehydratase from *A. fermentans* revealed that helix 5 of each subunit points with its N-terminus toward the cluster, thereby forming a helix–cluster–helix architecture with an angle of 105°. ¹⁹⁹ Four cysteine residues, two from each subunit, coordinate the [4Fe-4S]²⁺ cluster, which is easily and reversibly reduced to [4Fe-4S]⁺ by ferredoxin or flavodoxin. Each of the two subunits contains one ADP occupying the ATP-binding site with an acetate and sugar kinases/heat shock protein 70/actin (ASKHA) motif.²⁰⁰ A similar structure around a [4Fe-4S]²⁺ cluster comprises the iron protein of nitrogenase, though the helix–cluster–helix

angle is wider by 45° and the ATP binds at a “Walker motif.”²⁰¹ The FeMoCo protein and the iron protein of nitrogenase form a complex that can be stabilized by ADP-AlF₄[−], a transition state analog of ATP hydrolysis. Interestingly, the structure of the complex revealed an opening of the helix–cluster–helix angle to 180°. ²⁰² With 2-hydroxyisocaproyl-CoA dehydratase and its activator from *C. difficile*, a similar complex was formed in the presence of ATP-AlF₄[−]. Accordingly, it was suggested that in the 2-hydroxyacyl-CoA dehydratases, the helix–cluster–helix angle also opens to approximately 180°, which enables docking and electron transfer to the dehydratase.²⁰³

EPR spectroscopy demonstrated ATP-dependent reduction of 2-hydroxyisocaproyl-CoA dehydratase by one electron from the reduced activator [4Fe-4S]¹⁺ cluster and the subsequent handover of the electron to the substrate. The radical species detected by EPR spectroscopy has been characterized as the most stable radical of the cycle, the product-related allylic ketyl radical (Scheme 16). The radical couples with the single protons at the γ - and δ -carbons but only weakly at the β -carbon, which was elucidated by deuterium substitution.¹⁹³

The crystal structure of 2-hydroxyisocaproyl-CoA dehydratase revealed two [4Fe-4S]²⁺ clusters, one in each subunit, at a distance of 12 Å. Each cluster is coordinated by three cysteines. In the somewhat larger α -cluster (in the α -subunit, 408 amino acid residues), a hydroxyl group is attached to the fourth iron, whereas in the β -cluster (in the β -subunit, 375 residues), the higher electron density at the corresponding iron is consistent with a hydrosulfide ligand (HS[−]), which was never detected in any cluster before. The structure with the substrate demonstrated a binding of the thioester carbonyl to the special iron of the α -cluster replacing the hydroxyl. In addition, glutamate α -55 is located at hydrogen-bonding distance to the carbonyl. Now the mechanism of the dehydration can be presented in more detail (Scheme 17).¹⁹⁸

Inside the actively growing anaerobic bacterial cell, ferredoxin occurs mainly in the reduced form and the ATP/ADP ratio is high, which keeps the activator loaded with one electron and ATP. This opens the helix–cluster–helix angle, making the activator cluster ready to interact with the dehydratase and to introduce the electron into the β -cluster. This process replicates the action of archers using ATP in their muscles to shoot



Scheme 17 Detailed mechanism of 2-hydroxyisocaproyl-CoA dehydratase (glutamate $\alpha 55$ transfers the proton shown).

an arrow. Hence, the activator has also been termed *archer*.¹⁹⁶ The extra electron of the dehydratase can be seen by EPR via the reduced β -cluster. Binding of the substrate to the α -cluster probably increases the redox potential that enables the electron to traverse the distance of 12 Å from the β - to the α -cluster, where it reduces the substrate to the ketyl radical via inner shell electron transfer. The ketyl radical formed binds more weakly to the cluster than the thioester carbonyl and is replaced by the hydroxyl group of the substrate, a process called *ligand swapping*. The proton is taken up by glutamate $\alpha 55$. The ketyl radical eliminates $^-\text{O}-\text{Fe}$, which acts as a base to remove the β -proton consistent with the observed *syn*-geometry. Glutamate $\alpha 55$ protonates $\text{HO}-\text{Fe}$ to give water and the allylic ketyl radical recycles the electron back to the cluster. The product isocaprenoyl-CoA leaves the enzyme and the open Fe site of the cluster binds either the next substrate

or water, which is deprotonated by glutamate $\alpha 55$ (Scheme 17).

Although Scheme 17 appears complicated, the use of just one electron provides an explanation as to how an “impossible” dehydration can occur. “Impossible” means that a standard E2 elimination cannot work, because the β -hydrogens have a pK_a that is too high. Ultimately, the electron is recycled back to the enzyme, ready for the next turnover and is used about 10 000 times until a new activation is required. The need to regenerate the electron is because of its dissipation by a second electron transfer, either to the substrate or to an external oxidant.¹⁹²

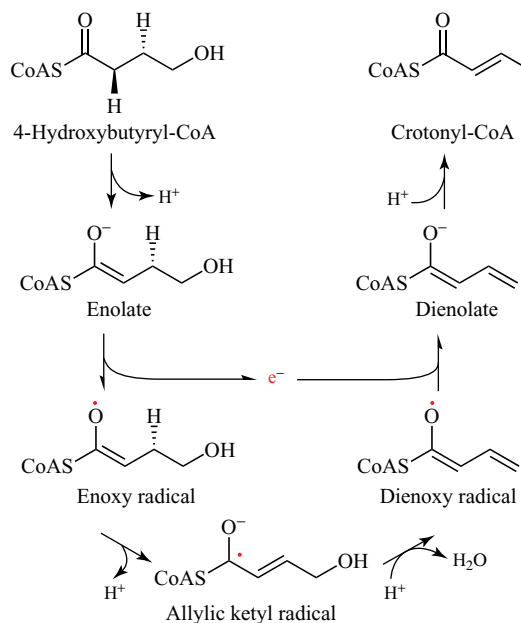
Hence, 2-hydroxyacyl-CoA dehydratases demonstrate a new mode of radical formation in biology, which proceeds without the use of complex cofactors such as coenzyme B_{12} or SAM. The α -cluster in the 2-hydroxyacyl-CoA dehydratases has a dual function, namely electron transfer and Lewis acid

catalysis to facilitate elimination. This function resembles the SAM radical enzymes by coordination of SAM to the fourth iron of the cluster and electron transfer to generate the 5'-deoxyadenosyl radical. The three cysteines of both dehydratase clusters, however, are not part of a consensus sequence but are spread over the whole polypeptide chains.¹⁹⁸

2.4.2 4-Hydroxybutyryl-CoA Dehydratase

Decarboxylation of glutamate yields 4-aminobutyrate (γ -aminobutyric acid, gamma-aminobutyric acid (GABA)) that is fermented by *Clostridium aminobutyricum* to ammonia, acetate, and butyrate. The pathway proceeds via succinic semialdehyde, 4-hydroxybutyrate, and 4-hydroxybutyryl-CoA that is dehydrated to crotonyl-CoA [(*E*)-but-2-enoyl-CoA]. Crotonyl-CoA disproportionates oxidatively to acetate and reductively to butyrate. The key enzyme of this pathway is 4-hydroxybutyryl-CoA dehydratase that catalyzes the reversible elimination of water²⁰⁴ probably also via a ketyl radical (Scheme 18).⁵⁴ This enzyme also occurs in *Clostridium kluyveri* during reduction of succinyl-CoA via succinic semialdehyde to butyrate.²⁰⁵ Recently, the enzyme has been detected in novel CO₂-fixation pathways occurring in Archaea, where it is involved in the conversion of succinate to two acetates.^{36,37}

4-Hydroxybutyryl-CoA dehydratase faces the same problem as 2-hydroxyacyl-CoA dehydratase because the β -hydrogen to be removed is not activated ($pK_a \approx 40$). In contrast to 2-hydroxyacyl-CoA, 4-hydroxybutyryl-CoA may be converted to the enoxy radical with an acidic β -proton ($pK_a \approx 14$) by α -deprotonation to the enolate and one-electron oxidation. Now, removal of the β -proton leads to an allylic ketyl radical that eliminates the hydroxyl group. The dienoxyl radical formed recycles the electron back to the enzyme, which protonates the dienolate to yield crotonyl-CoA.⁵⁴ This mechanism (Scheme 18) is consistent with the structure of the homotetrameric enzyme that contains in each subunit one FAD and one [4Fe–4S] cluster. As isolated, part of the FAD of the enzyme is in the semiquinone state. Full activity is obtained by brief oxidation with air, whereas longer exposure to air (5 hours at 20 °C) completely inactivates the enzyme. A controlled



Scheme 18 Proposed mechanism of the reversible dehydration of 4-hydroxybutyryl-CoA to crotonyl-CoA.

oxidation to full activity and to an EPR-silent preparation was achieved by treatment with ferricyanide [hexacyanoferrate(III)]. On addition of substrate, the EPR spectrum appeared again with the main signal of a neutral semiquinone and features attributed to partial reduction of the [4Fe–4S] cluster, but a carbon-based substrate-derived radical could not be identified.^{206,207} Chemical synthesis of stereospecifically deuterium- and tritium-labeled 4-hydroxybutyryl-CoA species revealed that the enzyme abstracts the 2*Re* and the 3*Si* hydrogen, whereas the substitution of the hydroxyl group occurs with retention of configuration.^{206,208}

The crystal structure indicated that 4-hydroxybutyryl-CoA dehydratase contains a channel between the cluster and FAD (Figure 9).²⁰⁹ The cluster is coordinated by three cysteines and a histidine. Although crystals with substrate or product could not be obtained, the fold and the position of the FAD resemble that of medium chain acyl-CoA dehydrogenase, whose structure has been solved in the presence of substrate. Therefore, 4-hydroxybutyryl-CoA was modeled into the channel, whereby similar hydrogen bonds to the thioester carbonyl could be formed as in the acyl-CoA dehydrogenase. In this orientation, the

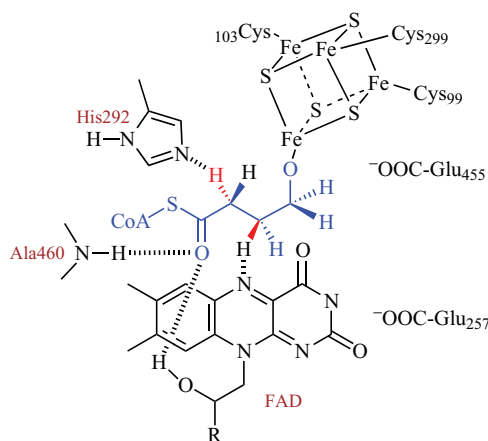


Figure 9 Modeling of 4-hydroxybutyryl-CoA into the active site of 4-hydroxybutyryl-CoA dehydratase from *Clostridium aminobutyricum*. RCHOHCH₂ = ADP ribitol. Numbers at the amino acids denote their position in the amino acid sequence of the enzyme.

hydroxyl group replaces histidine 292 coordinated to the cluster; the 2*Re* hydrogen can be removed by this histidine and the 3*Si* hydrogen by the FAD semiquinone. The elimination of the hydroxyl group is facilitated by the cluster acting as Lewis acid. The protonated histidine probably transfers the proton to the hydroxylated cluster leading to the formation of water. Finally, the dienolate is protonated at C-4 by the conserved glutamic acid 455 to yield the methyl group (Figure 9).

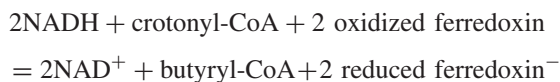
Mutations of the amino acids depicted in Figure 9 yielded a completely inactive enzyme with the exception of the A460G mutant that retained 2% activity. Although the NH of a glycine residue should be a hydrogen bond donor comparable to alanine, the greater flexibility with glycine may disturb the structure of the enzyme. The other mutations strongly support the importance of His292 as a base and of the structural integrity of the [4Fe-4S] cluster. Glutamate 455 probably donates the proton for the methyl group of crotonyl-CoA and Glu257 might be involved in the proton transfer from FAD semiquinone to the solvent. The exchange of tyrosine 296 by phenylalanine reduced the activity to 1%, which might suggest participation of a tyrosyl radical in catalysis.²¹⁰

4-Hydroxybutyryl-CoA dehydratase also catalyzes the irreversible Δ -isomerization of vinylacetyl-CoA to crotonyl-CoA.²⁰⁴ This activity

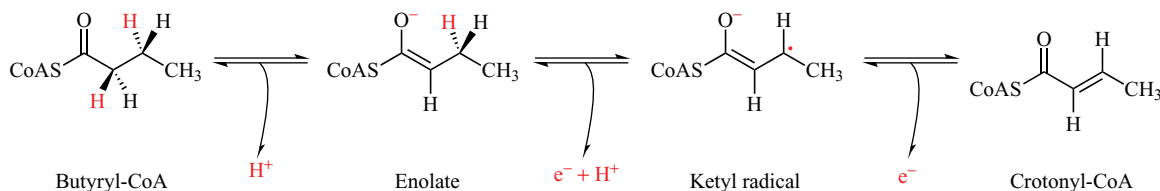
is less oxygen sensitive than that of the dehydratase. Important residues are histidine 292 as proton acceptor and glutamate 455 as donor; with the mutants H292C or E455Q retaining about 1% activity. As expected, the iron sulfur cluster and FAD are not required for the isomerization. Notably, C299A and E257Q are almost fully active and are completely stable under air.²¹⁰

2.4.3 Acyl-CoA Dehydrogenases

The β -oxidation of fatty acids starts with the formation of the CoA-thioester that is dehydrogenated to the (*E*)-2-enoyl-CoA catalyzed by FAD-containing acyl-CoA dehydrogenases. The electron transferring flavoprotein (Etf) serves as an electron acceptor, which transports the electron from the dehydrogenase in the cytoplasm to the respiratory chain in the cytoplasmic membrane of bacteria and archaea or in the mitochondrial membrane of eukaryotes. There, Etf:quinone oxidoreductase catalyzes the oxidation of Etf by a quinone. Clostridia-producing short-chain fatty acids use this reaction sequence in the reverse direction, the reduction of enoyl-CoA to the saturated acyl-CoA by NADH. Recently, it has been shown that this reaction is coupled to the endergonic reduction of ferredoxin, whereby a second NADH is consumed.^{211–213} In this energetic coupling, the electrons bifurcate from NADH ($E^{\circ'} = -320$ mV) exergonically to enoyl-CoA ($E^{\circ'} = -20$ mV) and endergonically to ferredoxin ($E^{\circ'} = -420$ mV) according to following equation:



Thus, the high free energy change for enoyl-CoA reduction is conserved in the powerful reductant ferredoxin, which the cell uses either for the production of hydrogen or recycles to regenerate NADH mediated by a complex membrane protein designated as Rnf. This hetero hexameric complex, which contains riboflavin, covalently and noncovalently bound riboflavin-5'-phosphate (FMN), as well as 6–7 [4Fe-4S] clusters, acts as proton or sodium ion pump and thus contributes to the energy metabolism of the bacterial cell.^{214,215}



Scheme 19 Proposed radical mechanism for butyryl-CoA dehydrogenase after Cornforth.²¹⁶ The first proton is removed by a conserved glutamate; FAD accepts the first electron and the second proton; FADH semiquinone takes the second electron to become the hydroquinone FADH[−]. Note that the stereochemistry of the *anti*-elimination of the α - and β -protons is identical to that of 4-hydroxybutyryl-CoA dehydratase.

The generally accepted mechanism of acyl-CoA dehydrogenases starts—similar to 4-hydroxybutyryl-CoA dehydratase—with the abstraction of the α -proton, $\text{p}K_{\text{a}} = 8$, from the hydrogen bonded acyl-CoA.²¹⁷ The β -hydrogen is thought to be removed from the enolate as hydride by the flavin. Considering the mechanism of 4-hydroxybutyryl-CoA dehydratase, however, one would expect a proton-coupled one-electron transfer from the enolate to the flavin to yield the semiquinone and the product-related allylic ketyl radical followed by a second one-electron transfer to afford the flavin hydroquinone and enoyl-CoA (Scheme 19). On the basis of the observation of a putative flavin semiquinone deduced from the absorbance between 500 and 650 nm during catalysis of acyl-CoA dehydrogenases by Helmut Beinert in 1957,^{218,219} Sir John Cornforth already proposed this mechanism 50 years ago (Scheme 19).²¹⁶ Experiments with a radical trap support the idea of radical intermediates,²²⁰ but EPR spectroscopy detected no signal.²¹⁹ Furthermore, the putative semiquinone turned out to represent a tight charge-transfer complex between FADH[−] and the product enoyl-CoA.²¹⁷

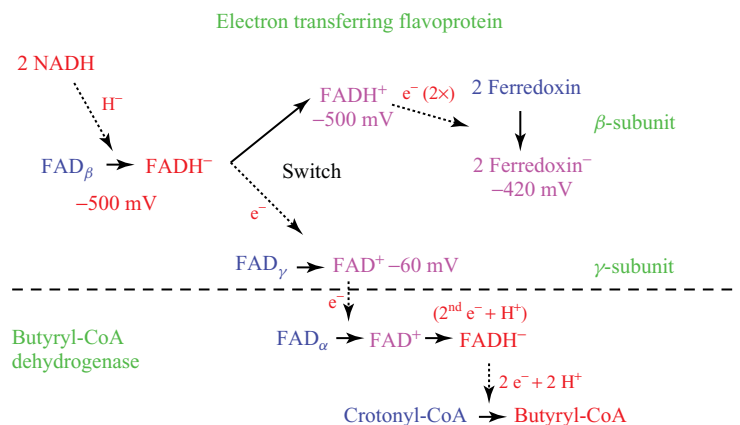
2.4.4 Etf and Electron Bifurcation

The redox potentials of flavins are extremely dependent on their surroundings. While free flavin exhibits $E^{\circ'} = -230$ mV (semiquinone/hydroquinone) and $E^{\circ'} = -170$ mV (quinone/semiquinone),²²¹ the values for flavodoxin from *A. fermentans* are $E^{\circ'} = -430$ and -60 mV, respectively.¹⁸⁹ Cell extracts from *A. fermentans*¹⁸⁹ and *Fusobacterium nucleatum* (D. Brügel and W. Buckel, unpublished data) prepared

under anaerobic conditions contain flavodoxin as a stable blue semiquinone radical. FAD within an acyl-CoA dehydrogenase shows a typical $E^{\circ'} = -145$ mV (quinone/hydroquinone), which on substrate addition increases to -26 mV.²²² These considerations allow the proposal of a mechanism for electron bifurcation catalyzed by the clostridial complex of Etf and butyryl-CoA dehydrogenase (Scheme 20). The heterodimeric Etf, which probably resembles that of *Megasphaera elsdenii*,²²³ contains two FAD molecules in different surroundings, say β -FAD in the β -subunit and γ -FAD in the γ -subunit. β -FAD should have a negative redox potential (quinone/hydroquinone; $E^{\circ'} = -500$ mV). Thus, it cannot be reduced by NADH ($E^{\circ'} = -320$ mV) to β -FADH[−] unless γ -FAD accepts one electron, whereas the remaining electron reduces ferredoxin ($E^{\circ'} = -420$ mV). γ -FAD ($E^{\circ'} = -60$ mV) takes up only one electron, because its semiquinone/hydroquinone transition for a second electron is much too negative ($E^{\circ'} < -500$ mV). The electron is further delivered to the FAD of acyl-CoA dehydrogenase. This process is repeated to obtain the FADH[−] (hydroquinone) state in the dehydrogenase and a second molecule of reduced ferredoxin.

2.4.5 DNA Photolyase

In contrast to dry DNA in bacterial spores (see SAM radical enzymes), irradiation of DNA in the cytoplasm of a cell with UV-B light (290–320 nm) causes two adjacent thymidine residues to form a cyclobutane–pyrimidine dimer (CPD) by [2+2] cyclophotoaddition. DNA photolyase repairs this lesion in a radical reaction driven by blue light (350–450 nm). The enzyme from *E. coli* contains



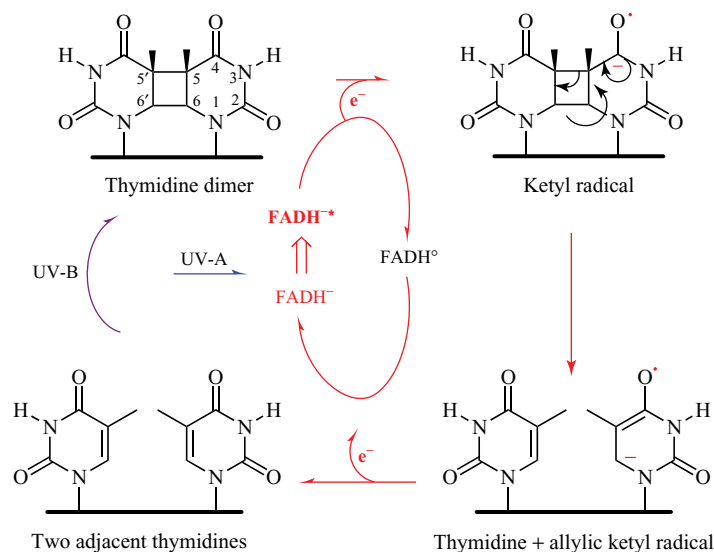
Scheme 20 Proposed mechanism of electron bifurcation. Green: proteins; blue: oxidized forms; magenta: reduced by one electron; orange: reduced by two electrons.

methylenetetrahydrofolate ($CH_2=FH_4$) and FAD as prosthetic groups. For catalysis, FAD needs to be in the reduced anionic state ($FADH^-$), which absorbs almost no blue light. The $CH_2=FH_4$ group ($\lambda_{\max} = 380\text{ nm}$) acts as light antenna and transfers the energy to $FADH^-$ to yield the excited state $FADH^{-*}$.²²⁴ Binding of the lyase to the DNA lesion results in flipping of CPD into the active site of the enzyme.²²⁵ Then, $FADH^{-*}$ transfers a high-energy electron to CPD to form a ketyl radical at C-4, adjacent to the cyclobutane ring. Similar to 2-hydroxyacyl-CoA dehydratases, the ketyl radical may act as a nucleophile that cleaves the 5–5' and 6'–6 bonds of the cyclobutane ring to give a resonance-stabilized ketyl radical and one restored thymidine residue. Finally, the electron recycles back to the transiently formed $FADH$ semiquinone to yield the second restored thymidine and regenerated $FADH^-$. Thus, the next photon can drive another turnover (Scheme 21).

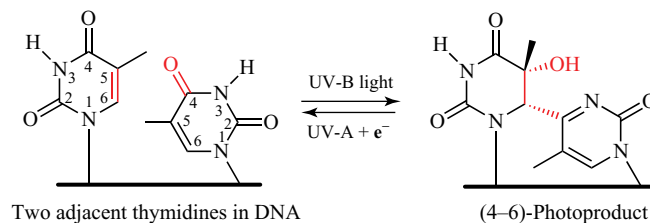
A similar mechanism cleaves the (6–4) lesion in DNA (Scheme 22). Again, one high-energy electron from $FADH^{-*}$ repairs the lesion in two-electron steps.²²⁶ The lesion derives from [2+2] cyclopho-toaddition of the 5'=6' double bond of one thymidine residue at the C-4 carbonyl group of the other thymidine residue, probably with a four-membered oxetane ring as an intermediate. Thereby, the oxygen is transferred without solvent exchange. Hence, the mechanisms of the photolyases and 2-hydroxyacyl-CoA dehydratases are similar. A high-energy electron forms a substrate-derived ketyl

radical, and the most likely concerted reaction proceeds to a product-related ketyl radical that recycles the electron back for the next turnover. Only in one aspect do the mechanisms differ: While the photolyases require light energy for every turnover, the 2-hydroxyacyl-CoA dehydratases are able to recycle the electron 10^4 times without external energy input. With photolyase, the energy difference between the two radicals is probably too high to allow recycling in the dark as in the dehydratase. In addition, the lifetime of $FADH^{-*}$ might not be long enough for the enzyme to find another lesion.

Homologues of the DNA photolyase that repairs the CPD lesion are cryptochromes, the blue light receptors of many organisms.²²⁷ The N-terminal part contains the domains that bind methylenetetrahydrofolate and FAD, whereas the C-terminal part conveys the specific function of the receptor to other proteins and, in case of animals, finally to the nervous system. Experiments with migrating birds suggest the involvement of cryptochromes in magnetoreception, a compass by which these animals achieve remarkable intercontinental travel.²²⁸ The receptor is a radical pair that can exist in the triplet and singlet states, whose interconversion and life times are influenced by the magnetic field.²²⁹ Irradiation of the oxidized FAD with blue light forms the radical pair. Thereby, FAD is reduced to the anionic flavin semiquinone by an electron from one of three conserved tryptophans of the protein that is oxidized to a cation radical. Hence, radical pair formation is involved in the reduction of FAD to



Scheme 21 Formation of thymidine dimers in DNA by irradiation with UV-B and repair by catalysis with DNA photolyase, energized by UV-A.¹⁸¹



Scheme 22 Formation and enzymatic cleavage of the DNA (4-6)-photoproduct.¹⁸¹

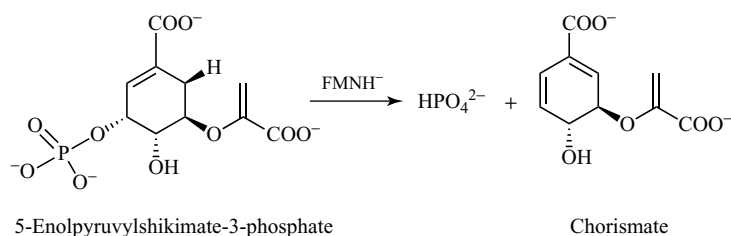
the semiquinone, whereas the photolyase uses the excited state of the fully reduced $\text{FADH}^{\bullet-}$.

2.4.6 Chorismate Synthase and 2-Haloacrylate Hydratase

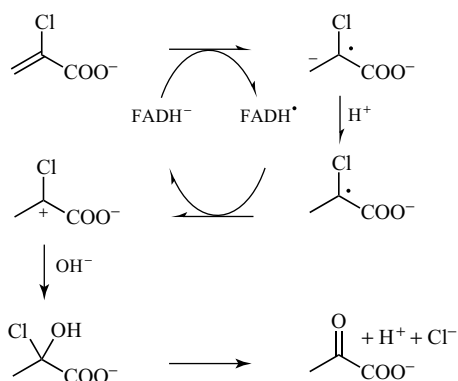
The amino acids phenylalanine, tyrosine, and tryptophan are synthesized by the so-called shikimate pathway. At the intermediate chorismate, as indicated by its Greek name, the path diverts either to prephenate, the precursor of phenylalanine and tyrosine, or to tryptophan via anthralinate. The synthesis of chorismate from 5-enolpyruvoylshikimate-5-phosphate by *anti*-1,4-elimination of phosphate is catalyzed by a reduced riboflavin-5'-phosphate (FMNH^-)-containing enzyme (Scheme 23). The reaction attracted much interest, because

it was expected that the apparently simple 1,4-elimination of phosphate should occur with *syn*-geometry.^{230,231} This was deduced from the observed *anti*-1,2-elimination of water from many hydroxy acids (not hydroxyacyl-CoA!). However, in contrast to elimination of water from 3-hydroxy acids, the hydrogen to be removed as proton is not acidic. Therefore, it appears most likely that the enzyme proceeds via a radical mechanism, analogous to that of 2-hydroxyacyl-CoA dehydratases. A one-electron transfer from FMNH^- to the double bond of the substrate 3-enolpyruvylshikimate-5-phosphate would yield the flavin semiquinone and a radical anion that readily eliminates the phosphate. The resulting allyl radical is deprotonated to an allylic radical anion that is finally oxidized to the product.^{4,232}

A similar mechanism most likely operates with the FADH^- -dependent 2-haloacrylate hydratase that



Scheme 23 Reaction catalyzed by chorismate synthase.



Scheme 24 Proposed mechanism for the hydration of 2-chloroacrylate to pyruvate and HCl.

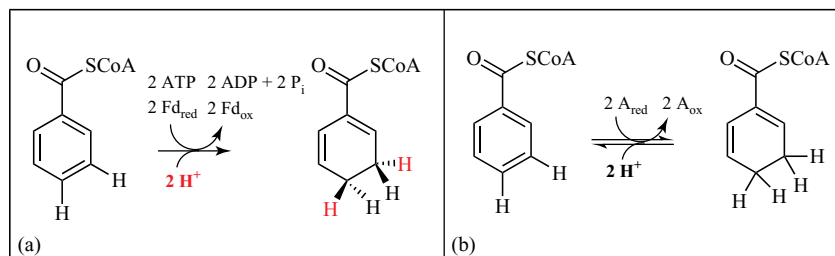
catalyzes the hydration of 2-chloroacrylate to pyruvate and chloride. A simple hydration of chloroacrylate would lead to 2-chloro-3-hydroxypropionate, which is not observed.²³³ Addition of one electron from FADH^- to 2-chloroacrylate would cause an “Umpolung” and directs the proton to the methylene group. The resulting 2-chloropropionate radical returns the electron back to the flavin semiquinone to yield a carbocation that reacts with water to 2-chloro-2-hydroxypropionate. α -Elimination of HCl affords the final product pyruvate (Scheme 24).

2.5 Reduction of Aromatic Compounds

Although many useful natural products are aromatic compounds, the formation of benzene and polycyclic aromatic compounds in combustion processes is responsible for environmental contamination with substances that are potentially damaging to all forms of life. Fortunately, mechanisms exist

for the destruction of these pollutants. In the aerobic metabolism of aromatic compounds, degradation is initiated by addition of an oxygen atom, mediated by cytochrome *P*450 mono-oxygenases,²³⁴ or dioxygen catalyzed by dioxygenases, to the ring π -system. In contrast, anaerobic bacteria abolish aromaticity *without* the aid of (di)oxygen and do so by reductive reactions. For benzoic acid, there are two classes of enzymes that are key to the reduction of its CoA ester.²³⁵ In the best studied example from *Thauera aromatica*, de-aromatization of benzoyl-CoA is effected by a class I BCR.²³⁶ This type of BCR contains four subunits ($\alpha\beta\gamma\delta$) and three [4Fe–4S] clusters and is extremely oxygen sensitive. The α - and δ -subunits each bind a molecule of ATP and effect electron transfer to benzoyl-CoA at the active site, which is housed within the $\beta\gamma$ -subunits. The functions of the four subunits were deduced from their sequence similarity with the 2-hydroxyacyl-CoA-dehydratases.²³⁷ The α - and δ -subunits are related to the activator and most likely coordinate one of the three [4Fe–4S] clusters in between. The β - and γ -subunits that are related to the actual dehydratase contain the conserved cysteines of the α - and β -clusters of the dehydratase.¹⁹⁸

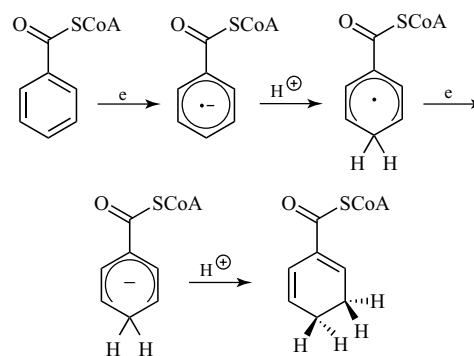
The two-electron reduction of benzoyl-CoA utilizes reduced ferredoxin, hydrolyzes the two molecules of ATP and affords cyclohexa-1,5-diene-1-carboxyl-CoA via a stereoselective *trans*-dihydro addition (Scheme 25a).²³⁸ This reaction is astonishing because its chemical analogy, the “Birch reduction” of benzenoid compounds employing sodium in liquid ammonia, has a redox potential of circa -3 V .²³⁵ The class I BCR is quite “catholic” in that it reduces a range of substrate analogs (i.e., benzoyl-CoA substituted with F, Cl, CH_3 , OH, and NH_2), and the benzene ring can be replaced by a pyridine.²³⁶



Scheme 25 Reaction catalyzed by class I BCR (a, Fd = ferredoxin; the stereochemistry of addition is shown by the red color) and class II BCR (b, A_{red} and A_{ox} = electron donor/acceptor).

The same overall reaction but with different cofactors (Scheme 25b) is accomplished by the class II BCR from, for example, *Geobacter metallireducens*, which is an ATP-independent enzyme containing tungstopterin [W^V], one [3Fe-4S] cluster, three [4Fe-4S] clusters, and selenocysteine.^{235,239} While class I BCRs are irreversible, the class II version is fully reversible. With $E^{\circ'} = -622$ mV, this BCR exhibits a midpoint redox potential significantly lower than that of other redox enzymes.²³⁵ While in class I BCR, this low redox potential is achieved by coupling to the hydrolysis of two ATP, how this is accomplished in class II BCR remains an enigma. It has been speculated that the ATP-independent electron transfer to the aromatic ring is driven either by an electrochemical membrane potential or by electron bifurcation (see Section 2.4.4) from ferredoxin ($E' = -500$ mV) to NAD⁺ ($E' = -270$ mV).^{235,239}

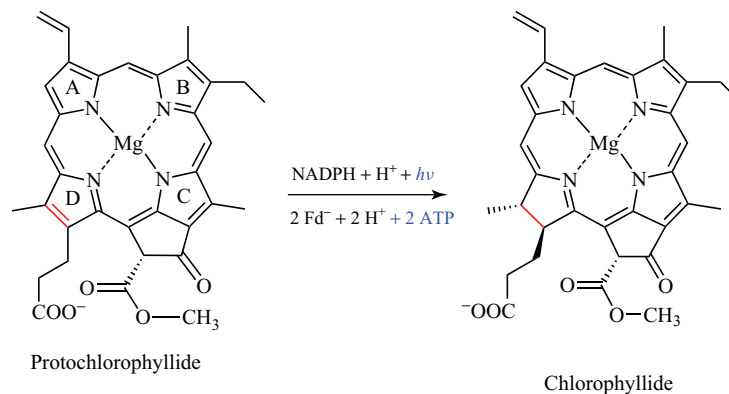
A mechanism for reduction of benzoyl-CoA by BCR has been proposed that is analogous to the one well established for the Birch reduction (Scheme 26).²³⁶ The first step is electron addition to give a radical anion analogous to the ketyl radicals discussed in Section 2.4. This is the most difficult step and is presumably achieved by a sufficiently low redox potential (see above) applied to a sufficiently electron-deficient substrate. The intermediate radical anion is intrinsically stable as a highly delocalized ketyl species and could be further stabilized by interactions with active site residues, for example, hydrogen bonding to the carbonyl oxygen.⁵⁴ Protonation of this intermediate, a further electron addition, and another protonation affords cyclohexa-1,5-diene-1-carboxyl-CoA. Presumably, the observed regio- and stereochemistry is controlled by appropriately positioned groups at the BCR active site. Notably, the proposed mechanism



Scheme 26 Mechanism for BCR reduction of benzoyl-CoA.

of the phylogenetically related 2-hydroxyacyl-CoA dehydratases also starts with a ketyl radical (Schemes 16 and 17).^{82,193} Benzoyl-CoA can be regarded as a central intermediate in the anaerobic catabolism of many benzenoid compounds. For example, phenol is converted to benzoyl-CoA by a sequence of phosphorylation, carboxylation coupled to phosphate hydrolysis, and deoxygenation of 4-hydroxybenzoyl-CoA.^{240–242} 4-Hydroxybenzoyl-CoA reductase, which catalyzes this deoxygenation to benzoyl-CoA, contains molybdopterin, FAD, and a [4Fe-4S] cluster with ferredoxin as reductant. The reduction probably involves a ketyl radical⁸² and Mo^V.²⁴² The degradation of naphthalene proceeds via 2-naphthoyl-CoA, which is a substrate for naphthoyl-CoA reductase (NCR) and yields tetrahydronaphthoyl-CoA.²⁴³ The mechanism of NCR is expected to be similar to that of BCR, that is, electron transfers and protonations, with an intermediate ketyl radical.

Similar to BCRs, the reduction of the C₁₇=C₁₈ double bond of the D-ring of the aromatic 22- π system of protochlorophyllide by NADPH requires



Scheme 27 Two types of protochlorophyllide reductases. Angiosperm plants use NADPH and light; all other organisms take reduced ferredoxin (Fd^-) and ATP.

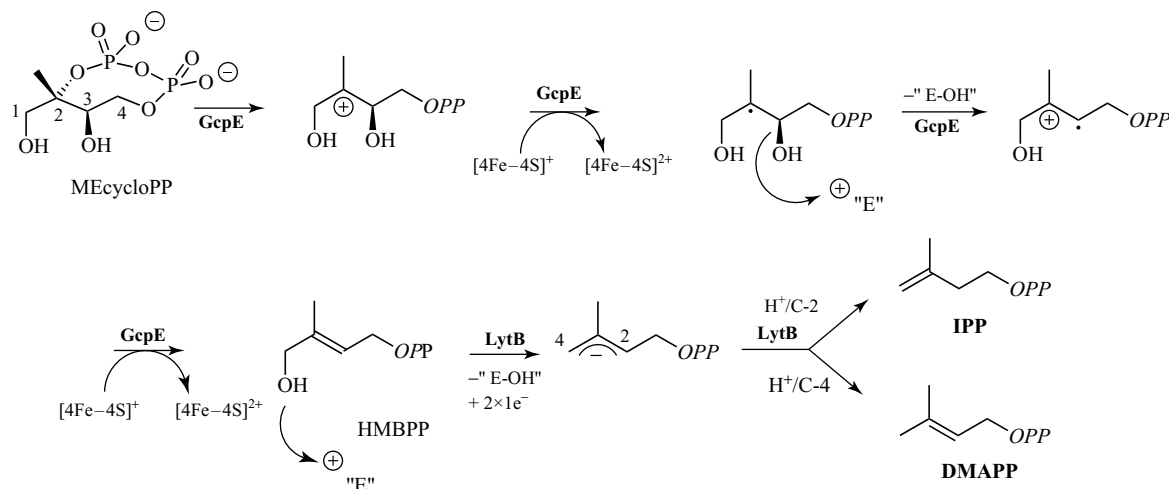
energy either from light or ATP (Scheme 27). While angiosperm plants use light, all other chlorophyll and bacteriochlorophyll-containing organisms reduce protochlorophyllide in the dark with ferredoxin but need ATP for this process. The enzyme is not only functionally but also phylogenetically related to nitrogenase (NifDK)₂ and its Fe protein (NifH)₂.²⁴⁴ It consists of a homodimeric Fe protein (BchL)₂ with one [4Fe–4S] cluster between the subunits and a heterotetrameric actual reductase (BchBN)₂, which contains 2×1 [4Fe–4S] cluster between the BchB and BchN subunits but lacks the P cluster and the MoFe cofactor.^{245–247} Therefore, the reductase is more closely related to the scaffold protein of nitrogenase (NifEN)₂, on which the MoFe cofactor is assembled before it is transferred to the nitrogenase MoFe protein (NifDK)₂.²⁴⁸ A similar enzyme system, chlorophyllide reductase composed of (BchX)₂ + (BchYZ)₂, catalyzes, in addition, the reduction of the opposite double bond in ring B of chlorophyllide to yield bacteriochlorin, the precursor of bacteriochlorophylls. Although EPR spectroscopy could not detect radical intermediates in the ATP-dependent reductases, there is evidence that the two electrons required for reduction are transferred one by one, in the same way as to nitrogenase.²⁴⁴

2.6 Isoprenoid Biosynthesis

The biosynthesis of isoprenoids from deoxyxylulose-5-phosphate in green algae, plant chloroplasts, pathogenic bacteria, and in

the malaria parasite *Plasmodium falciparum* but not in animals and fungi, occurs via the methyl-D-erythritol-2,4-cyclodiphosphate (MEP) pathway, rather than by the well-known mevalonate pathway.²⁴⁹ Like the mevalonate pathway, the MEP pathway produces isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP).²⁵⁰ The putative radical enzymes (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate synthase (abbreviated as GcpE or IspG) and (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate reductase (LytB or IspH) catalyze steps in the MEP pathway. They have been isolated from *E. coli* and other organisms, and both contain an oxygen-sensitive [4Fe–4S] cluster.^{251,252}

GcpE/IspG catalyzes the conversion of methylerythritol-2,4-cyclodiphosphate (MECycloPP) to (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP), while LytB/IspH converts the latter to a mixture of IPP and DMAPP. GcpE/IspG and LytB/IspH are coupled with a system that reduces the oxidized [4Fe–4S]²⁺. In *E. coli*, flavodoxin/ferredoxin reductase and NADPH fulfill this function. The reduced [4Fe–4S] cluster in GcpE/IspG was suggested to effect two one-electron transfers generating intermediate radicals (Scheme 28). Cleavage of the cyclodiphosphate ring to a tertiary carbocation is followed by one-electron reduction to give a β -hydroxyalkyl radical that eliminates the C-3 hydroxyl group in the manner of RNR or diol dehydratase (see above). The resulting alkene radical cation is reduced to an alkene by a further one-electron transfer from the cluster. Studies of GcpE/IspG by EPR and



Scheme 28 Hypothetical biogenetic pathway for the reactions catalyzed by GcpE and LytB ("E" represents an electrophilic entity that might be a Fe of the [4Fe-4S] cluster).

ENDOR detected several paramagnetic species on the reaction pathway and they all interacted with the Fe-S cluster.²⁵³ The data were interpreted as evidence for substrate binding to the cluster and its involvement in the elimination of substrate hydroxyl. A quite different thesis was put forward from the results of a similar spectroscopic study aided by isotopic labeling of MEP with ²H, ¹³C, and ¹⁷O.²⁵⁴ In this case, a series of intermediate metalocycles were proposed and the pathway was claimed to be supported by the finding that propargyl diphosphate is a potent inhibitor of GcpE/IspG (*K_i* ~ 300 nM), possibly by formation of a ferracyclopropene.

(*E*)-4-Hydroxy-3-methylbut-2-enyl diphosphate reductase (LytB/IspH) reduces HMBPP to a mixture of IPP and DMAPP via two successive one-electron transfers from the reduced [4Fe-4S] cluster. This yields, probably via radicals, an intermediate allylic anion, which is protonated either at C-2 affording IPP or at C-4 giving DMAPP (Scheme 28). The removal of the hydroxyl group from HMBPP might be assisted by an interaction with the Fe-S cluster (cf. 4-hydroxybutyryl-CoA above). Mössbauer studies of LytB/IspH revealed that a [4Fe-4S]²⁺ cluster is bound to the protein by three sulfur atoms from cysteines and by additional nitrogen and/or oxygen ligands surrounding a hexacoordinate iron centre.²⁵² Five crystal structures were obtained for LytB/IspH bound to substrate, products, or diphosphate and were interpreted as supporting the

mechanism outlined and shown in Scheme 28.²⁵⁵ Activation of substrate hydroxyl by coordination to an iron centre was compared with the similar mode of action of aconitase. For LytB/IspH, expulsion of the hydroxyl group is assisted by a proton-coupled electron transfer to the substrate double bond. Again, an opposing proposition suggested a role for organometallic species in the mechanism of LytB/IspH.²⁵⁶ Arising from this study were the "first potent IspH inhibitors," for example, an alkynyl diphosphate with IC₅₀ = 0.45 μM.

Inhibitors of the MEP pathway are potential selective drugs against pathogenic bacteria and certain parasites. In attempt to target the pathway at an earlier point, a high-throughput screen of a large library of compounds identified thiazolopyrimidines as modest inhibitors (IC₅₀ = low micromolar) of methyl-D-erythritol-2,4-cyclophosphate synthase (IpsF) from *Arabidopsis thaliana*.²⁵⁷

2.7 Pseudo Radical Enzymes

The so-called pseudo radical enzymes mediate the main reaction on the catalytic pathway in two-electron steps, whereas the subsequent recycling of the cofactors occurs by two one-electron transfers. This section deals with two examples of this group, the degradation and formation

of 2-oxoacids and the reversible reduction of methyl-coenzyme M (methyl-CoM) to methane.

2.7.1 2-Oxoacid Dehydrogenases/Oxidases

2-Oxoacids are important intermediates in catabolism and anabolism of sugars and amino acids. In chemotrophic organisms, 2-oxoacids are usually degraded to acyl-CoA and a C₁ compound, either CO₂ or formate. In anaerobic autotrophic organisms, 2-oxoacids are synthesized by reductive carboxylation of acyl-CoA. The enzymes involved are pyruvate formate lyase, a glycyl-radical enzyme, which has been discussed in a previous section, 2-oxoglutarate and pyruvate dehydrogenases, pyruvate oxidase, as well as 2-oxoglutarate and pyruvate:ferredoxin oxidoreductases (2-oxoglutarate and pyruvate synthases). With the exception of pyruvate formate lyase, these enzymes require ThDP as cofactor, which forms an adduct with the 2-oxoacid. With pyruvate as substrate, the 2-lactyl-ThDP formed resembles an imine of a 3-oxoacid, which readily decarboxylates to α -hydroxyethyl-ThDP.²⁵⁸ While these two-electron steps occur with all ThDP-dependent enzymes, the subsequent oxidation to acyl-CoA is different. In the reversible pyruvate ferredoxin oxidoreductase, the first electron transfer to a [4Fe-4S] cluster and then to ferredoxin generates a relatively stable thiamin-based radical, which was one of the first radicals observed in enzymatic catalysis.²⁵⁹ This exciting result was probably due to the fact that the enzyme from the facultative anaerobe *Halobacterium salinarum* is much more tolerant to dioxygen than those from strict anaerobes. Later the same radical could be observed and structurally characterized in crystals of the pyruvate:ferredoxin oxidoreductase from the sulfate reducer *Desulfovibrio africanus*.²⁶⁰ The second electron is only transferred in the presence of CoA leading to acetyl-CoA. Model studies have shown that acetyl-ThDP is a poor electrophile, unable to acetylate CoASH at a reasonable rate. Therefore, the second electron derives from CoASH that is converted to a thiyl radical, which recombines with the thiamin-based radical to yield acetyl-CoA and regenerate the cofactor.

The FAD and ThDP containing pyruvate oxidase catalyzes the irreversible dioxygen- and inorganic

phosphate-dependent conversion of pyruvate to H₂O₂ and acetyl-phosphate. Again, in the absence of phosphate, the stable thiamin-based radical was obtained.²⁵⁸ The most elaborate enzyme of this group is the huge enzyme complex pyruvate dehydrogenase, composed of a decarboxylase with ThDP, a lipoamide-containing transacetylase with covalently bound lipoamide, and an NAD⁺-dependent and FAD-containing dehydrogenase. The initially formed hydroxyethyl-ThDP donates both electrons, apparently in one-electron steps, to the protein-bound lipoamide (see Section 2.3.2.3 for lipoamide biosynthesis via a SAM radical enzyme). Chemical considerations indicate that the strained five-membered dithiolane ring of lipoamide is not amenable to a two-electron reduction (Perry A. Frey, personal communication). Furthermore, the thiamin-based radical has been observed by EPR spectroscopy during catalysis of the *E. coli* enzyme (Kai Tittmann, Antonio J. Pierik, and Wolfgang Buckel, unpublished data). Concomitant with the second electron transfer, the acetyl moiety and the proton are combined to yield S⁶-acetyl-dihydrolipoamide. In the second step, the acetyl group is transferred to CoASH, yielding acetyl-CoA. The final re-oxidation of dihydrolipoamide is catalyzed by the FAD-containing lipoamide dehydrogenase using NAD⁺ as electron acceptor, certainly via FAD semiquinone as intermediate.

2.7.2 Methyl-Coenzyme M Reductase

Methyl-CoM reductase from methanogenic Archaea mediates the formation of methane from methyl-S-CoM (CH₃-S-CoM) and coenzyme B (CoB-SH). The enzyme contains nickel bound within factor 430 (F₄₃₀), a yellow Ni-porphyrinoid with λ_{max} 430 nm.²⁶¹ Methane could arise by homolysis of a labile methyl-Ni σ -bond, although a methyl radical has not been detected. Most experimental data collected with the reductase fit a mechanism that starts with nucleophilic attack of Ni(I) at the methyl group of methyl-CoM. Protonation of the resulting methyl-Ni^{III}-F₄₃₀ releases methane, and Ni(I) is regenerated by two one-electron reductions from CoB-SH to form CoB-S-S-CoM via thiyl and sulfuranyl radicals.²⁶² Recently, evidence has been obtained

that methyl-CoM reductase is also able to catalyze the oxidation of methane, just the reverse of its formation. This is the first example of the cleavage of the strongest known C–H bond without oxygen. Compared to a methyl group in a saturated hydrocarbon, the C–H bond of methane is 18 kJ mol^{−1} stronger.²⁶³

Recently, another problem of methanogenesis has been solved, the source of the reduced ferredoxin ($E' = -500$ mV) to drive the first step, the reduction of CO₂ to formyl-methanofuran. While in cytochrome-containing methanogens, for example, *Methanosarcina barkeri*, this is achieved via an electrochemical H⁺ gradient (proton motive force), in cytochrome-less methanogens, for example, *Methanothermobacter marburgensis*, the energy-conserving heterodisulfide reductase is a soluble enzyme that cannot form such a gradient. Experiments with the isolated hydrogenase/heterodisulfide complex from *M. marburgensis* revealed that even low hydrogen concentrations (10 Pa; $E' = -300$ mV) are able to reduce ferredoxin if coupled with the reduction of the heterodisulfide ($E^{\circ'} = -140$ mV).^{264,265} Interestingly, the core of the FAD- and [4Fe–4S] cluster-containing heterodisulfide complex resembles that of the core of class II BCR complex. This similarity led to the speculation that the low redox potential required for the reduction benzoyl-CoA is also achieved by electron bifurcation (see Section 2.4.4).

2.8 Radical Reactions Initiated by Oxygen

This review has mainly focused on enzymes that generate radicals without using the diradical oxygen. The only exception reported so far is class I RNR, which employs oxygen for generation of a tyrosyl radical that is propagated over a distance of 35 Å to the active site cysteine to form a thiyl radical.²⁶⁶ Although this tyrosyl radical is exceedingly stable and was the first radical to be discovered in an enzymatic reaction, in most oxygen-dependent reactions, radicals were only detected by indirect methods due to their short lifetimes. An example is isopenicillin synthase that contains a nonheme Fe(II) species at the active site. The enzyme catalyzes the formation of the penicillin core of isopenicillin N from the tripeptide δ -(L- α -aminoadipoyl)-L-cysteinyl-D-valine. This is

a four-electron oxidative bicyclization, resulting in formation of both the β -lactam and thiazolidine rings of the isopenicillin N product. The complete reduction of dioxygen to water via a Fe peroxide and a Fe(IV) oxo species drives formation of the strained bicyclic ring system.²⁶⁷ Each species is thought to abstract a hydrogen atom necessary for each ring closure.

In many oxidases, oxygenases, and hydroxylases, flavin cofactors are involved which are transiently reduced to the semiquinone radical. The oxidation of primary amines to aldehydes and ammonia catalyzed by amine oxidase is proposed to proceed via one-electron transfer from the amine to FAD, yielding the amine radical cation and the semiquinone, which equilibrates with an adjacent tyrosine residue. The second electron transfer affords the imine that hydrolyzes to the aldehyde and ammonia. Finally, oxygen reacts with resulting flavin hydroquinone (FADH₂) to recycle the initial quinone state of FAD, whereby hydrogen peroxide is produced. The detection of a tyrosyl radical during catalysis is of interest because the redox potentials of FAD and tyrosine differ by about 1.0 V. Presumably, tunneling effects are responsible for this surprising result.²⁶⁸

2.9 Biotechnological Applications

There is only one radical enzyme that is currently applied in biotechnology, the coenzyme B₁₂-dependent glycerol dehydratase.²⁶⁹ The enzyme catalyzes the dehydration of glycerol to 3-hydroxypropanal that is reduced by a subsequent enzyme to 1,3-propanediol, a valuable monomer for polyesters, from which fabrics are made. The company Dupont advertises the fabrics as “Cloths from Corn.” The coenzyme B₁₂-dependent enzyme has the disadvantage of rapid inactivation during catalysis, which has to be overcome by adding expensive vitamin B₁₂ to the growth medium. The more recently discovered glycy radical enzyme glycerol dehydratase may solve this problem.²⁷⁰ The process, however, has to be performed under strict anaerobic conditions, whereas the B₁₂-dependent enzyme tolerates some oxygen.

An old dream in biotechnology is the production of acrylate via lactate from sugars. Although the radical enzyme lactyl-CoA dehydratase has been available for some time,¹⁸⁵ its extreme oxygen sensitivity and the unfavorable equilibrium

($K' = [\text{acrylyl-CoA}]/[(R)\text{-lactyl-CoA}] = 0.02$)¹⁸⁷ prevented its application. The thermodynamic problem appeared to be tractable by converting acrylyl-CoA to 3-hydroxypropionyl-CoA catalyzed by crotonase. More than 10 years ago, the food company Cargill, Minneapolis, USA, started a program to produce 3-hydroxypropionate (3-HP) in *E. coli*. 3-HP is easily dehydrated to acrylate by heating in acid. Because lactate could not be completely converted to 3-HP, probably again because of thermodynamic reasons, the company abandoned this project and started to convert the SAM-dependent radical enzyme lysine-2,3-aminomutase into alanine-2,3-aminomutase by specific and random mutagenesis, which has been achieved. The new pathway starts from glucose to pyruvate, which is transaminated to α -alanine. The resulting β -alanine readily affords 3-HP via malonic semialdehyde. An alternative nonradical pathway to 3-HP could proceed via pyruvate, oxaloacetate, and aspartate, which can be α -decarboxylated to β -alanine. The authors of this review are not aware which routes are currently pursued by the biotechnological industry.

The genes coding for (*R*)-2-hydroxyglutarate dehydrogenase, glutaconate-CoA transferase, and the radical enzyme (*R*)-2-hydroxyglutaryl-CoA dehydratase with its activator or “archerases” from *A. fermentans* and *C. symbiosum* were expressed in *E. coli* and led to the production of (*E*)-glutaconate from glucose, though at the low level of 3 mM.²⁷¹ Currently, attempts are made to reduce the intermediate glutaconyl-CoA to glutaryl-CoA, which would yield glutarate, a dicarboxylic acid for the production of polyesters. Experiments on the substrate specificity of the transferase and dehydratase indicated that these enzymes could also be used to synthesize adipic acid, a constituent of nylon-6,6, if *E. coli* can be engineered to provide the necessary (*R*)-2-hydroxyadipic acid.²⁷²

Many bacteria store surplus carbon as poly-3-hydroxybutyrate (PHB), which is a useful biodegradable polymer for making disposable bottles, cups, and so on. Copolymerization of 3-hydroxybutyryl-CoA with its 4-hydroxy isomer changes the physical properties of the polymer and makes it more suitable for specific applications. This has been achieved by adding 4-hydroxybutyrate to the growth medium of the PHB-producing bacterium. A more elegant method would be via expression of the gene coding for the radical enzyme

4-hydroxybutyryl-CoA dehydratase.²¹⁰ The enzyme may take crotonyl-CoA from the central metabolism and hydrate it to 4-hydroxybutyryl-CoA, ready for polymerization. An alternative nonradical pathway from succinyl-CoA of the Krebs cycle to 4-hydroxybutyryl-CoA uses three enzymes from *C. kluyveri*.²⁷³

3 EVOLUTIONARY ASPECTS

One theory of the origin of biochemical pathways proposed an iron–sulfur world, dominated by one-electron transfers mediated by iron–sulfur clusters.²⁷⁴ Thus, radical reactions may have been widespread in the primeval world, and some have survived in extant anaerobic organisms and to a lesser degree in aerobes. Radical enzymes that only contain iron–sulfur clusters are GcpE and LytB of the nonmevalonate isoprenoid biosynthesis pathway, as well as the “archerases” of 2-hydroxyacyl-CoA dehydratases and class I BCRs on the one hand and the light-independent protochlorophyllide and chlorophyllide reductases related to nitrogenase on the other hand. In the primeval world, the precursors of these enzymes might have used different substrates and even have catalyzed other reactions, cf. dehydratases versus reductases. Nevertheless, they give an idea about the broad spectrum of “iron-only” radical enzymes devoid of any other cofactor. The “archerases” are homodimeric proteins that contain a $[4\text{Fe}-4\text{S}]^{1+}$ cluster between the subunits and bind ATP. The electron is injected into the target enzyme at the expense of ATP, like an archer shooting arrows (see Section 2.4). This system, by which the electron gains a very negative redox potential, has two different origins, which during evolution converged to similar functions. The “archerases” of 2-hydroxyacyl-CoA dehydratases and class I BCRs originated from the ATP kinase/actin family,²⁰⁰ whereas those of nitrogenase, as well as the light-independent protochlorophyllide and chlorophyllide reductases, are related to the Walker motif containing ATP-dependent enzymes.²⁷⁵

The cofactor-requiring radical enzymes probably appeared later in evolution than the “iron-only” radical enzymes. The biosynthesis of the radical generator coenzyme B₁₂ involves six SAM-dependent methylations.²⁷⁶ Therefore, it can be concluded

that SAM radical enzymes could have preceded those which depend on adenosylcobalamin. Note that the biosynthesis of SAM not necessarily requires cobalamin, because there is an alternative but less efficient Zn-containing methyl transferase, that is, a methionine synthase.²⁷⁷ Despite its exceedingly complex biosynthesis, the advantage of coenzyme B₁₂ over SAM is its oxygen tolerance, especially in reversible radical recycling reactions, and its possible involvement as conductor rather than spectator in the mutase reactions.³² There is structural evidence, however, that SAM and coenzyme B₁₂ radical enzymes are related. Evolution conserves structural elements much longer than amino acid sequences. As mentioned above, the overall folds of the SAM radical enzyme ThiC, involved in thiamin biosynthesis, and the adenosylcobalamin-dependent glutamate mutase are very similar. Just the radical-generating subdomains/subunits have been exchanged during evolution. Most likely the coenzyme B₁₂-binding subunit replaced the SAM domain.¹⁵³

Riboflavin, present in FMN and FAD, is certainly an early cofactor, which is necessary for hundreds of different enzymes. In this review, only a few of those have been mentioned, in which radicals have been detected or are most likely involved. Probably in most, if not all flavin enzymes, a semiquinone radical intermediate is involved, which in most cases escapes detection due to its short lifetime.

Many cofactors and active sites of enzymes are synthesized by SAM radical enzymes, which supports the idea of an early appearance of this type of radical generation, as for biotin, lipoamide, thiamin, molybdopterin, heme, and chlorophyll, as well as [FeFe]hydrogenase, [Fe]hydrogenase, PQQ enzymes, sulfatases, and glycyl-radical enzymes. The anaerobic pathway of chlorophyll biosynthesis needs coenzyme B₁₂ in addition to SAM. Among the most intriguing radical reactions are those that lead to thiamin,^{148,151} a cofactor of pyruvate synthesis and catabolism that is of central importance to metabolism. It has been proposed that pyruvate synthesis from an acetyl-thioester and CO₂ is one of the key reactions involved in the autotrophic origin of life.²⁷⁴ Probably in the primeval world, cyanide or similar compounds were used instead of thiamin. Addition of cyanide to carbonyl group causes the same “Umpolung” as thiamin, exemplified by the benzoin condensation. Thiamin has the advantage that the $pK_a = 18$ of the proton at C-2

of the thiazole ring is much higher than that of HCN ($pK_a = 9$). When bound to the protein, however, the proton at C-2 of ThDP can be removed, because the pyrimidine amino group is oriented into a position where it acts as a base.²⁷⁸ Thus, the metabolism of 2-oxoacids and ketosugars can be controlled by regulation of the activities of the corresponding enzymes.

4 CONCLUDING COMMENTS

After the publications^{40,102,216,259,279,280} of the pioneers of radical enzymes, the field developed slowly at first, but then markedly accelerated in the past two decades.¹⁸¹ Not even mature, the field has now sired some of the most mesmerizing reactions in biochemistry. The evolution of life quite possibly depended on radical reactions and its continuation most certainly requires them. The discovery of new radical enzymes, exhibiting extraordinary “molecular acrobatics” that are guaranteed to satiate our scientific curiosity, seems assured. And the translation of some of the pathways into laboratory and industrial synthetic processes will benefit mankind.

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Theoretical Studies of Radical Enzymes

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1 INTRODUCTION

In recent years, theoretical calculations have become an important part of mechanistic chemistry. Whether serving for the validation or modification of existing mechanistic proposals, or for the predictive development of new mechanisms, it is clear that the theoretical approach has much to offer.¹ This is particularly true in the case of highly reactive short-lived intermediates such as radicals, for which it is often difficult to obtain detailed information through experiment alone. As will be evident throughout this article, the study of radicals is a challenging field. Thus, the ability to achieve molecular-level insight via computational modeling of complex biological processes is truly invaluable. Theoretical modeling allows the calculation of structures, reaction energies, barriers, rates, reduction potentials, spectroscopic parameters, and many other molecular properties (see **Radical Stability—Thermochemical Aspects**). In the modeling process, however, it is necessary to construct a model system that is sufficiently small to allow accurate calculations but sufficiently large to include the catalytically essential portions of the enzyme, which may not always be a trivial task. Because the computational costs rise rapidly with the size of the system being investigated, finding the appropriate balance between size and accuracy is of utmost importance.

The chemical models that are constructed to describe biophysical phenomena vary greatly. For instance, one may examine isolated gas-phase substrates and reaction intermediates (i.e., in the absence of bulk enzyme), with an aim of capturing the intrinsic reactivity.^{2,3} Such an approach enables one to quantify with high precision the extent to which it is necessary for the enzyme to activate its substrate and transform intermediates. In an approach of this kind, it may also be desirable to include in the model additional species that mimic active-site amino acids so as to gain insight into their possible function. These so-called small models are particularly useful because specific interactions that may be responsible for facilitating the reactions can be turned “on” or “off” straightforwardly.

It is sometimes desirable to move beyond a small-model approach to capture longer range effects. The development of hybrid quantum mechanics/molecular mechanics (QM/MM) procedures is therefore another popular means of gaining insight into complex biophysical phenomena.^{4,5} The basic premise of the QM/MM scheme is to combine the accuracy of QM methods with the speed of MM methods in an effort to increase the efficiency of a theoretical investigation for larger systems. QM/MM schemes separate the overall system into distinct QM and MM regions such that

the chemically active part, which requires a sophisticated electronic structure treatment (for bond breaking, bond forming, charge transfer, and/or electronic excitation processes), is described in the QM region, while the MM region encompasses the remainder (e.g., protein plus solvent). The MM region is described classically with predefined parameters.

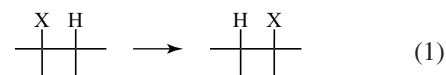
Once a chemical model is chosen, the next step is to identify a level of theory that is suitable to study radical species (see also, **Radical Stability—Thermochemical Aspects**). For example, in our previous work on the reactions catalyzed by coenzyme B₁₂-dependent enzymes, high-level conventional *ab initio* and density functional theory (DFT) procedures were used.³ Relative energies were often obtained with high-level composite methods such as G3(MP2)-RAD⁶ or CBS-RAD,⁷ that have been found to perform well when assessed against reliable thermochemical data for reactions related to those being investigated.⁸ In addition, the more economical B3-LYP^{9–11} DFT method with a large basis set was often found to be comparable in performance for these systems to that of more expensive procedures, thus providing confidence in its use when the computational cost of higher level *ab initio* methods becomes prohibitive. QM/MM schemes typically use a DFT procedure for the QM region in combination with a standard force field (e.g., AMBER¹²).

The aim of this review is to provide an overview of how theoretical modeling has been applied to the understanding of reactions catalyzed by enzymes that rely on radicals (the so-called radical enzymes,^{13–15} see also **Radical Enzymes**). We note that the enzyme systems reviewed herein are not intended to represent an exhaustive overview of this field. Instead, an attempt is made to show the reader examples of the kinds of radical-related biological problems that can be addressed with theory. Thus, the rich and extensive theoretical work on cytochrome P450 is excluded,¹⁶ as are the reactions catalyzed by methane monooxygenase.^{17,18} In fact, we do not include any situations in which the formal radical center is located on a metal that participates directly in the substrate catalysis. A proper description of such metalloenzymes often requires a specialized theoretical treatment, such as broken-symmetry DFT for multimetal systems,^{19,20} and is beyond the scope of this article. The reader is directed elsewhere for excellent reviews on

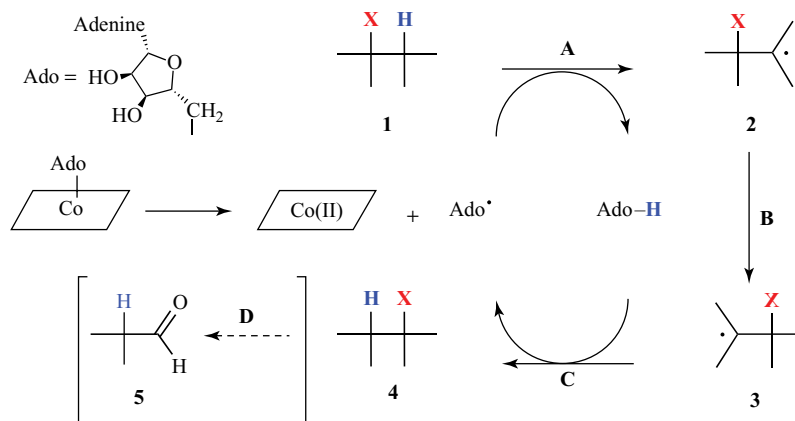
these topics.^{21–25} In this article, we discuss the reactions catalyzed by coenzyme B₁₂-dependent enzymes, the glycol radical enzymes pyruvate formate lyase (PFL) and benzylsuccinate synthase (BSS), class III ribonucleotide reductase (RNR), and methyl-coenzyme M reductase (MCR). Collectively, these examples represent a broad range of radical enzymes for which theory has played an important role in contributing to understand their mechanisms of action.

2 COENZYME B₁₂-DEPENDENT ENZYMES

Enzymes that rely on coenzyme B₁₂ (5'-deoxyadenosylcobalamin, AdoCbl) are involved in physiological pathways that are vital to life, including energy generation and DNA synthesis and regulation.²⁶ The reactions made possible by these enzymes share a common origin in that radical intermediates are used to interchange a hydrogen atom (H) and functional group (X) on adjacent carbon atoms of the substrate (1)²⁷:



One of the defining features of AdoCbl-dependent enzymes is the identity of X which, depending on the enzyme, is either a small carbon-skeleton fragment (class I) or a small heteroatom-containing group such as OH or NH₂ (classes II and III). The accepted mechanism for these reactions is shown in Scheme 1,²⁶ which begins with the homolytic cleavage of the Co–C bond of AdoCbl to generate the 5'-deoxyadenosyl radical (Ado•) plus cob(II)alamin. Ado• serves to abstract an H atom from the substrate (**1**) to form 5'-deoxyadenosine (Ado–H) plus a substrate-derived radical **2** (step A). Rearrangement of **2** then gives the product-related radical **3** (step B), which is followed by a second H-atom transfer between Ado–H and **3** to give the product **4** and to regenerate Ado• (step C). In some cases, elimination of H₂O or NH₃ from **4** occurs to produce an aldehyde (**5**, step D). Understanding the details of each step of Scheme 1 has attracted considerable interest over the years, both because of the biological importance as well as the simple yet elegant chemistry that is involved. In the next few sections, we highlight the insights that have been gained through



Scheme 1 General mechanism for the rearrangements catalyzed by coenzyme B₁₂-dependent enzymes.³ [Reprinted with permission from Ref. 3. Copyright 2010 American Chemical Society.]

computational modeling for the reactions catalyzed by a variety of AdoCbl-dependent enzymes.

2.1 Co–C Homolysis

One of the most contentious issues concerning the reactions catalyzed by coenzyme B₁₂-dependent enzymes is how the Co–C bond of AdoCbl is cleaved and how this step is coupled to the ensuing H-atom abstraction step. Arguably, one of the most complex coenzymes in nature, AdoCbl possesses a six-coordinate central cobalt atom that is flanked by a corrin ring, 5,6-dimethylbenzimidazole (DMB) as the lower α -axial ligand and 5'-deoxyadenosyl (Ado) as the upper β -axial ligand. The C5' atom of Ado forms a σ -bond to the central cobalt atom—a very rare chemical bond in nature—whose length has been determined as 2.03 Å in a recent high-resolution X-ray structure (Figure 1).²⁸

The bond dissociation enthalpy (BDE) of the Co–C bond of AdoCbl in solution is $\sim 130 \text{ kJ mol}^{-1}$ and is associated with a thermal homolysis rate at 25 °C of just $10^{-9\pm 1} \text{ s}^{-1}$.²⁹ Remarkably, AdoCbl-dependent enzymes enhance the rate of Co–C cleavage by up to one trillion-fold, implying that the enzyme reduces the BDE relative to solution by roughly 60 kJ mol^{-1} . Clearly, this unprecedented chemistry is made possible by an extremely efficient and well-regulated mechanism. But how is this achieved? Responding to this question has been a challenge to researchers in the field for almost 40 years.³⁰

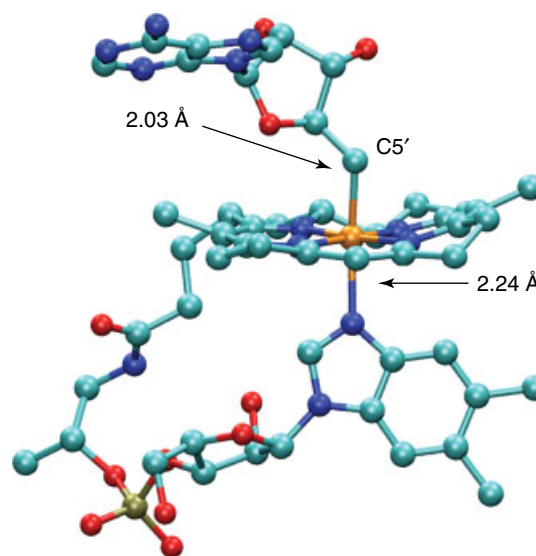


Figure 1 Isolated coenzyme B₁₂ (5'-deoxyadenosylcobalamin, AdoCbl) obtained from X-ray crystallography.²⁸

Several mechanisms have been considered to account for the dramatic rate acceleration of Co–C bond cleavage of AdoCbl in the enzyme environment.³⁰ Often, the interaction between the cofactor and the enzyme is cited to play a major role in AdoCbl activation. In the absence of coupled Co–C bond homolysis and H-atom abstraction from the substrate, the dissociation of the Co–C bond may be regarded as a Morse potential curve whose energy rises with increasing Co–C bond distance.³¹

In this scenario, there is no transition structure (TS) along the reaction pathway, and so facilitating the homolysis requires either destabilization of the reactant state or stabilization of the product state or some combination of the two.

Early structural and spectroscopic studies tended to favor a mechanism involving ground-state destabilization. In particular, the mutases belonging to class I²⁷ were thought to operate by this mechanism since these enzymes displace the lower α -axial DMB ligand of the cofactor for a mobile endogenous histidine residue from the enzyme. Furthermore, it is known that modifications to the lower α -axial ligand have the ability to influence the bond strength of the upper β -axial ligand.³² Another hypothesis put forward to account for Co–C bond activation in AdoCbl is the so-called mechanochemical triggering (or the *trans*-effect).³³ In this proposal, Co–C bond cleavage is accelerated via enzymatic compression of the Co–N_{ax} bond. Such compression is understood to elicit unfavorable steric interactions on the lower face of the corrin ring, which causes an increase in the upward fold angle of the ring.

Various spectroscopic studies with methylmalonyl-CoA mutase (MCM)—including resonance Raman,^{34,35} electronic absorption (Abs), and magnetic circular dichroism (MCD)³⁶—have suggested that ground-state destabilization is likely to contribute little to the rate acceleration of Co–C bond homolysis. Instead, product-state stabilization is suggested to be operative.³⁷ Again using MCD and Abs, and in conjunction with DFT calculations, significant deviations in metal-to-ligand charge transfer in the MCM-bound Co²⁺ Cbl species were observed, both in the presence and absence of a substrate.³⁷ The source of stabilization was identified to be the Co²⁺ 3d orbitals, and it was postulated that product-state stabilization is enhanced by proton uptake from the “catalytic triad.” Concurrent MCD and Abs studies with the related glutamate mutase (GM) revealed spectra similar to those of MCM,³⁸ indicating that the Co²⁺ 3d orbitals of AdoCbl may also be important in stabilizing the product state in this enzyme. Taken together, these studies imply that a common mechanism might be operational for Co–C bond activation for the class I mutase family of AdoCbl-dependent enzymes.

Combined QM/MM studies on MCM,³⁹ and GM⁴⁰ have also been performed to determine the Co–C bond-cleavage mechanism.⁴¹ In MCM, a

significant conformational change in the adenosyl portion of AdoCbl was found to precede the actual Co–C bond cleavage, which was interpreted to suggest that a two-step process for homolysis is operative.³⁹ The barrier for Co–C bond cleavage was determined to be ~ 40 kJ mol^{−1} and the reaction was found to be endothermic by ~ 10 kJ mol^{−1}. Interestingly, the large conformational change observed in the cofactor positioned the resulting 5'-deoxyadenosyl radical (Ado•) close to the substrate for subsequent hydrogen-atom abstraction.³⁹

In computational studies of GM, four components that contribute to lower the energy for Co–C bond homolysis were identified⁴⁰: (i) the enzyme keeps Ado• bound at a Co–C bond distance of 3.2–4.2 Å, which is equivalent to the so-called cage effect and corresponds to a decrease in the computed BDE of 20 kJ mol^{−1}; (ii) there is differential electrostatic stabilization of the Co(II) state by the surrounding protein, which amounts to a decrease in the BDE of the Co–C bond of 42 kJ mol^{−1}; (iii) there is van der Waals and electrostatic stabilization of the surrounding protein in the Co(II) state, which amounts to 11 kJ mol^{−1}; and (iv) the enzyme distorts AdoCbl, especially in the Co(III) state. This last contribution was shown to provide the dominant catalytic contribution to Co–C homolysis, amounting to 61 kJ mol^{−1}. It is notable that Brooks *et al.*³⁸ have questioned the validity of these computational studies because the geometric distortions predicted for the Co(III) state are not consistent with their spectroscopic data.

Buckel *et al.*⁴² have recently proposed a new role for the cob(II)alamin portion of AdoCbl in the class I mutase family of enzymes. They suggest that it acts to stabilize radical intermediates in the mutases and that by doing so, the energy of the TSs for H-atom abstraction and rearrangement are lowered. In this scenario, cob(II)alamin is described as a “conductor” rather than the traditional view of it as merely being a “spectator” in the reactions catalyzed by AdoCbl-dependent enzymes. This proposal is principally based on the fact that the reactions catalyzed by these enzymes involve the reversible conversion of an unactivated methyl group to a methylene radical and the nonexistence of alternative sources for 5'-deoxyadenosyl radicals in the mutase family of enzymes.

Two computational studies have investigated whether cob(II)alamin can act as a conductor in the reactions catalyzed by AdoCbl-dependent enzymes.^{43,44} DFT calculations of a small gas-phase model relevant to GM found that a concerted pathway involving Co–C5' cleavage and H-atom abstraction is $\sim 30 \text{ kJ mol}^{-1}$ lower in energy than one that is purely stepwise, implying that cob(II)alamin can indeed act to modulate the energy requirements of the reaction.⁴³ However, in another study, it was found that whether a concerted or stepwise pathway exists is largely determined by the initial configuration of the system.⁴⁴ Specifically, the orientation of the ribose moiety of AdoCbl relative to the corrin ring is the key factor; the OH groups of the ribose are found to interact favorably in one configuration, amounting to a stabilization of $\sim 30 \text{ kJ mol}^{-1}$ relative to the relevant separated species. The interaction of C19–H of the corrin ring and O3' of the ribose appears to provide a lowering of the energy requirement for the concerted pathway, but the question was raised as to whether such interactions are relevant in the enzyme system.⁴⁴

Empirical valence bond (EVB) calculations of MCM provided support for a concerted pathway for Co–C5' cleavage and H-atom abstraction.⁴⁵ In this case, it was necessary to couple these steps in order to reproduce the experimental reaction free energy of approximately zero. Electrostatic interactions between the OH groups of the ribose portion of AdoCbl and an adjacent glutamate residue (Glu370) were identified as being important. In contrast, strain effects between AdoCbl and the active site of the enzyme were not observed and thus were considered not to be an important contributor to the catalysis. It was argued that such effects were overestimated in previous energy minimization schemes (e.g., QM/MM) because conformational sampling was not considered.

In contrast to these EVB results, a stepwise pathway for Co–C5' cleavage and H-atom abstraction in the MCM-catalyzed reaction has been advocated on the basis of QM/MM ONIOM(DFT/MM) calculations.⁴⁶ Models of increasing size were used to identify important contributors to catalysis. As before, the interaction of Glu370 with the OH groups of AdoCbl was identified as being important as well as the interaction of Gln330 to O1' of the ribose. Three contributors were found to affect Co–C bond cleavage: (i) the cage effect

contributes $\sim 20 \text{ kJ mol}^{-1}$; (ii) geometric distortions of AdoCbl in the enzyme, especially of the Ado moiety itself, amounts to $\sim 30 \text{ kJ mol}^{-1}$; and (iii) the protein MM effect due to electrostatic and van der Waals interactions of nearby residues with the Ado moiety contributes $\sim 40 \text{ kJ mol}^{-1}$. A concerted TS for the Co–C5' cleavage and H-atom abstraction could not be located. Indeed, relaxed scans along the Co–C5' coordinate with fixed C5'–H and substrate:C–H distances (where substrate:C refers to the methyl carbon of the substrate) showed the energy to rise sharply as the Co–C5' distance is decreased.

Most recently, we have performed an investigation of MCM that combines the effects of conformational sampling, as presented in the EVB study, with the first-principles nature of the QM/MM approach.⁴⁷ Our calculations provide strong evidence that the Co–C5' cleavage and H-atom abstraction occur in a stepwise manner and that the Ado' intermediate indeed corresponds to a minimum on the free energy surface. We find that the two ribose hydroxyl groups play a dual role in the catalytic process, as they facilitate the Co–C5' cleavage and assist the diffusion of the radical toward the substrate. Part of these effects can be attributed to the C19...O3' interaction, which is found to be relevant in the enzymatic environment. Its magnitude therein, however, appears to be somewhat less than that in the gas-phase treatments.⁴⁴ The overall mechanism is consistent with Rétey's idea of negative catalysis,⁴⁸ where the role of the B₁₂-dependent enzymes is not simply to lower energy barriers but also to manipulate highly reactive intermediates.

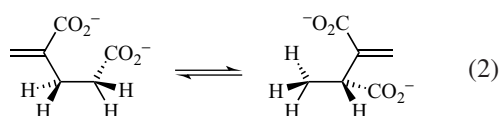
2.2 Class I Mutases

The class I mutases comprise a group of AdoCbl-dependent isomerases that mediate the interchange of a hydrogen atom and carbon-skeleton fragment on adjacent carbons. Members of this class include 2-methyleneglutarate mutase (MGM), glutamate mutase (GM), isobutyryl-CoA mutase, and methylmalonyl-CoA mutase (MCM). All these enzymes are found within the bacterial kingdom, but only the last one is also found in mammals. A longstanding problem for these enzymes has been to understand the mechanism(s) of the carbon-skeleton rearrangement (step B, Scheme 1), as several possible radical rearrangement pathways

can be conceived. We have explored a number of these possibilities using high-level *ab initio* procedures, as outlined below.

2.2.1 2-Methyleneglutarate Mutase

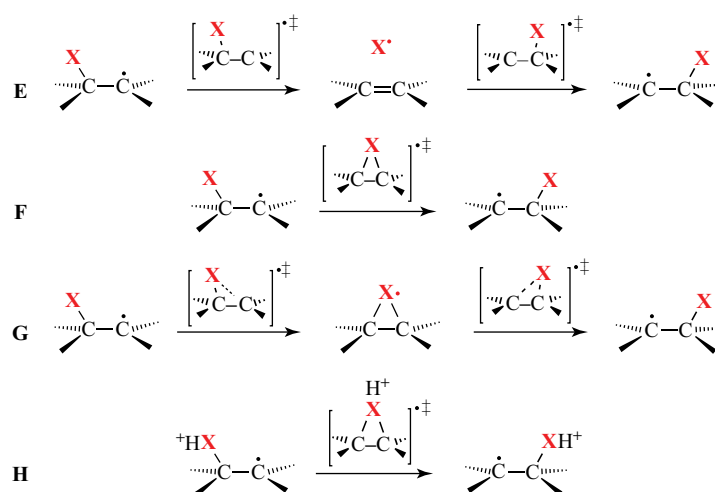
MGM catalyzes the reversible conversion of 2-methyleneglutarate to (*R*)-3-methylitaconate in bacterial fermentation(2)²⁷:



Considering the general mechanism of AdoCbl-dependent reactions, one can envision several ways in which this rearrangement might proceed via radical intermediates. In Scheme 2, we highlight four possible radical-based pathways that lead to the migration of a group X between adjacent carbon centers. One pathway (E), which is termed *fragmentation–recombination* (F/R), involves homolytic cleavage of the bond from carbon to X to yield two distinct species that can recombine at the adjacent carbon to produce the rearranged product-related radical. Pathway F represents a concerted rearrangement that does not involve complete fragmentation of the substrate. Instead, a bridged cyclopropyl-type TS connects

the substrate-derived and product-related radicals. In another pathway (G), the cyclopropyl-type species corresponds to a stable intermediate. This pathway requires the presence of appropriate unsaturation in the migrating group X, as found, for example, in 2-methyleneglutarate (2), to facilitate rearrangement. This so-called addition–elimination (A/E) pathway can then be described as the intramolecular addition of the unpaired electron to the π -system of X to form the cyclopropyl-type species, which can then ring-open via homolytic cleavage of the adjacent bond. Finally, pathway H involves protonation of the migrating moiety to facilitate a concerted rearrangement mechanism, since early theoretical investigations predicted that such a scenario lowers the energy requirements for rearrangement.^{49,50}

Using the but-3-enyl radical as a model for the substrate in the MGM-catalyzed reaction (Scheme 2, X = CH=CH₂, and (2)), pathways E, G, and H were investigated.⁵¹ Pathway E possesses a very large barrier of almost 150 kJ mol^{−1} for C–X bond cleavage, suggesting that this pathway is unlikely to be operational in the MGM-catalyzed reaction. Much lower barriers of ~40 kJ mol^{−1} were found for the ring-closing and ring-opening steps in the A/E mechanism (pathway G). Even more striking is the prediction that full protonation of the terminal methylene group in the but-3-enyl radical (pathway H) reduces the barrier for rearrangement to only ~10 kJ mol^{−1}.



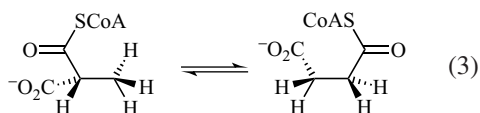
Scheme 2 Possible 1,2-migration pathways involving radical intermediates.³ [Reprinted with permission from Ref. 3. Copyright 2010 American Chemical Society.]

Similar observations resulted from the use of an improved substrate model (i.e., the substrate-derived radical of 2-methyleneglutaric acid).⁵¹ In these cases, the reaction profiles were modified slightly due to intramolecular interactions as well as preferential stabilization of the radical center by the adjacent CO₂H group. Nevertheless, the qualitative finding that the F/R pathway lies considerably higher in energy than the A/E pathway is maintained. Moreover, the reduction in the rearrangement barrier accompanying protonation of the migrating group is again observed.

In terms of addressing the question of the preferred mechanism for rearrangement, the theoretical analysis identifies the intramolecular A/E pathway as being of low energy, especially when combined with protonation of the migrating group.⁵¹ On the other hand, on the basis of isotopic labeling studies and conformational arguments, it has been argued that an F/R pathway is the most consistent with the experimental results.⁵² Furthermore, kinetic modeling studies predict that an A/E mechanism would be too slow to account for the observed rate constant and, on the basis of these results, a modified version of the F/R pathway involving *heterolytic* cleavage of the ionized substrate-derived radical has been proposed.⁵³ Clearly, further research is required to reconcile these seemingly conflicting conclusions. The availability of a crystal structure for MGM, which would enable more detailed molecular modeling, would undoubtedly prove useful in this regard.

2.2.2 Methylmalonyl-CoA Mutase

In humans, MCM is involved in the catabolism of odd-chain fatty acids, branched-chain amino acids, and cholesterol via the reversible rearrangement of methylmalonyl-CoA to succinyl-CoA (3)²⁷:



Problems associated with this transformation can lead to methylmalonic acidemia, a potentially fatal disease characterized by excessive levels of methylmalonyl-CoA.⁵⁴

Like the MGM-catalyzed reaction, the presence of unsaturation in the migrating thioformyl-CoA moiety allows the possibility of both A/E and F/R rearrangement pathways. Similarly, the barrier for the F/R pathway is calculated to be quite high (93.2 kJ mol⁻¹) when 3-propanal radical is used as a model for the substrate-derived radical of methylmalonyl-CoA.^{55,56} A considerable reduction in the rearrangement barrier is observed for the intramolecular A/E pathway (to 46.9 kJ mol⁻¹). Even more striking is the finding that the barrier is reduced to just 10.0 kJ mol⁻¹ when the carbonyl oxygen is fully protonated. However, because it is very unlikely that the carbonyl oxygen would be fully protonated in the enzyme environment, the possibility of *partial* protonation by the enzyme was explored using a series of small gas-phase molecules as potential proton donors (Figure 2).^{55,56}

Relative to the rearrangement barrier for the uncatalyzed A/E pathway (46.9 kJ mol⁻¹), partial protonation of the migrating group with the weak gas-phase acid hydrogen fluoride (HF) reduces the barrier by 5.5 kJ mol⁻¹. The slightly stronger gas-phase acid ammonium cation NH₄⁺ reduces the barrier to 24.5 kJ mol⁻¹, while the strong gas-phase acid H₃O⁺ leads to a barrier (10.3 kJ mol⁻¹) similar to that observed with full protonation.

This systematic lowering of the rearrangement barrier can be understood in terms of the relative strength of the hydrogen bond between the acid catalyst and the migrating carbonyl oxygen in the TS versus the reactant. In effect, this interaction is stronger in the TS than that in the reactant, hence the lowering of the barrier. The trend in barriers can be rationalized in terms of the relative proton affinities of the conjugate bases of the acid catalysts and the substrate and is reflected geometrically in the distance between the acidic proton and the carbonyl oxygen of the substrate. Thus, we observe the distance between these entities to decrease across the series from infinity (no protonation) to 1.727 (HF), 1.503 (NH₄⁺), 1.046 (H₃O⁺), and 0.976 (full protonation) Å.

From an enzymatic point of view, the result obtained with NH₄⁺ is the most relevant because it provides a realistic model for amino acids such as histidine. The moderately large proton affinity of NH₃ (848.6 kJ mol⁻¹) maintains the relatively strong binding of the proton, while allowing sufficient proton transfer to the substrate to facilitate the rearrangement. Importantly, this

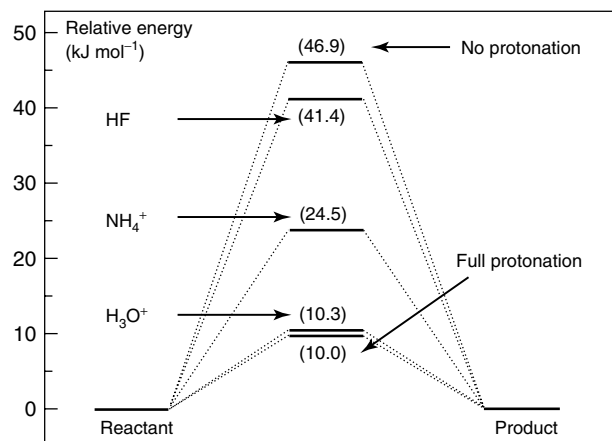


Figure 2 Schematic energy profiles for the rearrangement of the 3-propanal radical, showing barriers (CBS-RAD(p), kJ mol^{-1}) associated with various degrees of protonation.^{3,55} [Reprinted with permission from Ref. 3. Copyright 2010 American Chemical Society.]

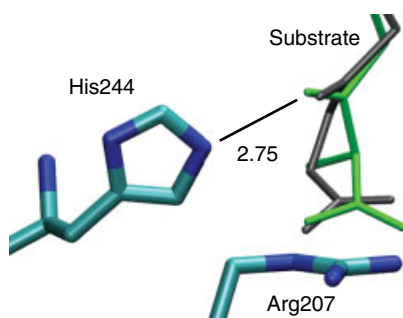


Figure 3 Active-site region of MCM showing the close proximity (in Å) of His244 to the carbonyl oxygens of the substrates methylmalonyl-CoA (green) and succinyl-CoA (gray) (PDB code: 4REQ⁵⁷).

demonstrates that a significant lowering of the barrier can be achieved without full proton transfer by the enzyme.

In the context of the MCM-catalyzed reaction, the crystal structure of MCM reveals that a histidine residue (His244) lies within H-bonding distance of the migrating carbonyl oxygen of the substrate (Figure 3).⁵⁷ This arrangement potentially offers an attractive H-bond donor to mediate substrate rearrangement via partial proton transfer. On the basis of the theoretical partial-proton-transfer hypothesis,⁵⁵ Banerjee and coworkers performed mutagenesis experiments involving His244 and observed a 300-fold decrease in catalytic efficiency in experiments using an H244G mutant of MCM.⁵⁸ Other experiments with H244A and H244Q mutants

in the laboratory of Leadlay and coworkers found similar reductions in catalytic efficiency (100- to 1000-fold, respectively).⁵⁹ Overall, these combined experiments provide strong support for the involvement of His244 in the rearrangement of carbon skeletons in the MCM-catalyzed reactions. More generally, they provide support for the concept of facilitation of these rearrangements through partial proton transfer.

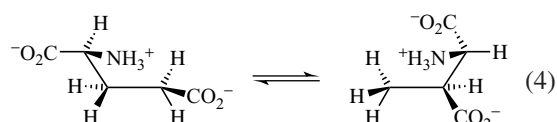
Despite these data, the experimental studies produced rate changes somewhat smaller than those expected on the basis of the theoretical results. While the experiments indicated an enhancement of catalytic efficiency by His244 of roughly two orders of magnitude,^{58,59} the theoretical models predict as much as four orders of magnitude. Moreover, other kinetic modeling solvation studies are not supportive of an acid-catalyzed A/E pathway.⁶⁰

In an attempt to reconcile some of these disparities, Wetmore *et al.*⁶¹ extended the original theoretical investigations to more elaborate calculations, including the first investigation of the hydrogen-abstraction reactions of MCM. Importantly, the theoretical study found that there is a change in the rate-determining step between wild-type MCM and its His244 mutants. Specifically, the rate-determining step changes from the hydrogen-atom re-abstraction (and additional, possibly coupled factors such as product release) in the wild-type enzyme to the substrate rearrangement for the His244 mutants. This change can be attributed to the loss of partial protonation from

His244 to the migrating carbonyl group. Furthermore, the use of a more sophisticated model for His244, that is, protonated imidazole, predicts that His244 would enhance the catalytic efficiency of the reaction by roughly three orders of magnitude,⁶¹ which is consistent with the two–three orders of magnitude observed experimentally. Overall, it is clear that His244 plays an important role in facilitating the radical rearrangement step in the MCM-catalyzed reaction.

2.2.3 Glutamate Mutase

GM catalyzes the reversible isomerization of (*S*)-glutamate to (2*S*, 3*S*)-3-methylaspartate (4)⁶²:



The nature of the migrating moiety (i.e., glycy) in these substrates makes it unlikely that an A/E mechanism is operative in GM, since the glycy fragment does not possess unsaturation. On the other hand, Marsh and coworkers have demonstrated that glycy radical is a kinetically competent intermediate in this reaction, suggesting that a dissociative F/R pathway may be operational.⁶³

The critical importance of the protonation state of the participating species in this reaction has been demonstrated theoretically.⁶⁴ For instance, the intermediate fragments derived from *protonated* 4-glutamyl radical are found to lie 182.5 kJ mol^{−1} higher in energy than the reactant, and the overall reaction is endothermic by 41.7 kJ mol^{−1}. For *neutral* 4-glutamyl radical, however, the energy requirements for the F/R pathway are much lower. Specifically, the barrier to fragmentation is 59.9 kJ mol^{−1}, the intermediate fragments lie 34.7 kJ mol^{−1} higher than the reactant, and the reaction endothermicity is just 20.3 kJ mol^{−1}.⁶⁴ The low energy of the separated fragments may be attributed to captodative stabilization of the glycy radical intermediate by the amino and carboxylic acid substituents adjacent to the unpaired electron.^{65–67} This stabilization is greatly reduced by protonation of the amino group.

The crystal structure of GM reveals the substrate (glutamate, Figure 4) to be bound by three

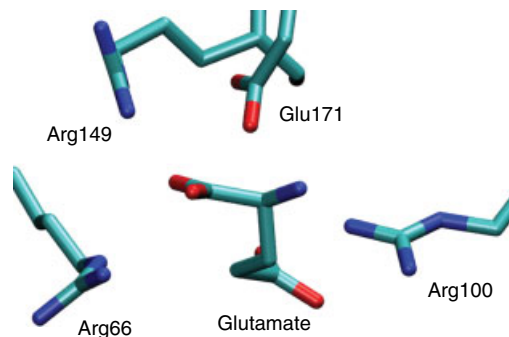


Figure 4 Selected region of the active site of GM showing the close proximities of Glu171 to the nitrogen atom of glutamate, and the so-called arginine claw to the substrate carboxylates (PDB code: 1I9C⁷⁰).

arginine residues—the so-called arginine claw—and Glu171.⁶⁸ It is evident that Glu171 is well positioned to interact and partially deprotonate the amino group of the substrate. Its role as a proton acceptor has been corroborated with mutagenesis experiments that demonstrated a 50-fold reduction in the catalytic activity of the wild-type enzyme with the Glu171Gln mutant of GM.⁶⁹

Further evidence for GM utilizing hydrogen bonding for both binding and catalysis is provided by its observed inactivation with (*S*)-2-thiolglutarate.⁷¹ Simulations of the experimental EPR spectrum for this reaction system suggested an interaction between cob(II)alamin and a sulfur-stabilized thioglycolyl radical (H[•]C(CO₂H)–SH), which would be formed via fragmentation of the C4-centered substrate-derived radical.⁷¹ The thioglycolyl radical was found to accumulate on the enzyme, and it was therefore proposed that it was too stable to undergo further reaction.

We have examined this reaction computationally and found the energy profile of neutral (*S*)-2-thiolglutaric acid to be not very different to that of another known catalytically active substrate analog (i.e., (*S*)-2-hydroxylglutarate), suggesting that some activity might have been expected to be observed.⁷² On the other hand, we find that the F/R products of the reaction involving the S-centered anion of (*S*)-2-thiolglutaric acid are of especially low energy because of effective captodative stabilization, which *would* account for the ability of this analog to inactivate GM.

In addition, an analysis of radical stabilization energies (RSEs) reveals that the thioglycolyl radical

Table 1 Comparison of calculated (G3(MP2)-RAD, 0 K kJ mol^{-1}) radical stabilization energies (RSEs) for species pertinent to the fragmentation step of the glutamate mutase reaction.⁷²

Radical	RSE
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--H}$	21.2
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--NH}_2$	94.3
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--SH}$	81.4
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--S}^{\cdot}$	126.4
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--OH}$	77.5
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--O}^{\cdot}$	83.4
$\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--F}$	43.0

($\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--SH}$) does not possess any significant stabilization that would cause the reaction to terminate prematurely (Table 1); indeed, the RSE of the thioglycolyl radical (81.4 kJ mol^{-1}) is quite similar to that of the glycolyl radical (77.5 kJ mol^{-1}). The RSE of the S-centered anion of the thioglycolyl radical ($\text{H}^{\cdot}\text{C}(\text{CO}_2\text{H})\text{--S}^{\cdot}$), on the other hand, demonstrates a significant degree of stabilization. With a calculated RSE of $126.4 \text{ kJ mol}^{-1}$, this species does indeed constitute a large energy sink for the reaction of GM with (*S*)-2-thiolglutarate. Bearing in mind the role of Glu171 as a general base in the GM-catalyzed reactions,⁶⁹ the possibility that the S-centered anion of the thioglycolyl radical contributes to the inactivation of GM with (*S*)-2-thiolglutarate as a substrate is indeed plausible. Encouragingly, calculations of the full reaction profiles for these various substrates support the notion that RSEs provide a useful qualitative measure of the ability of substrate analogs to generate kinetically competent intermediates.⁷²

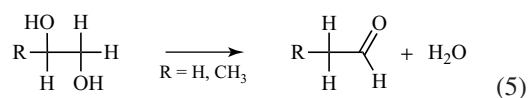
2.3 Class II Eliminases

The class II eliminases differ from the class I mutases primarily in the composition of the migrating moiety; specifically, these enzymes interchange a heteroatom group such as OH or NH_2 , rather than a carbon-skeleton fragment, with hydrogen. Furthermore, and as their name suggests, elimination (of H_2O or NH_3 , depending on the enzyme) occurs following substrate rearrangement. Like the class I mutases, the mechanisms of substrate rearrangement have long been contested. Unlike the mutases, however, the eliminases are prone to substrate-induced suicide inactivation on

account of their relative promiscuity of substrate selectivity. To better understand these processes, we and others have carried out extensive theoretical modeling to delineate the dominant factors responsible for facilitating substrate rearrangement and for irreversible inactivation of these enzymes.

2.3.1 Diol Dehydratase

Diol dehydratase (DDH) catalyzes the irreversible dehydration of two-carbon and three-carbon 1,2-diols into their corresponding aldehydes (5)⁷³:



Inspired by earlier work,^{49,50} we examined the interactions of the migrating OH group with a series of Brønsted acids and found that the resulting *partial* protonation reduces the barrier for 1,2-OH migration monotonically with increasing acid strength.⁷⁴ The uncatalyzed rearrangement barrier for the 1,2-dihydroxyethyl radical was determined to be $113.1 \text{ kJ mol}^{-1}$, which was decreased substantially when the following acids were allowed to facilitate the rearrangement: protonated methylamine (76.1 kJ mol^{-1}), ammonium (49.6 kJ mol^{-1}), protonated propan-2-one (18.5 kJ mol^{-1}), and protonated methanol (2.8 kJ mol^{-1}). Full protonation resulted in a barrierless reaction. All of these examples showed a significant lengthening of the acidic bond involving H in the TS as the strength of the acid increases, with a concomitant elongation of the C–O bond of the substrate.

In a later study, the partial proton transfer concept was extended to include partial *deprotonation* of the spectator OH group.⁷⁵ As shown in Figure 5, relative to the uncatalyzed case ($110.4 \text{ kJ mol}^{-1}$, obtained with a slightly different level of theory³), partial deprotonation of the spectator OH group of the 1,2-dihydroxyethyl radical is found to reduce the barrier to rearrangement with either NH_3 ($108.1 \text{ kJ mol}^{-1}$) or HCO_2^- (94.5 kJ mol^{-1}).

If the effect of combining partial protonation and deprotonation within a system corresponded to the sum of the individual contributions, then one would expect a rearrangement barrier of

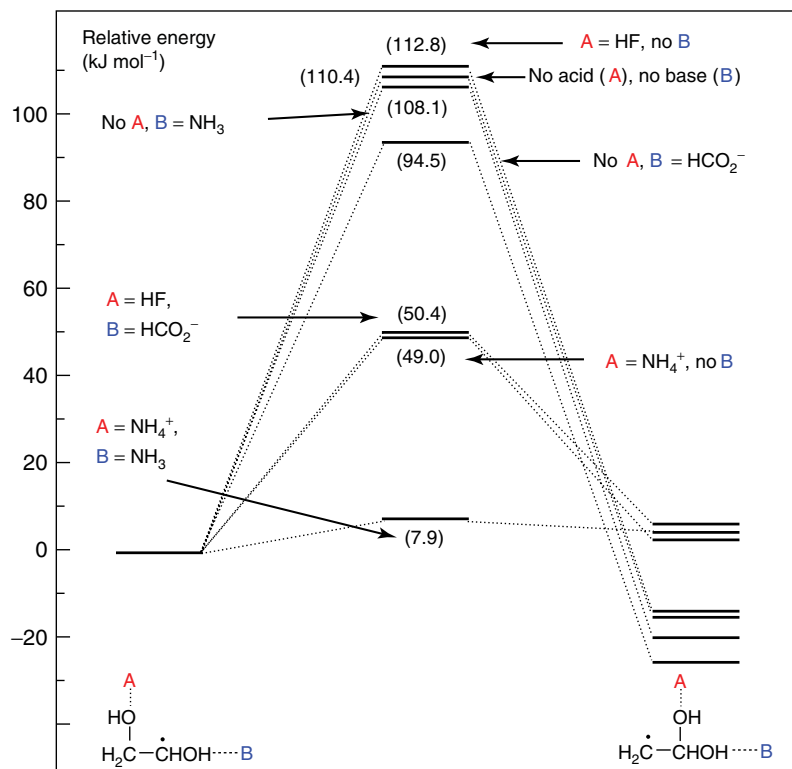


Figure 5 Schematic energy profiles for the rearrangement of the 1,2-dihydroxyethyl radical resulting from the interaction of acids (a) with the migrating OH together with the interaction of various bases (b) with the spectator OH.^{3,75} Relative energies (G3(MP2)-RAD, kJ mol^{-1}) are given in parentheses. [Reprinted with permission from Ref. 3. Copyright 2010 American Chemical Society.]

46.7 kJ mol^{-1} when NH_4^+ and NH_3 are used as the acidic and basic catalysts, respectively (Figure 5). However, this is not the case at all. In a powerful demonstration of the synergistic effect that occurs to reduce the barrier to rearrangement with the combined action of both an acid and base, we calculate a rearrangement barrier of just 7.9 kJ mol^{-1} for NH_4^+ and NH_3 . This behavior has been referred to as “push–pull” catalysis to indicate that the acidic catalyst “pushes” the migrating OH group through the 1,2-rearrangement, while the basic catalyst “pulls” it. This kind of synergism is also observed with the push–pull combination of HF and formate (Figure 5). We believe that this mechanism provides a straightforward rationalization of how DDH (and other AdoCbl-dependent enzymes) might use active-site residues to facilitate the radical rearrangement step.

The crystal structure of DDH reveals the substrate to be located near histidine (His143)

and glutamate (Glu170) residues, which are likely to serve as appropriate acidic and basic catalysts in the reaction (Figure 6).⁷⁶ Indeed, mutagenesis experiments have shown that the interaction of His143 with the substrate both assists catalysis and protects the radical intermediates from inactivation.⁷⁷ Moreover, QM/MM computational mutational investigations have demonstrated the importance of both His143 and Glu170 in the conversion of 1,2-propanediol to 1,1-propanediol.⁷⁸ The His143Ala mutant was found to increase the rearrangement barrier by $\sim 20 \text{ kJ mol}^{-1}$, while the Glu170Gln mutant increased the barrier by $\sim 25 \text{ kJ mol}^{-1}$. Disruption of partial proton transfer between these residues and the radical intermediate was identified as being the cause of these barrier increases.

Also shown in Figure 6 is a metal ion coordinating the substrate. In addition to the two coordination

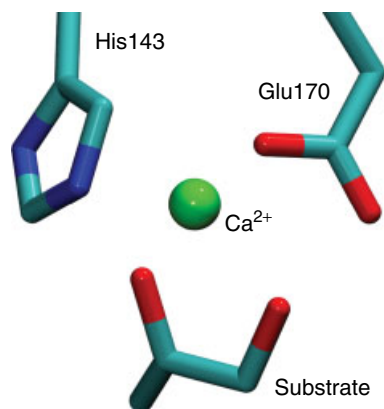


Figure 6 Portion of the active site of DDH showing the substrate (*S*)-propane-1,2-diol, His143, and Glu170 and Ca^{2+} (PDB code: 1DIO⁷⁶).

positions occupied by the substrate, this ion is also coordinated by five oxygen atoms from the side chains of Gln141, Glu170, Glu221, and Gln296 and the carbonyl group of Ser362. Originally, this ion was believed to be potassium, but recent computational and experimental studies predict it instead to be calcium. Yoshizawa and coworkers used QM/MM calculations to compare metal–oxygen bond lengths for substrate binding using K^+ , Na^+ , Mg^{2+} , and Ca^{2+} as the metal.⁷⁹ It was found that Ca^{2+} gives the best agreement with experiment for the seven metal–oxygen bond distances. In addition, the best agreement with the experimental X-ray structure for the adenine-binding site is found for K^+ , which rationalizes experimental evidence indicating that K^+ plays an essential role in the binding of AdoCbl with DDH. Collectively, these results suggest that the metal ions in the substrate- and adenine-binding sites are Ca^{2+} and K^+ , respectively. Subsequent experiments supported this interpretation.⁸⁰

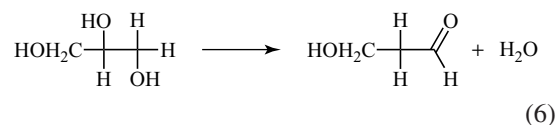
Another aspect of the DDH-catalyzed reaction is its susceptibility to irreversible inactivation with substrate analogs. Glycolaldehyde has long been known to lead to the inactivation of DDH,⁸¹ and more recently, the causative agent for this inactivation has been proposed on the basis of EPR experiments to be the *cis*-ethanesemidione radical.⁸² It was argued that this species is too stable to allow the reaction to proceed further. Likewise, the substrate analog chloroacetaldehyde was found to elicit a similar outcome. Subsequent

computational investigations determined that the inactivation was indeed due to the intervention of a very stable species. However, it was found that it is not the *cis*-ethanesemidione radical, because the latter is actually a TS connecting a pair of equivalent glycolaldehyde radicals that lie 38.0 kJ mol^{-1} lower in energy. Rather, the very stable species involved in the reaction is in fact glycolaldehyde radical, which can be generated from both glycolaldehyde and chloroacetaldehyde.⁸³ Thus, the suicide inactivation appears to be a consequence of the inability of the glycolaldehyde radical to re-abtract an H atom from Ado–H to generate the final product and regenerate Ado[•] (step C of Scheme 1). Indeed, the barrier and reaction enthalpy for this process are calculated to be >110 and $+85 \text{ kJ mol}^{-1}$, respectively. Such energy requirements are likely to be too demanding for the enzyme to overcome under physiological conditions.

Subsequent computational investigations highlighted several additional instances of similar termination mechanisms to be operational in the reactions catalyzed by DDH with various other substrate analogs, including ethane- and propane-triols, glyceraldehyde, and glyoxal.⁸⁴ In each case, the catalytic cycle is terminated prematurely because a very stable radical intermediate prevents the H-atom re-abstraction step from Ado–H from occurring.

2.3.2 Glycerol Dehydratase

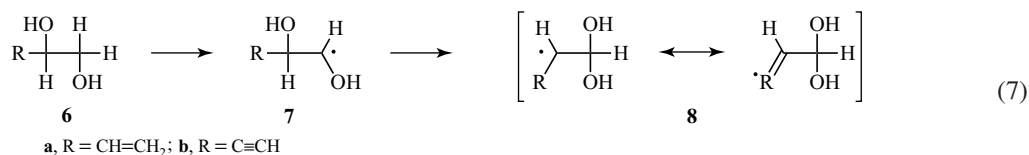
An enzyme that shares striking similarities with DDH is glycerol dehydratase (GDH).⁸⁵ Like DDH, GDH catalyzes a 1,2-OH shift and dehydration of its substrate. In this case, glycerol is converted to 3-hydroxypropionaldehyde plus water (6):



Because glycerol is available in good supply as a byproduct in the biofuel industry, there is currently significant interest in exploiting this reaction to convert glycerol to valuable feedstock chemicals.

Recently, GDH has been observed to undergo time-dependent inhibition with the substrate

analog but-3-ene-1,2-diol (**6a**).⁸⁶ EPR studies, in combination with deuterium labeling at C1, C2, and C4 of **6a**, indicate spin density to be located at C1, suggesting the presence of the 1,2-dihydroxybut-3-en-1-yl radical (**7a**), which would be formed directly via an initial H-atom abstraction from C1 of **6a** (7):



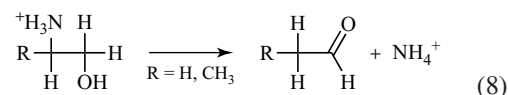
Separate studies involving reaction of the related enzyme DDH with 3-unsaturated 1,2-diols, which included **6a** as well as but-3-yne-1,2-diol (**6b**, (7)), have demonstrated that these reactions also terminate prematurely.⁸⁷

We have compared the reaction profiles involving the reaction of GDH with glycerol and with the substrate analogs **6a** and **6b** to investigate these phenomena.⁸⁸ Our calculations indicate that the energy requirements for the catalytic pathway for GDH with glycerol are very similar to those obtained for DDH (Section 2.3.1). In addition, our calculations indicate that the initial radicals **7a** and **7b** produced from the substrate analogs **6a** and **6b** can rearrange to **8a** and **8b** with exothermicities of 83.4 and 67.5 kJ mol⁻¹, respectively, consistent with expectations based on the stabilizing effect of vinyl or ethynyl substituents adjacent to the radical center in the latter. Furthermore, the barrier to generate **8a** from **7a** is calculated to be 94.3 kJ mol⁻¹, which is lower than that calculated for glycerol (116.8 kJ mol⁻¹), and likely to be lowered further through partial proton transfer to/from the migrating and spectator OH groups. It thus appears quite likely on energy grounds that GDH has the capacity to transform the initially formed radicals in these substrate analogs (**7**) to their rearranged products (**8**). It is therefore curious that isotopic labeling studies involving GDH and **6a** suggest the presence of **7a**. Further experiments are desirable in order to help understand why the transformation of **7a** to **8a** appears not to take place, particularly given that both GDH and DDH exhibit similar inactivation outcomes.

2.3.3 Ethanolamine Ammonia-Lyase

Ethanolamine ammonia-lyase (EAL) catalyzes the irreversible deamination of (protonated) 2-aminoethanol (R = H) to acetaldehyde plus ammonium cation and (protonated) 2-amino-3-propanol (R = CH₃) to propionaldehyde plus

ammonium cation (8)⁷³:



As found with DDH and GDH, the ability of EAL to tolerate substrate modifications has led to a set of diverse and interesting side reactions. As in DDH, glycolaldehyde was found to inactivate EAL and to give an EPR spectrum that parallels that observed with DDH⁸²; the inactivation is therefore likely to again be caused by the highly stabilized glycolaldehyde radical.⁸⁹ Reed and coworkers have established that the substrate analog 2-hydroxyethylhydrazine (HEH) also causes the rapid, irreversible inactivation of EAL, with acetaldehyde and the hydrazinium radical cation identified as products.^{90,91} Interestingly, the energy requirements for the reaction of HEH were found to be very similar to those calculated for (8) with the native substrate, suggesting that in the absence of another pathway, HEH ought to be a catalytically viable substrate analog.⁸⁹ However, a lower energy pathway involving the hydrazinium radical cation exists, which may in principle occur from either the substrate-derived or product-related radicals; quite possibly, it occurs during a failed 1,2-migration event. Like the glycolaldehyde radical, the hydrazinium radical cation is apparently too stable to permit the necessary H-atom re-abstraction step, thus terminating the catalytic cycle.⁸⁹

In yet another situation involving irreversible inactivation, 2-aminoacetaldehyde was found to elicit inactivation of EAL, with acetic acid and 4',5'-anhydroadenosine as major products from the reaction as well as degradation of the corrinoid cofactor.⁹² On the basis of similar energy requirements for the EAL-catalyzed reaction of (protonated) 2-aminoethanol, our calculations provide evidence that (protonated) 2-aminoacetaldehyde can generate acetic acid, though they do not easily account for the formation of 4',5'-anhydroadenosine. It was suggested that the presence of an unbound carboxylate, as might be made available from acetic acid, may participate in the subsequent oxidation of 5'-deoxyadenosyl radical to yield this unusual product.⁸⁹

Another important aspect of interest in the EAL-catalyzed reaction involves the mechanism of radical rearrangement. The generally accepted mechanism for the 1,2-shift of the (protonated) amino group in the substrate-derived radical to form a product-related radical is a direct migration pathway (cf. Scheme 1, step B). In principle, it is also possible that NH_4^+ dissociates from the substrate-derived radical to give a vinyloxy radical, which could generate acetaldehyde directly via re-abstraction of an H atom from Ado-H. However, calculations indicate this direct elimination route to be less likely because it would require a high-energy re-abstraction of an unactivated H atom from Ado-H by the stabilized vinyloxy radical.^{93,94}

The energy requirements for the intramolecular 1,2-shift (cf. pathway F, Scheme 2) have also been examined. The barrier for this transformation in protonated 2-amino-1-hydroxyethyl radical is found to be 65.8 kJ mol^{-1} ,⁹³ which is consistent with the experimental reaction rate. Interestingly, the result of either full or partial deprotonation of the amino group serves to increase the barrier to rearrangement. At the extreme, full deprotonation was found to yield a fragmentation barrier some 30.7 kJ mol^{-1} higher in energy (at 96.5 kJ mol^{-1}) than its protonated counterpart. In another related study, the use of imidazole to partially deprotonate the amino group in protonated 2-amino-1-hydroxyethyl radical leads to a rearrangement barrier of $114.6 \text{ kJ mol}^{-1}$.⁹⁴ Taken together, these results suggest that full protonation of the migrating group results in the most efficient rearrangement of the substrate and that any deprotonation is likely to be anti-catalytic. However,

since H-bonding within the active site of EAL is likely to result in at least some partial deprotonation of the amino group of (protonated) aminoethanol, EAL must use an additional strategy to facilitate catalysis.

Apparently, this strategy takes the form of partial deprotonation of the spectator OH group of aminoethanol, which plays a crucial role in lowering the rearrangement barrier in this reaction. Indeed, we find that the rearrangement barrier for neutral 2-amino-1-hydroxyethyl radical (96.5 kJ mol^{-1}) is reduced by 1.8, 18.2, and 33.8 kJ mol^{-1} , respectively, when NH_3 , CN^- , and OH^- interact with the spectator OH group. In the limit of full deprotonation, the barrier to fragmentation is just 29.5 kJ mol^{-1} .⁹³ Similar findings were reported by Semialjac and Schwarz.⁹⁴

Perhaps the most striking conclusion from these studies is that a combination of "push-pull" catalysts constitutes the most plausible mechanism for the EAL-catalyzed rearrangements. In this scenario, the protonated migrating group and the OH spectator groups are bound by basic catalysts, which significantly reduce the barrier to rearrangement. As an example, consider the results for neutral 2-amino-1-hydroxyethyl radical, which possesses a rearrangement barrier of 96.5 kJ mol^{-1} in the absence of any catalysts.⁹³ A small increase (of 2.6 kJ mol^{-1}) in the rearrangement barrier is observed for the interaction of NH_4^+ at the migrating NH_2 group, while a very small lowering in the barrier (of -1.8 kJ mol^{-1}) is observed if NH_3 interacts with the spectator OH group. However, the combination of both of these interactions reduces the barrier to 66.0 kJ mol^{-1} . Analogous synergistic benefits of this type have also been observed using imidazole and acetate.⁹⁴ In this case, the catalyzed rearrangement barrier is 57.3 kJ mol^{-1} . Both results are consistent with experimental rate data and provide an attractive mechanism for the EAL-catalyzed reaction.

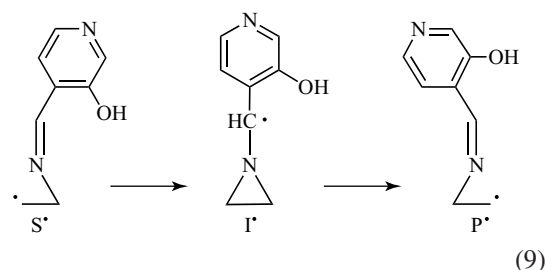
Very recently, X-ray crystal structures of an N-terminal truncation of the *Escherichia coli* EAL β -subunit have been obtained in the presence and absence of the substrate.⁹⁵ The substrates are bound by six H-bonds involving Arg160, Gln162, Asn193, Glu287, and Asp362. With 2-amino-1-propanol as substrate, both Arg160 and Glu287 are found to be within H-bonding distance of O1 of the substrate (2.71 and $2.80 \text{ \AA}$, respectively). The oxygen of Gln162 is $2.80 \text{ \AA}$ from the migrating N atom of

the substrate. It is interesting to note that the position of Arg160 in the crystal structure of EAL corresponds to the metal ion position in both diol and glycerol dehydratases,⁹⁵ suggesting that its role may, at the very least, serve to correctly position the substrate for its subsequent rearrangement. Of relevance here are mutagenesis experiments that have revealed a critical role for Arg160 in the EAL-catalyzed reactions.⁹⁶ Glu287 almost certainly serves to partially deprotonate the O1 hydroxyl group, while the position of Gln162 is consistent with a weak conjugate base interacting with an almost fully protonated migrating N atom. Now that an EAL crystal structure is available, future computational modeling studies will be of interest in order to further examine the role of the partial proton transfer concept in the EAL-catalyzed reaction.

2.4 Class III Aminomutases

The third and final class of AdoCbl-dependent enzymes that we have examined corresponds to the aminomutases. These enzymes catalyze the reversible 1,2-amino shift in certain amino acids for their subsequent cleavage into easily metabolized intermediates.²⁷ Members from this class include lysine-5,6-aminomutase (5,6-LAM) and ornithine-4,5-aminomutase. In addition to their requirement for AdoCbl, these enzymes also require pyridoxal-5'-phosphate (PLP), a derivative of vitamin B₆, for activity. PLP is believed to form an imine linkage to the migrating group of the substrate, thereby facilitating catalysis.

Despite the additional requirement of PLP, these reactions are proposed to be closely related to those of the other AdoCbl-dependent enzymes. The rearrangement step is thought to proceed via an intramolecular A/E pathway involving an azacyclopropylcarbinyl radical (I') intermediate (9) (see also pathway G, Scheme 2):



We note that of all the AdoCbl-dependent enzymes, the aminomutases are likely to be the only class to possess discrete intermediates during the rearrangement step. For example, GM proceeds via a F/R mechanism, while the substrate rearrangement in MCM is likely to proceed in a single direct step.

In any event, uncertainties concerning the rearrangement mechanism for the aminomutases prompted us to investigate the role of PLP and how it might facilitate the 1,2-NH₂ shifts. First, we examined the energy requirements for a 1,2-NH₂ shift in the absence of PLP. Using 2-aminoethyl radical as our simplest model, we found a rearrangement barrier of 90.5 kJ mol⁻¹. Interestingly, protonation of the amino group was found to increase the barrier to 104.8 kJ mol⁻¹.⁹⁷

Next, we examined models including the essential features of PLP in order to examine its effect on the energy requirements for rearrangement. In principle, the imine linkage formed between PLP and the migrating group of the substrate can permit an intramolecular rearrangement pathway. Furthermore, the OH group could also lower the energy requirements through its action as an intramolecular H-bond donor. To examine the effect that the imine may have on the rearrangement barrier, 2-(*N*-methylidene)ethyl radical was initially used. In this case, the barrier for ring closure to generate the cyclic 1-aziridinylcarbinyl radical is 76.2 kJ mol⁻¹ and the reaction is endothermic by 42.2 kJ mol⁻¹ (Figure 7). The barrier to ring closure is found to decrease further (to 61.3 kJ mol⁻¹) when models incorporating the added functionality of the pyridoxal moiety are used (as in S', (9)). The barrier is reduced to 37.2 kJ mol⁻¹ on protonation at the pyridine nitrogen, and the cyclic intermediate is stabilized considerably (Figure 7).

These calculations reveal two critical roles for PLP in the facilitation of the 1,2-NH₂ shifts. The first role is to introduce unsaturation into the substrate via the aldimine linkage, which lowers the energy of the radical intermediates via an intramolecular pathway. The second important role of PLP is to stabilize high-energy intermediates, for example, the aziridinylcarbinyl radical, through the cooperation of electron donation (by the C–N bonds) to the radical center and π -electron withdrawal from the radical center (by the pyridoxal ring). In addition, this is enhanced with protonation of the pyridoxal ring.

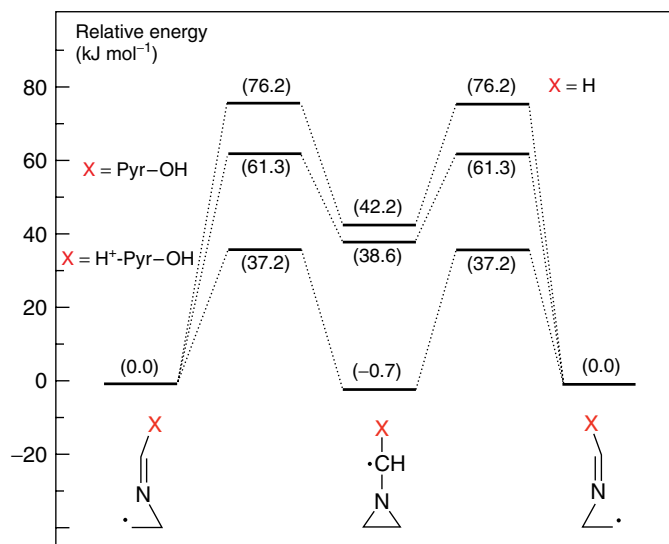


Figure 7 Schematic energy profiles (RMP2/G3MP2Large, kJ mol^{-1}) for the degenerate rearrangement of substituted 2-(*N*-methylidene)ethyl radicals.^{3,97} [Reprinted with permission from Ref. 3. Copyright 2010 American Chemical Society.]

Much of what has been learned in these reactions has been obtained through experiments with 2,3-LAM.⁹⁸ This enzyme is similar to 5,6-LAM in that it catalyzes a 1,2- NH_2 shift. However, instead of using AdoCbl to initiate substrate catalysis via Ado $^{\bullet}$, 2,3-LAM generates Ado $^{\bullet}$ via reductive cleavage of the C–S bond of *S*-adenosylmethionine (AdoMet or SAM) by a 4Fe4S cluster. Both the P $^{\bullet}$ and S $^{\bullet}$ intermediates have been identified via EPR spectroscopy for the 2,3-LAM-catalyzed reaction. However, detection of the putative cyclic intermediate (I $^{\bullet}$) remains elusive.

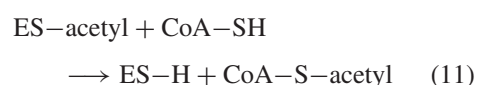
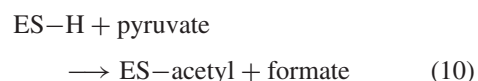
We have sought to remedy this situation by examining energy profiles of model substrates and their analogs. Importantly, substitution with π -acceptors of increasing strength at the exocyclic carbon is found to stabilize I $^{\bullet}$ to an extent that experimental verification, especially in the reactions catalyzed by 5,6-LAM, may be possible.⁹⁹ For example, Figure 8 shows that the π -acceptors $\text{Z} = \text{C}\equiv\text{CH}$ and $\text{CH}=\text{CH}_2$ are able to stabilize I $^{\bullet}$ by 30–40 kJ mol^{-1} relative to the unsubstituted system. It is presently unclear whether the enzymes can tolerate such changes in the substrate. However, strategies such as these may enable the first experimental characterization of an I $^{\bullet}$ -like structure in the aminomutase-catalyzed reactions.

3 GLYCYL RADICAL ENZYMES

The enzymes in the second group that we examine are known to utilize a peptide backbone glycy radical in their reaction mechanism. These so-called glycy radical enzymes require post-translational activation by specific iron–sulfur proteins¹⁰⁰ that belong to the *S*-adenosylmethionine (SAM) radical enzyme superfamily.^{101,102}

3.1 Pyruvate Formate Lyase

Pyruvate formate lyase (PFL) is an enzyme found in *E. coli* and other microorganisms that catalyzes the coenzyme A (CoA)-dependent reversible cleavage of pyruvate into acetyl-CoA plus formate during anaerobic glucose metabolism.¹⁰³ The transformation proceeds via a stepwise transfer of an acetyl group, firstly from pyruvate to an enzyme-bound cysteine residue (ES–H) and then from the acetylated enzyme (ES–acetyl) to CoA (10) and (11):



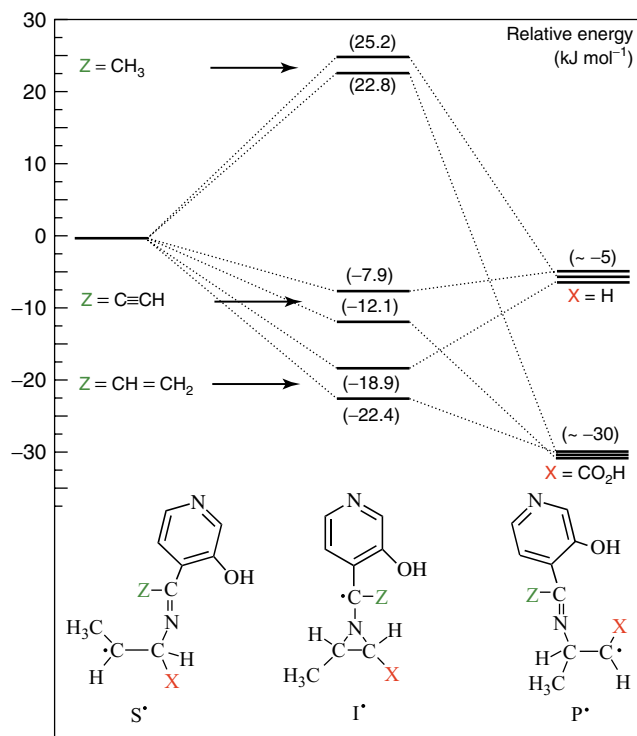


Figure 8 Relative energies of S[•], I[•], and P[•] for various Z-modified PLP derivatives pertinent to the 2,3-LAM-(X = CO₂H) and 5,6-LAM-(X = H) catalyzed reactions.⁹⁹

The active form of PFL contains a backbone glycyl radical (Gly734)¹⁰⁴ that is generated by the stereospecific abstraction of its C-2 *pro-S* H atom via a specific activating enzyme called *PFL activase*.¹⁰⁵ In addition to Gly734, two cysteines (Cys418 and Cys419) are required for catalysis.¹⁰⁶ Figure 9 shows the active site of PFL, including two arginines (Arg176 and Arg435) that bind and position the substrate via salt bridges.¹⁰⁷

The currently accepted mechanism for PFL catalysis was first proposed in 1999 by Knappe and coworkers¹⁰⁸ and developed with insights from theoretical calculations¹⁰⁹ based on an earlier mechanistic proposal (Scheme 3).¹¹⁰ Following activation to generate the glycyl radical at Gly734, the radical center is shuttled to Cys418 via Cys419 (steps a and b, Scheme 3). The Cys418 cysteinyl radical then attacks the carbonyl carbon (C2) of pyruvate to generate a tetrahedral oxy-radical intermediate (step c), which fragments to CO₂^{•-} and acetylated Cys418 (step d). CO₂^{•-} then abstracts an H atom from Cys419 (step e), which in turn

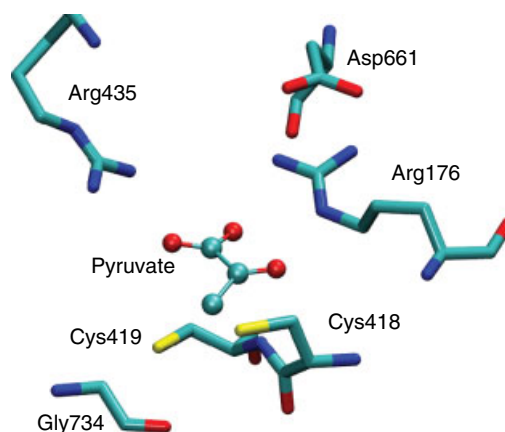
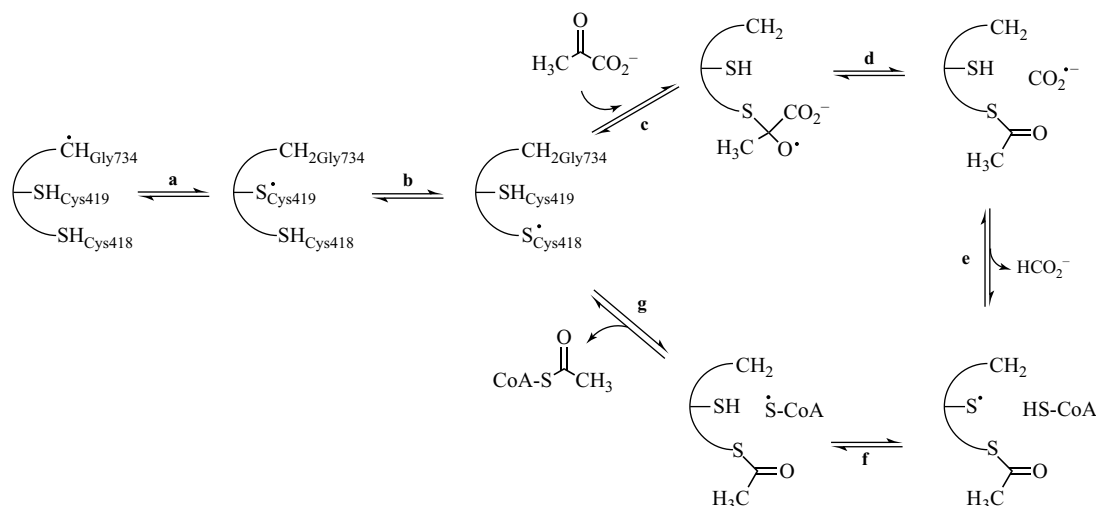


Figure 9 Crystal structure of the active site of PFL (PDB code: 1H16¹⁰⁷).

abstracts an H atom from CoA-SH to generate CoA-S[•] (step f). Finally, condensation of the acetyl group bound to Cys418 with CoA-S[•] generates acetyl-CoA plus a Cys418 radical (step g). The



Scheme 3 Currently accepted mechanism for the PFL-catalyzed reaction.¹⁰⁸

mechanism is interesting because, in contrast to the coenzyme B₁₂-dependent reactions, the substrate is activated by radical addition rather than H-atom abstraction.

Himo and Eriksson¹⁰⁹ were the first to investigate the complete PFL-catalyzed reaction using small-model calculations in combination with the B3-LYP/6-311+G(2 d,2p) level of theory. Their model used the methyl thiyl radical to represent the protein-bound cysteinyl radical, which was justified on the basis of comparable S–H bond dissociation energies, and protonated pyruvate as the substrate. Protonation of the substrate was assumed on account of the active-site arginine residues that would likely neutralize the substrate carboxylate. In order to accurately describe the expected π -electron delocalization in the backbone glycyl radical,⁶⁵ an extended CHO–NH–CH₂–CO–NH₂ fragment was used as a model for glycine.

The barrier for H-atom transfer between cysteine and the glycyl radical (step a, Scheme 3) was calculated to be 41.4 kJ mol^{−1} and the reaction was found to be endothermic by 14.2 kJ mol^{−1}. The reaction energy highlights the differential thermodynamic stabilization of the glycyl radical compared with the thiyl radical, which is relevant for all glycyl radical enzymes. Despite the endothermicity, the calculations suggest that the proposed cysteine activation is feasible, both for PFL and in the general case.

The next phase of the PFL-catalyzed reaction involves the formation and the collapse of the tetrahedral radical intermediate (steps c and d, Scheme 3). The requisite addition of the thiyl radical to the carbonyl carbon of pyruvate (step c) has a calculated barrier of 51.5 kJ mol^{−1} and an endothermicity of ~40 kJ mol^{−1}. Dissociation of the intermediate into acetylated cysteine and [•]CO₂H (step d) is associated with a barrier of 11.7 kJ mol^{−1} and an exothermicity of 16.3 kJ mol^{−1}. The acetyl transfer from pyruvate to the methyl thiyl radical was calculated to be endothermic by 25.1 kJ mol^{−1}. These relatively moderate energy requirements suggest that, in the case of PFL, substrate activation by radical addition, as opposed to H-atom transfer, is indeed reasonable.

The quenching of [•]CO₂H by the model for cysteine (Cys419, step e, Scheme 3) was found to possess a barrier of just 4.6 kJ mol^{−1} with an exothermicity of 60.0 kJ mol^{−1}, which appears sufficient to compensate for the previously outlined endothermic steps. It was noted that a direct H-atom transfer could in principle occur between Gly734 and [•]CO₂H. However, the higher barrier (of 20.5 kJ mol^{−1}) and larger distance associated with the glycine suggested this to be unfavorable. The barrier for the H-atom transfer involving Cys419 and CoA–SH (step f) is calculated to have a barrier of 10.0 kJ mol^{−1} and, on account of the models used, is thermoneutral. The transfer of the acetyl group between Cys418 and CoA–S[•] (step g) has

a calculated barrier of 48.5 kJ mol^{-1} . Finally, the regeneration of the glycyl radical involves H-atom transfer to the cysteinyl radical (the reverse of step a, Scheme 3), with a barrier of 27.2 kJ mol^{-1} and an exothermicity of 14.2 kJ mol^{-1} . The net conversion of pyruvic acid plus methane thiol to formic acid plus the thioester is exothermic by 33.8 kJ mol^{-1} .

Overall, the calculations of Himo and Eriksson demonstrate that the mechanism shown in Scheme 3 is, in principle, feasible. Indeed, this theoretical study, which was performed before the resolution of the X-ray crystal structure of PFL, was instrumental in discriminating between varying mechanisms that had been proposed in the literature.

Following the release of the X-ray crystal structure, the PFL-catalyzed reaction was re-examined using similar theoretical protocols (i.e., B3-LYP/6-311++G(3df,3pd)) but with slightly different chemical models.¹¹¹ While Gly734 was again modeled with $\text{CHO-NH-CH}_2\text{-CO-NH}_2$, the cysteine model was extended to include the neighboring cysteine side chains and the associated peptide backbone. Anionic forms of the substrate pyruvate and the reaction product formate were used. The justification for this choice was primarily based on the likely protonation state of pyruvate under physiological conditions (pK_a is 2.5).

The principal difference arising from the use of the anionic pyruvate is the prediction of a concerted mechanism for the addition of the thiyl radical to pyruvate and the elimination of $\text{CO}_2^{\cdot-}$ (steps c and d, Scheme 3). In other words, in contrast to the neutral pyruvic acid, there is no evidence for a tetrahedral intermediate in the anionic case. The barrier for this step is calculated to be 49.4 kJ mol^{-1} using the large cysteine model, with an endothermicity of 32.6 kJ mol^{-1} . The product complex shows the leaving $\text{CO}_2^{\cdot-}$ group to be in close contact with the acetyl-cysteine moiety (C–C bond distance of $2.03 \text{ \AA}$). Moreover, a significant degree of electron spin (0.53) remains on the acetyl-cysteine moiety, suggesting that further dissociation of $\text{CO}_2^{\cdot-}$ will further lower the energy of the product complex. As in the previous study,¹⁰⁹ H-atom transfers from either Gly or Cys to $\text{CO}_2^{\cdot-}$ species were investigated. Using $\text{CO}_2^{\cdot-}$ leads to smaller H-atom abstraction barriers than when $\cdot\text{CO}_2\text{H}$ is used, but the preference for H-atom abstraction involving Cys419 is maintained.

Following this study, Guo and Himo¹¹² re-investigated the PFL-catalyzed reaction using an extended model. Selected atoms of the included amino acid residues were frozen to their X-ray coordinate values in a so-called “frame model” in order to mimic the enzyme structure. Two positively charged arginine side chains were included in the model in order to bind the negatively charged pyruvate. This model was considered to be superior to both the fully neutral¹⁰⁹ and anionic¹¹¹ pyruvate models used earlier.

The X-ray structure of PFL shows Gly734 to be located within a loop. The use of a frame model is found to constrain the geometry of the glycyl radical such that it cannot adopt its preferred planar conformation. Relative to the ideal geometry, the BDE is 33.9 kJ mol^{-1} higher for the constrained glycine model, which translates into an exothermicity of 19.2 kJ mol^{-1} for the H-atom-transfer step between Cys419 and Gly734. Although this result contradicts EPR experiments, which identify a stable glycyl radical, it is argued that the activation of PFL permits the loop containing the glycyl radical to open to accommodate a more favorable glycyl radical geometry.¹¹²

In contrast to the mechanism with an isolated anionic pyruvate, the frame model predicts a step-wise transfer of the acetyl group from pyruvate to cysteine (steps c and d, Scheme 3).¹¹² Instead of a single tetrahedral intermediate in this process, however, Guo and Himo located two shallow intermediates separated by a small barrier. The second of these, which precedes the C–C bond cleavage, was similar in its relative energy, structure, and spin characteristics to the one obtained by Lucas *et al.*¹¹¹ Another difference arising from the use of the frame model was the proposal that the $\text{CO}_2^{\cdot-}$ abstracts an H atom from CoA-SH rather than from Cys419. This proposal is based on observations that indicate H-atom transfer from Cys419 to the C atom of the $\text{CO}_2^{\cdot-}$ to be difficult on structural grounds.¹¹²

More recently, Smith and coworkers have used the PFL-catalyzed reaction as a prototypical radical-enzyme-catalyzed reaction in order to determine the most appropriate manner with which to truncate an arginine-bound carboxylate motif in small-model studies.¹¹³ The focus of this study was on the acetyl transfer from pyruvate to the cysteine (steps c and d, Scheme 3). Therefore, only the substrate and methanethiyl radical were considered.

The *syn* orientation of the carboxylic acid proton of (neutral) pyruvic acid was chosen over the lower energy *anti* orientation used earlier, since it was argued that an intramolecular H-bond (i.e., *anti*) is unlikely to be present in the active site of the enzyme, especially when an arginine residue lies close to the carboxylate group.

With the *syn* pyruvic acid model, two shallow minima were found for the acetyl-transfer step, in agreement with the frame-model study of Guo and Himo.¹¹² The results obtained with B3-LYP/6-31G(d) were found to overestimate those obtained with the high-level G3(MP2)-RAD procedure, by 10–20 kJ mol⁻¹, whereas the use of the larger G3MP2Large basis set with B3-LYP slightly improved the agreement with the higher-level approach.¹¹³

With anionic pyruvate, the thiyl radical addition to the substrate was predicted to be concerted,¹¹³ in agreement with a previous study using a similar model.¹¹¹ However, the reaction was found to be exothermic with higher levels of theory, which, in contrast to the previous results, implies that the anionic pathway may not benefit energetically from reacting further.¹¹³

This study went on to compare the small-model results of neutral/anionic pyruvate with those obtained with the zwitterionic complex of anionic pyruvate with an adjacent protonated methylguanidinium, where the latter ion was used as a model for arginine.¹¹³ Overall, this model more closely resembles the results obtained using neutral pyruvic acid than anionic pyruvate and gives results in very good agreement with those obtained previously using a much larger model. On this basis, it was suggested that, when the inclusion of species such as the methylguanidinium ion is not practical, neutral (*syn*) carboxylic acids provide a much more realistic treatment of an arginine-bound carboxylate motif than the bare anionic form.

Smith and coworkers also used the PFL-catalyzed reaction to develop a compound QM/MM procedure called ONIOM(G3(MP2)-RAD:MM),¹¹⁴ which is based on the multilayered ONIOM method of

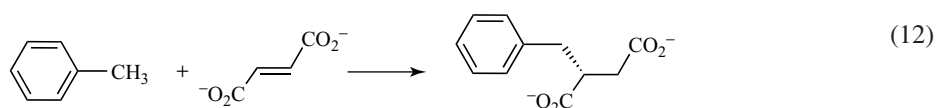
Morokuma and coworkers.¹¹⁵ In their QM/MM division, pyruvate was placed in the QM region, while the methylguanidinium ion was treated with an MM description. The resulting ONIOM(G3(MP2)-RAD:MM) results were assessed against pure QM G3(MP2)-RAD results to determine the viability of using high-level QM treatments in the QM/MM formalism.

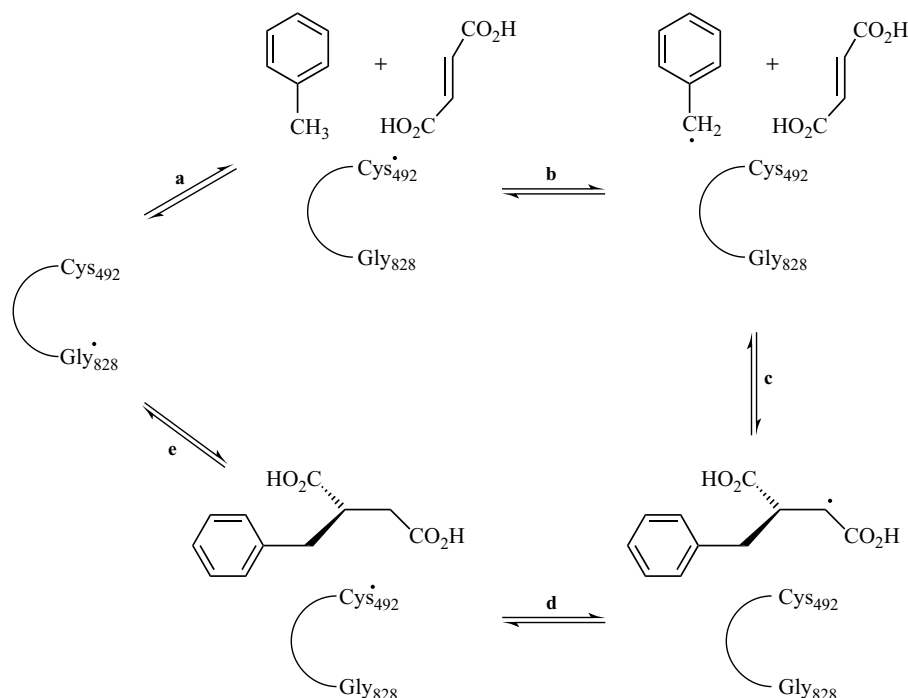
Interestingly, similar results for the radical addition to pyruvate were obtained regardless of whether the methylguanidinium fragment was treated classically or quantum mechanically. Both methods give two intermediates and three TSs. Despite some minor discrepancies, which appear to be the result of charge transfer from pyruvate to the methylguanidinium, the ONIOM(G3(MP2)-RAD:MM) procedure was found to provide a reliable high-level QM/MM treatment for enzyme-catalyzed reactions.

In addition to the methodological aspects, this study addressed the inhibitory effect of oxamate and an alternative mechanism involving activation by H-atom abstraction.¹¹⁴ Oxamate was found to exhibit a significantly higher barrier for thiyl radical addition than the substrate pyruvate. Although H abstraction of the substrate was found to be energetically competitive with radical addition, the former pathway is not productive and hence not expected to be observed.

3.2 Benzylsuccinate Synthase

Benzylsuccinate synthase (BSS) is an enzyme that is involved in the anaerobic toluene degradation that occurs in denitrifying and sulfate-reducing bacteria such as *Thauera aromatica* and *Desulfobacula toluolica*.^{116,117} The discovery that these bacteria survive on toluene and related aromatic compounds as their sole source of carbon and energy has generated significant interest for the possible use of BSS in bioremediation strategies.¹¹⁸ BSS catalyzes the addition of toluene to fumarate to produce (*R*)-benzylsuccinate (12)¹¹⁹:





Scheme 4 Proposed mechanism for the benzy succinate synthase-catalyzed reaction.^{120,121}

The proposed mechanism for the reaction catalyzed by BSS is shown in Scheme 4.^{120,121} Catalysis is initiated by the activation of BSS to form a glycy radical (Gly828).¹²¹ This radical is transferred to an active-site cysteine (Cys492) (step a, Scheme 4) which, in the forward direction as shown in Scheme 4, is likely to be rate limiting.¹²² In line with the vast majority of radical enzymes, the substrate is activated by H-atom abstraction. In this case, Cys492 abstracts an H atom from toluene to generate a benzyl radical (step b). Addition of the benzyl radical to the double bond of fumarate generates a benzy succinyl radical (step c),¹²³ which then abstracts an H atom from cysteine (step d). At this stage, the cysteinyl radical either abstracts an H atom from Gly828 to regenerate the starting state (step e) or initiates the next catalytic cycle with another H-atom abstraction from another toluene substrate.

Despite the fact that a crystal structure of BSS is not yet available, theoretical calculations can still provide important insights into the thermodynamic and kinetic feasibility of the proposed mechanism. Using models for the substrate and active-site glycine and cysteine residues, Himo¹²⁴

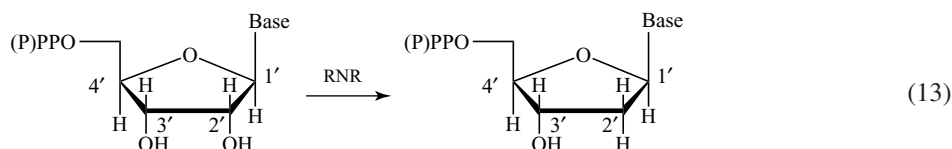
examined the proposed catalytic cycle of BSS using DFT. Consistent with the PFL results, the first H-atom-transfer step from cysteine to the glycy radical (step a, Scheme 4) is calculated to possess a barrier of 44.8 kJ mol^{-1} in a reaction that is slightly endothermic (by 14.2 kJ mol^{-1}).¹²⁵ The subsequent H-atom abstraction from the methyl group of toluene (step b) is calculated to have a barrier of 39.7 kJ mol^{-1} with a reaction energy of $+13.0 \text{ kJ mol}^{-1}$. It was pointed out that the overall endothermicity (of 27.2 kJ mol^{-1}) for these first two H-atom transfers is consistent with a constant EPR spectrum of BSS in the presence of toluene but not fumarate.¹²¹ The attack of the benzyl radical on the double bond of fumarate to generate the benzy succinyl radical intermediate (step c) has a barrier of 62.8 kJ mol^{-1} and an exothermicity of 42.3 kJ mol^{-1} . This step can be considered to be analogous to the recombination step of the F/R mechanism for the previously mentioned class I mutases (Section 2.2). H-atom transfer from the thiol to the benzy succinyl radical intermediate (step d) is exothermic by 24.3 kJ mol^{-1} with a barrier of 29.3 kJ mol^{-1} . Finally, H-atom transfer from Gly to the cysteinyl

radical (step e), which is calculated to possess a barrier and exothermicity of 30.5 and 14.2 kJ mol⁻¹, respectively, regenerates the initiating glycyl radical.

In the absence of structural information as to the positions of the Cys and Gly residues in the BSS active site, a direct H-atom transfer from glycine to the benzylsuccinyl radical intermediate was also considered. In this case, the barrier and exothermicity are calculated to be 73.2 and 38.5 kJ mol⁻¹. This barrier is significantly higher than that for H-atom transfer from Cys to the benzylsuccinyl radical intermediate (24.3 kJ mol⁻¹) and suggests that on an energy basis alone, the pathway shown in Scheme 4 is preferred.

4 RIBONUCLEOTIDE REDUCTASE

Ribonucleotide reductases (RNRs) are enzymes that convert ribonucleotides to 2'-deoxynucleotides and are therefore critical for both the synthesis and repair of DNA (13)^{126,127}:



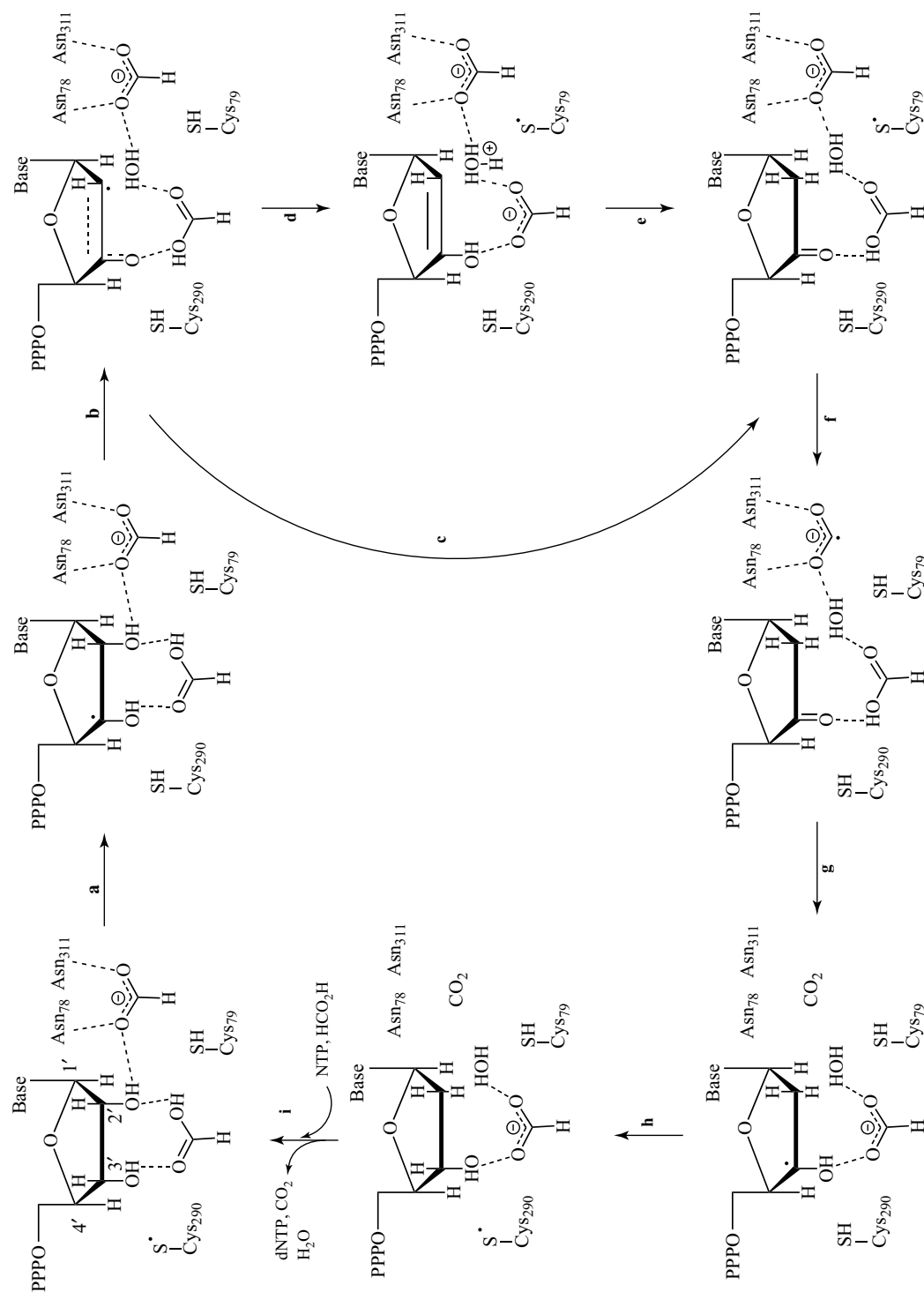
RNRs have been divided into three main classes that differ with respect to the composition of the metal cofactors used to initiate radical generation. Briefly, class I RNR enzymes are found throughout eukaryotes as well as some prokaryotes and viruses and rely on iron and oxygen to generate a tyrosyl radical. We will not review the theoretical studies of this class of RNRs and instead the reader is referred elsewhere for comprehensive reviews on this topic.^{18,128,129} Class II RNRs are found in aerobic and anaerobic bacteria and utilize coenzyme B₁₂ to interact directly with an active-site cysteine residue to form the reactive cysteinyl radical required for ribonucleotide reduction. These will not be reviewed either.

The third class of RNRs, which we will cover in this section, are class III RNRs, which are

found in strict or facultative anaerobic bacteria and some bacteriophages. The formation of radicals is initiated by one-electron reductive cleavage of *S*-adenosylmethionine (SAM) by a 4Fe4S cluster to generate the 5'-deoxyadenosyl radical (Ado[•]) plus methionine. Ado[•] then goes on to abstract an H atom from glycine to form the glycyl radical, which abstracts an H atom from cysteine to generate the reactive cysteinyl radical. Formate is another cofactor required for class III RNRs and is suggested to be a precursor of CO₂^{•-}, which serves as a reductant for the 3'-keto group of a reaction intermediate, a role that is served by two cysteine residues in the aerobic enzymes. Strictly speaking, class III RNRs may be classified as glycyl radical enzymes since they are activated in the same manner. Here, however, we differentiate them from PFL and BSS of Section 3 to highlight their distinct importance and their relationship with class I and II RNRs.

Siegbahn and coworkers have investigated the class III RNR reaction using DFT, with formic acid as a cofactor that catalyzes the loss of water from the substrate (Scheme 5).^{130,131} Their preliminary

small-model investigation focused on the role of formic acid in the uniquely anaerobic transfer of the radical center from Cys79 to C3' of the substrate with the concomitant formation of CO₂.¹³⁰ It was assumed that the initial stages of the substrate transformation in class III RNRs were largely the same as those obtained earlier for the corresponding aerobic enzymes (these are analogous to steps a–e, shown in Scheme 5). Starting from the 3'-keto form of the substrate and the cysteinyl radical at position 79 (cf. step f, Scheme 5), the barrier for H-atom abstraction by Cys79[•] from the carbon atom of formic acid was calculated to be 59.4 kJ mol⁻¹ and the reaction found to be endothermic by 40.6 kJ mol⁻¹. The high relative energy of the resultant [•]CO₂H species indicates that it is likely to be a very short-lived entity, which was suggested



Scheme 5 Complete reaction mechanism of class III RNR studied by Cho *et al.*¹³¹

to help explain why aberrant side reactions do not occur in class III RNRs. It was also suggested that the energetic cost (of $\sim 40 \text{ kJ mol}^{-1}$) for $\cdot\text{CO}_2\text{H}$ to break its strong H-bond with the substrate is not easily compensated for.¹³⁰

The $\cdot\text{CO}_2\text{H}$ intermediate was then proposed to transfer its hydroxyl H atom to the carbonyl oxygen of the 3'-keto-deoxyribose ring to give CO_2 and a 2'-deoxyribose-related radical (cf. step g, Scheme 5). This step has the attractive feature that the reduction of the substrate keto group can occur without the direct involvement of $\text{CO}_2^{\cdot-}$. This process was calculated to possess a barrier and reaction exothermicity of 42.7 and 51.0 kJ mol^{-1} , respectively. Relative to the starting point in this pathway, the energy of this latter H-atom abstraction TS is 83.2 kJ mol^{-1} , which suggests a rate approximately two orders of magnitudes too slow relative to experiment. Zero-point vibrational energy, thermal effects, and solvation were found to have a large influence ($\sim 30 \text{ kJ mol}^{-1}$) on reducing the energy of this TS.

In a subsequent and more comprehensive study, the class III RNR-catalyzed reaction was re-examined using a larger model that included, in addition to the substrate, Cys290, Asn78, Cys79, Asn311, and two formates (Scheme 5).¹³¹ One neutral formic acid was used to mimic the function of Glu144 in the related class I RNR, which facilitates the loss of water from C2' of the ribose. The second (anionic) formate was placed near two asparagines, which were previously suggested to serve as a carboxylate binding site. Unlike the previous small-model study,¹³⁰ which examined just two steps (cf. steps f and g, Scheme 5), the entire reaction pathway was examined in the second investigation.¹³¹

The barrier and reaction enthalpy for the initial H-atom abstraction (step a, Scheme 5) from C3' of the ribose by the Cys290 radical were calculated to be 18.8 and 20.0 kJ mol^{-1} , respectively. The high energy of the product was found to be due to solvation effects. Formic acid plays a critical role in the subsequent loss of water and the generation of a resonance-stabilized radical of the form $\text{O}=\text{CR}-\text{C}^{\cdot}\text{RH}$ (step b). Indeed, the product state of this step was found to be lower in energy than the reactant state, so it was suggested that steps a and b might be concerted. In the following step, C2' is proposed to abstract an H atom from Cys79. Two energetically similar pathways were located for this transformation. The direct

H-atom-transfer pathway (step c) possesses a barrier of 35.6 kJ mol^{-1} . An alternative pathway (steps d and e) that involves the intermediacy of H_3O^+ was located and found to possess a barrier of 37.2 kJ mol^{-1} . Clearly, neither pathway can be ruled out on energy grounds. However, the authors note that there may be advantages in utilizing a small mobile H_3O^+ species rather than directly involving a cysteine residue.¹³¹

The next step in the reaction generates $\text{CO}_2^{\cdot-}$ via H-atom abstraction by Cys79 from the formate coordinated by the two asparagines (step f, Scheme 5). We note that the combination of this form of the substrate, Cys79, and formic acid represents the starting point for the preliminary small-model study of Cho *et al.*¹³⁰ In the larger model study, the barrier is calculated to be 13.8 kJ mol^{-1} and the step is slightly endothermic (by 10.3 kJ mol^{-1}).¹³¹ The O3' atom can then abstract an H atom from the nearby formic acid to localize the spin density on C3' (step g). This step is found to be rate limiting, possessing a barrier of 48.9 kJ mol^{-1} , which is well below the experimental upper limit of $\sim 70 \text{ kJ mol}^{-1}$. Formally, this step transfers the unpaired electron spin density from $\text{CO}_2^{\cdot-}$ to C3' via HCO_2 . The last step in the catalytic pathway (step h) is virtually just the reverse of the first step in that it involves the transfer of an H atom from Cys290 to C3'. With solvation included, it is found to be endothermic by 6.4 kJ mol^{-1} and to have no barrier.

The calculations performed with the larger model have thus identified an energetically feasible manner for the generation and action of the $\text{CO}_2^{\cdot-}$ reductant. The key difference with the smaller model study is the inclusion of one molecule of formic acid (as a Glu mimic) to catalyze the water loss and another (anionic) formate to serve as a proton and electron source, rather than relying on a single formic acid to perform both functions. While this mechanism is yet to be proven, it nevertheless demonstrates the usefulness of computations in mechanistic enzymology.

5 METHYL-COENZYME M REDUCTASE

In methanogenic archaea, methyl-coenzyme M reductase (MCR) catalyzes the exergonic conversion of methyl-coenzyme M ($\text{CoMS}-\text{CH}_3$) and

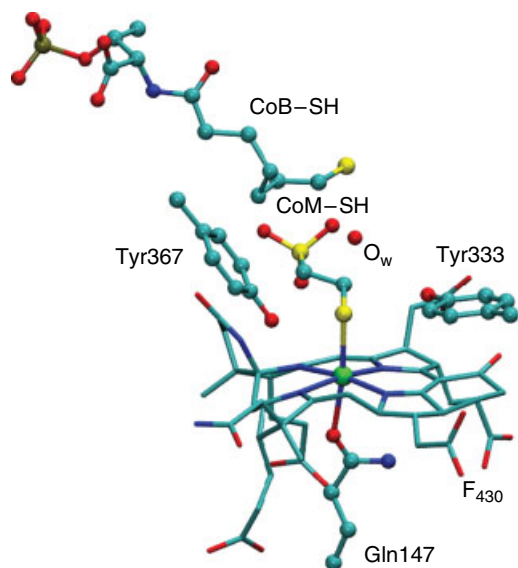
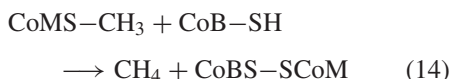


Figure 10 Crystal structure of the active site of the MCR_{ox1} -silent state (PDB code: 1MRO¹³³).

coenzyme B (CoB-SH) into methane and the heterodisulfide of coenzyme M (CoM-SH) and coenzyme B (14)¹³²:



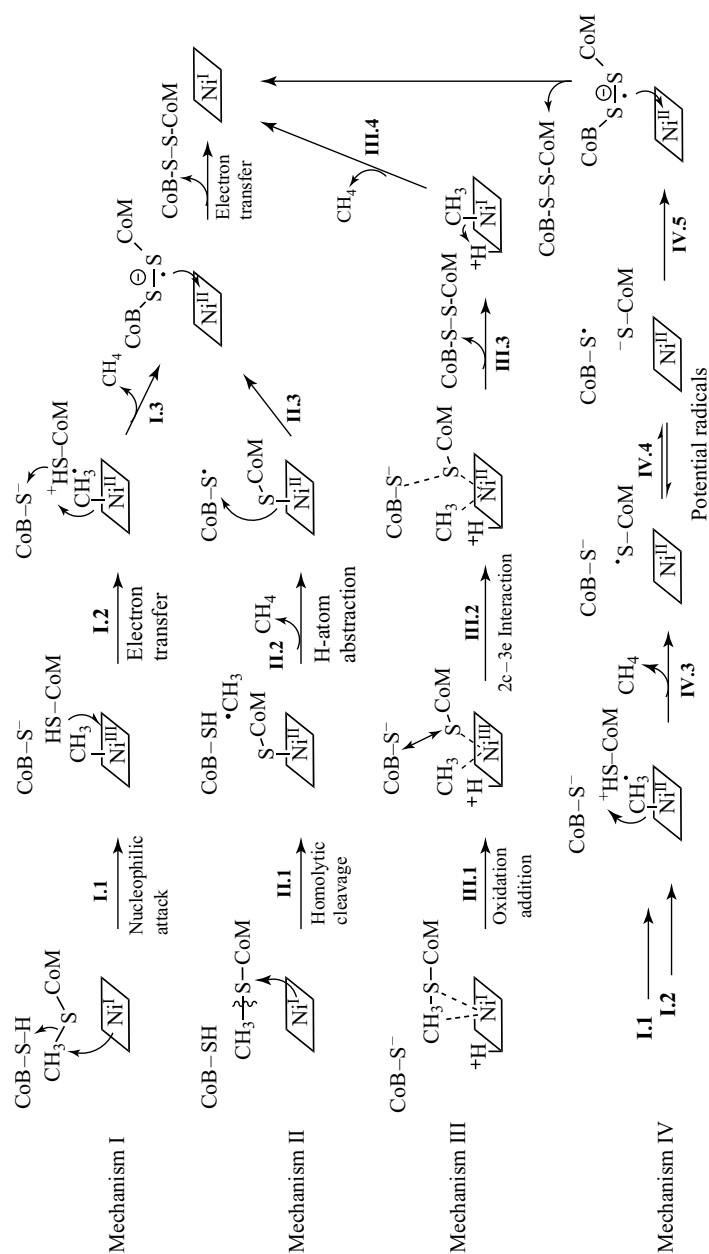
MCR contains a redox-active nickel-centered tetrahydrocorphinoid coenzyme (F_{430}) in its active site, which lies at the bottom of a 30-Å-deep hydrophobic pocket. The active form of MCR, called MCR_{red1} , possesses a low-valent Ni(I) ion. Figure 10 shows the X-ray crystal structure of the MCR_{ox1} -silent form of MCR, in which the nickel is in the 2+ oxidation state, with one bound CoM substrate analog and one CoB.¹³³ Despite considerable efforts, details of the reaction mechanism are still unclear, with several different mechanisms proposed.

In mechanism I, nucleophilic attack of Ni(I) on the methyl group of $\text{CH}_3\text{-SCoM}$ results in heterolytic cleavage of the C-S bond to generate an organometallic $\text{CH}_3\text{-Ni(III)F}_{430}^+$ intermediate and the CoMS^- thiolate anion, which is then protonated by CoBSH to form CoBS^- and CoM-SH (step I.1, Scheme 6). The $\text{CH}_3\text{-Ni(III)F}_{430}^+$ intermediate is a strong oxidant and in the next step (I.2), it

is proposed that CoM-SH is oxidized to form a CoMS-H^+ thiyl radical cation plus a $\text{CH}_3\text{-Ni(II)}$ species. Protonolysis of the latter using the CoMS-H^+ thiyl radical cation then yields methane, the Ni(II) state of F_{430} , and the $\text{CoM-S}^\bullet$ thiyl radical. Finally, the $^\bullet\text{SCoM}$ thiyl radical and CoBS^- react to form a disulfide radical anion, which reduces Ni(II) back to its resting state Ni(I) (step I.3).

To determine the feasibility of mechanism I (Scheme 6), Pelmeshnikov *et al.*¹³⁴ examined the energy cost of methyl binding to nickel by comparing bond strengths relevant to the MCR-catalyzed reaction. It was concluded that an Ni-CH₃ bond is too weak to compensate for the energy required to break the $\text{CH}_3\text{-SCoM}$ bond. Indeed, the reaction step involving $\text{CH}_3\text{-S-CoM} + \text{Ni(I)F}_{430} \rightarrow ^\bullet\text{S-CoM} + \text{CH}_3\text{-Ni(II)F}_{430}$ (step I.1, Scheme 6) was calculated to be endothermic by $\sim 190 \text{ kJ mol}^{-1}$. More recently, the possibility of an Ni-CH₃ intermediate was examined by explicitly calculating TSs and intermediates for stepwise and concerted methyl additions to Ni(I) using $\text{CH}_3\text{-I}$, $\text{CH}_3\text{-Br}$, $\text{CH}_3\text{-Cl}$, and $\text{CH}_3\text{-S-CH}_3$ as substrates, where the latter structure was used as a model for $\text{CH}_3\text{-SCoM}$.¹³⁵ Stepwise methyl transfers from the methyl halides to Ni were calculated to possess quite low barriers ($\sim 16\text{--}28 \text{ kJ mol}^{-1}$), which is consistent with experimental observations of the reactions of MCR_{red1} with alkyl halides. Tyr333 and Tyr367 were found to stabilize the leaving halide anions and facilitate bond cleavage, while the barriers for binding the Gln147 oxygen to Ni were found to be small ($5\text{--}10 \text{ kJ mol}^{-1}$). The species were described as resonance structures between the “doublet-triplet” $\downarrow\text{CH}_3\text{-}\uparrow\uparrow\text{Ni(II)}$ radical state and the “anion-doublet” $\text{CH}_3^--\uparrow\text{Ni(III)F}_{430}$ state. Concerted TSs involving the simultaneous transfer of methyl from the substrate to Ni and the binding of Gln147 to Ni were found to possess larger barriers (of $\sim 40\text{--}55 \text{ kJ mol}^{-1}$) than those observed for the stepwise pathways. Interestingly, when $\text{CH}_3\text{-S-CH}_3$ is used as a substrate, only a concerted TS could be located, which led directly to the hexacoordinated $\text{CH}_3\text{-Ni(F}_{430})$ intermediate. While the reactions involving methyl halides were exothermic, the reaction of $\text{CH}_3\text{-S-CH}_3$ was calculated to be endothermic by $\sim 100 \text{ kJ mol}^{-1}$ and described as “unreachable.”¹³⁵

Because of these large energy requirements, Pelmeshnikov *et al.*¹³⁴ have instead proposed



Scheme 6 Possible mechanisms for methane formation by MCR.

another mechanism. Here, Ni(I) reacts with $\text{CH}_3\text{-SCoM}$ to promote homolytic cleavage of the C–S bond to give a methyl radical plus an Ni(II)-thiolate complex (mechanism II, step II.1). The methyl radical is then proposed to abstract an H atom from CoBSH to generate a CoBS $\cdot$ thiyl radical and release CH_4 (step II.2), which then reacts with the Ni(II)-thiolate complex to form a disulfide radical anion (step II.3). As in mechanism I, this radical anion then reduces Ni(II) back to its resting state Ni(I).

At the time the study was carried out, the large system size (107 atoms) precluded the calculation of an accurate TS, so comparisons with a smaller model were used for its estimation.¹³⁴ The barrier for direct methane formation involving CoBSH and $\text{CH}_3\text{-SCoM}$ was calculated to be 118.4 kJ mol^{-1} , which was revised to 81.6 kJ mol^{-1} when estimates for zero-point energy, entropy, and solvation were included. A feature of this mechanism is that it rationalizes the experimentally observed stereoinversion at the reactive carbon atom as well as rationalizing the inactivity of MCR in the presence of trifluoromethyl-coenzyme M ($\text{CF}_3\text{-S-CoM}$). Indeed, the $\text{CF}_3\cdot$ radical is predicted to possess a very large inversion barrier (of $\sim 100\text{ kJ mol}^{-1}$). However, this mechanism is not supported by the findings that MCR fails to catalyze the reduction of allyl-CoM, although this latter species acts as a competitive inhibitor.¹³⁶ Indeed, the formation of a free allyl radical would be expected to be significantly more favorable than the formation of a free methyl radical.

The mechanism of heterodisulfide product formation (mechanism II, step II.3) was examined in a subsequent paper.¹³⁷ In principle, upward deformation of the corphin ring of the CoM-S-Ni(II) intermediate to interact with the $\text{CoB-S}\cdot$ radical could occur. However, relaxed scans along the Ni-S_{CoM} and $\text{S}_{\text{CoM-S}_{\text{CoB}}}$ bonds indicate this to be a high-energy process ($>70\text{ kJ mol}^{-1}$). In contrast, a late TS describing heterodisulfide product formation was located and found to possess a barrier of 39.7 kJ mol^{-1} , indicating that methane formation (and not heterodisulfide product formation) is the rate-limiting step for this reaction.

In a third mechanistic proposal based on DFT (B3-LYP) calculations, Duin and McKee¹³⁸ favor a mechanism (mechanism III, Scheme 6) that begins with protonation of the F_{430} cofactor on the

C-ring nitrogen of the tetrapyrrole ring. Protonation at the Ni site was also examined and found to be $\sim 5\text{ kJ mol}^{-1}$ lower in energy. However, it is proposed that the side-chain amido group of Gln147 acts as a proton relay to the C-ring nitrogen of the Ni(I) F_{430} cofactor. Protonated Gln147 was found to lie 46.0 kJ mol^{-1} higher in energy than the structure with the proton on the C-ring nitrogen. The H-atom transfer barrier from Gln147 to the ring is calculated to be 92.0 kJ mol^{-1} . Activation of $\text{CH}_3\text{-SCoM}$ occurs with its oxidative addition to Ni to form a four-coordinate Ni product complex involving CH_3 , SCoM^{2-} , and two of the four nitrogen atoms from the corphin ring (step III.1, Scheme 6). A large barrier of 96.7 kJ mol^{-1} is predicted for this step and the reaction is endothermic by 42.3 kJ mol^{-1} . The Ni atom was found to move $1.5\text{ \AA}$ out of the approximate plane formed by the four corphin nitrogen atoms. This feature was highlighted as being an important ingredient in the mechanism because it allows the SCoM^{2-} ligand to approach more closely to the CoBSH cofactor than would otherwise be possible. In the next step (III.2), $\text{CoBS}\cdot$ was constrained above the F_{430} cofactor to mimic the enzyme environment. The complexation energy was calculated to be 44.4 kJ mol^{-1} relative to the separated $\text{CoBS}\cdot$ and $\text{F}_{430}\text{:SCoM}$ species. Most of the unpaired spin density was located on the sulfur atoms of each cofactor and the interaction was described as a two-center, three-electron ($2c\text{-}3e$) bond. The next step (III.3) results in the formation of the $\text{CH}_3\text{S-SCoM}\cdot$ radical anion ligand. This complex is calculated to lie 31.4 kJ mol^{-1} higher in energy than the $2c\text{-}3e$ intermediate. A barrier of 22.6 kJ mol^{-1} is determined for loss of CH_4 , via proton transfer to the CH_3 group from the C-ring nitrogen of the Ni(I) F_{430} . This final step (III.4, Scheme 6) regenerates Ni(I) F_{430} and is exothermic by the remarkable amount of 267.0 kJ mol^{-1} .

Some aspects of this proposed mechanism are difficult to reconcile with the available experimental evidence. For instance, inversion of stereochemistry is known to occur for the $\text{EtSCoM}\cdot$ cofactor and is generally believed to be operative for the native $\text{MeSCoM}\cdot$ cofactor as well. However, this mechanism does not account for this behavior. A pathway involving inversion of stereochemistry was found, but it was associated with a barrier of 138.9 kJ mol^{-1} , which is not likely to be competitive. Moreover, MCR

has recently been shown to catalyze the (reverse) conversion of CH₄ into methyl-coenzyme M under equilibrium conditions.¹³⁹ The very large exothermicity for CH₄ loss in the final step in this mechanism (267.0 kJ mol⁻¹) instead suggests an irreversible pathway. It was proposed that a reversible pathway could exist if the CH₄ loss occurs simultaneously with the reformation of protonated Ni(I)F₄₃₀.¹³⁸

Finally, for completeness, we note that a fourth mechanism has been proposed for the MCR-catalyzed reaction,¹⁴⁰ though it has not yet been examined computationally. On the basis of the transient kinetic measurements using EPR and UV-visible spectroscopy with the substrate analogs 2-bromoethanesulfonate and CoB₆SH, mechanism IV is a variation of mechanism I insofar that the first two steps are identical, but mechanism IV includes radical intermediates (Scheme 6). Following the generation of the CH₃-Ni(II) intermediate, proton transfer from the CoMSH⁺ radical cation generates CH₄ plus a CoMS[•] radical (step IV.3). An equilibrium of S-based radical intermediates is then proposed to occur (step IV.4). In step IV.5, condensation of CoMS and CoBS species leads to the formation of a disulfide radical anion, which then reduces Ni(II) back to its resting state Ni(I), as also proposed in mechanisms I and II.

6 CONCLUSIONS

The aim of this review has been to describe the insights that can be gained from computational investigations of radical enzymes. Of the many possible enzyme systems that may fall into the category, we have focused on a few selected examples to illustrate how these systems operate and how theory may be used to enhance our understanding. For the AdoCbl-dependent enzymes, theoretical investigations have provided mechanisms for how these enzymes activate the Co-C bond of AdoCbl, how partial protonation and deprotonation facilitate the otherwise difficult rearrangement step, and how the inherent stability of the participating radical intermediates can profoundly affect the level of catalysis. Likewise, computational investigations have characterized intermediates and demonstrated the importance of certain active-site amino acid residues in the reactions catalyzed by PFL, BSS, and class III RNR. In the case of MCR, the use

of theory has offered new mechanistic ideas as to how this enzyme operates, which can then be tested experimentally. Overall, it is clear that the combination of experimental and computational investigations provides an excellent and highly synergistic approach to elucidate the cause-and-effect actions that govern enzyme catalysis.

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Lipid Peroxidation

Etsuo Niki

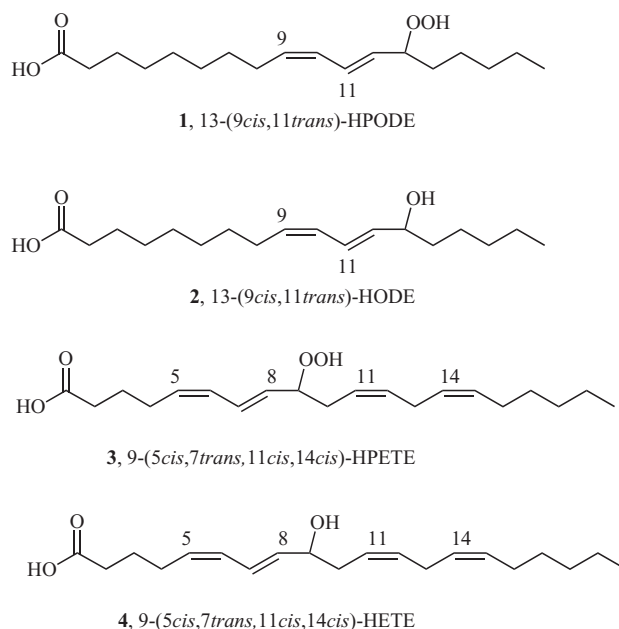
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1 INTRODUCTION

Free and ester forms of fatty acids and cholesterol are physiologically important lipids that are essential components of cellular membranes. Lipids containing polyunsaturated fatty acids (PUFAs) are quite susceptible to oxidant attack and their free-radical-mediated oxidation by molecular oxygen, referred to as *lipid peroxidation* (LPO), results in deleterious effects.^{1,2} The term *peroxidation* refers to dioxygenation and some oxidation of lipids proceeds, as described later, by monooxygenation, but the term “LPO” is used in this article to show the oxidation of lipids in general. LPO was first studied in 1930s in relation to the deterioration of foodstuffs. The autooxidation, oxidation by molecular oxygen, of lipids is responsible for rancidity in fat-containing food products. With increasing evidence showing the involvement of free radicals in health and disease, free-radical-mediated LPO has received renewed attention from wider viewpoints in the fields of chemistry, biochemistry, biology, nutrition, pharmacology, and medicine.^{3,4} LPO is now implicated in the pathogenesis of various diseases such as atherosclerosis, neurodegenerative diseases, cancer, inflammation, and cataract. For example, it was known in 1950s that LPO products were present in the atherosclerotic plaques⁵ and it is now generally accepted that LPO results in the modification of low density lipoprotein (LDL) and high density lipoprotein (HDL), which is a key initial event for the progression of atherosclerosis.⁶ Later studies

revealed that, similar to proteins, carbohydrates, and nucleic acids, lipids are targets of various reactive oxygen species (ROS) and reactive nitrogen species (RNS) and oxidized to give a diverse array products (see **Biological Chemistry of Reactive Oxygen Species**). The mechanisms, dynamics, and products of LPO *in vitro* have been studied extensively and are now fairly well understood and documented,^{1,7,8} but the physiological levels and biological effects of LPO and its products have not been well elucidated yet.

It has been shown that LPO induces disturbance of fine structure and alteration of integrity, fluidity, and permeability, and functional loss of biomembranes. Free radical addition–fragmentation as well as LPO induces the cis–trans isomerization, which may result in loss of important structural information linked to biological activity⁹ (see **Lipid Isomerization**). LPO also modifies LDL to pro-atherogenic and pro-inflammatory forms, and generates potentially toxic products. LPO products have been shown to be mutagenic and carcinogenic.¹⁰ As described later, the reactive carbonyl compounds, the secondary products of LPO, modify biologically essential molecules such as proteins and DNA bases.¹¹ Thus LPO *in vivo* has been implicated as the underlying mechanisms in numerous disorders and diseases such as cardiovascular diseases, cancer, neurological disorders, and aging. Consistent with this notion, numerous studies show increased levels of LPO products in the biological fluids and tissues from the patients,



Scheme 1 Structures of representative lipid peroxidation products H(P)ODE and H(P)ETE.

although the question whether LPO is a cause or consequence of these events is still not clear and remains to be elucidated in the future studies. In any event, the levels of LPO products such as hydro(pero)xyoctadecadienoic acid, H(P)ODE, and hydro(pero)xyeicosatetraenoic acid, H(P)ETE, produced in the oxidation of linoleic acid and arachidonic acid, respectively may serve as reliable marker for oxidative stress *in vivo*. The representative structures of H(P)ODE (**1** and **2**) and H(P)ETE (**3** and **4**) are shown in Scheme 1. Several regio- and stereoisomers are formed as described later.

At the same time, it became evident recently that LPO products as well as ROS/RNS exert various biological functions *in vivo* such as regulator of gene expression, signaling messenger, activator of receptors and nuclear transcription factors, and inducer of adaptive response^{12,13} (see **Free Radicals and Metabolic Disorders**). Recent studies provided evidence that many LPO products exert opposite dual effects depending on the conditions such as cytotoxic and cytoprotective effects, pro- and anti-atherogenic effects, pro- and anti-apoptotic effects, and pro- and anti-inflammatory effects.^{14,15} However, the physiological significance of such

effects by LPO products observed in cultured cell systems is not clear yet.

2 THREE MECHANISMS OF LPO

It has been known that LPO proceeds by three distinct mechanisms, that is, (i) free-radical-mediated chain oxidation, (ii) free radical-independent, nonenzymatic, stoichiometric oxidation, and (iii) enzymatic oxidation.¹ Characteristic products are formed from the respective mechanisms and specific antioxidants are required to inhibit each type of LPO. Singlet oxygen, ozone, and hypochlorite are typical oxidants which oxidize lipids by nonradical mechanism, whereas lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP) are important enzymes which oxidize lipids *in vivo*. The characteristics of each type of oxidation are summarized in Table 1, together with the major products from arachidonic acid (20:4) as an example of substrate lipid.

The characteristics of nonradical oxidation and enzymatic oxidation are described briefly below and the mechanism and products of free-radical-mediated LPO are described in detail in the subsequent section.

Table 1 Hydro(pero)xyeicosatetraenoic acid (H(P)ETE) isomers produced in the oxidation of arachidonic acid by different oxidants.^a

Oxidant	Isomers		
	Regio	Stereo	Enantio
Free radical	5, 8, 9, 11, 12, 15	cis,trans, trans,trans	<i>R</i> = <i>S</i>
Lipoxygenase	5, 12, 15	cis,trans	<i>R</i> or <i>S</i>
Cytochrome <i>P</i> 450	5, 8, 9, 11, 12, 15, 19, 20	cis,trans	<i>R</i> or <i>S</i>
Singlet oxygen	5, 6, 8, 9, 11, 12, 14, 15	cis,trans	

^a Oxidation by free radical, lipoxygenase, and singlet oxygen gives HPETE, while that by cytochrome *P*450 gives HETE as primary product.

2.1 Nonradical, Nonenzymatic Oxidation of Lipids

Singlet oxygen and ozone oxidize lipids by nonradical mechanisms. Singlet oxygen oxidizes unsaturated lipids mainly by ene-reaction to give hydroperoxide with concomitant double bond migration, with minor side reactions such as 1,4-addition to give 1,4-endoperoxide and 1,2-addition to give dioxetane, which readily decomposes to yield carbonyl compounds accompanying chemiluminescence.¹⁶ For example, the oxidation of linoleates by singlet oxygen gives 9-, 10-, 12-, and 13-hydroperoxyoctadecadienoic acid (HPODE 1), 10- and 12-HPODE being specific products for singlet oxygen oxidation.¹⁷ Squalene hydroperoxides formed by singlet oxygen have been observed in sunlight-exposed human skin.¹⁸

Ozone oxidizes double bonds to give ozonide as a primary product, which is unstable and readily undergoes secondary reactions to give cleavage products.¹⁹ It was reported that the cholesterol oxidation products by ozone were found in atherosclerotic plaque.²⁰ Recently it was found, however, that the products were formed in the oxidation of cholesterol by either ozone or singlet oxygen.^{21–23}

Hypohalide is an oxidant generated by the action of myeloperoxidase (MPO) with hydrogen peroxide and halide ion. MPO, a heme protein secreted by activated phagocytes, reacts with hydrogen peroxide in the presence of chloride and bromide to give hypochlorous acid and hypobromous acid, HOCl and HOBr, respectively, which are strong oxidants and oxidize biological molecules by several mechanisms including both free radical and nonradical pathways.^{24,25} It was reported that MPO and tyrosine produced tyrosyl radical and induced LPO.²⁶ The dissociated forms of hypochlorite and hypobromide oxidize lipids to give

chlorohydrines and bromohydrines, respectively, which yield epoxides. Hypochlorite reacts with hydrogen peroxide to yield singlet oxygen, while it reacts with organic hydroperoxides to give alkoxyl and/or peroxy radicals, with little concomitant formation of singlet oxygen.^{27,28} In support of this, it was observed that the oxidation of methyl linoleate by hypochlorite gave racemic 9- and 13-, *cis,trans*- and *trans,trans*-conjugated diene hydroperoxides, clearly showing that the oxidation proceeded by free radical mechanism. The rate constants for the reaction of hypochlorite with hydrogen peroxide and *tert*-butyl hydroperoxide were estimated as 1700 and 43 M^{−1} s^{−1}, respectively at 37 °C,²⁷ which are much smaller than those of hypochlorite with amino acids.²⁵ Hypochlorite and hypobromide react with amines much faster than with lipids to give chloramines and bromoamines, respectively, which undergo homolytic cleavage to give free radicals together with aldehydes.²⁹ These radicals may induce LPO.

2.2 Enzymatic Oxidation of Lipids

The enzyme-mediated oxidation of lipids has been the subject of extensive studies, because the products, above all those derived from arachidonic acid which are referred to as “eicosanoids,” have been found to exert potent biological functions and activities. Currently, over a hundred different eicosanoids have been identified and they have been implicated in a number of inflammatory and life-related diseases such as atherosclerosis, arthritis, and cancer.³⁰ It has been known that LOX and COX oxidize arachidonic acid to HPETE 3, prostaglandins, prostacyclin, thromboxane, and leukotrienes.

In contrast to free radicals, COX and LOX oxidize lipids regio-, stereo-, and enantiospecifically.³¹ For example, 15-LOX oxidizes linoleates to

give 13(*S*)-9-*cis*,11-*trans*-HPODE **1** exclusively, while the free-radical-mediated oxidation of linoleates gives four racemic products. Soybean LOX catalyzes the conversion of linoleic acid into 13(*S*)-9-*cis*,11-*trans*-HPODE **1**, but tomato or corn seed LOX preferentially produces 9(*S*)-10-*trans*,12-*cis*-HPODE **5**.³² LOX directly oxidizes fatty acid residues of phospholipids and cholesteryl esters in LDL particles as well as free fatty acids, although the stereo- and enantiospecificity decreases.^{33,34} It is also known that CYP oxidizes arachidonic acid to give hydroxyecosatetraenoic acid (HETE) **4**, epoxyecosatrienoic acid (EET), and dihydroxyecosatetraenoic acid.³⁵

It may be noted that the specificity of LOX oxidation depends on the reaction milieu. As mentioned above, 15-LOX oxidizes linoleates regio-, stereo-, and enantiospecifically, while free-radical-mediated oxidation gives random, racemic products. It was observed that the enantiospecificity in the oxidation of linoleates in LDL particles by 15-LOX was *S/R* = 71:29, while the products in the oxidation induced by copper were stereo-random and racemic, *S/R* being 50:50 as expected.³³ It was also found that the oxidation of phosphatidylcholine (PC) and cholesteryl esters in the plasma and membranes gave specific products preferentially, but with decreased specificity compared with the oxidation of free acids in aqueous solution.^{34,36}

3 FREE-RADICAL-MEDIATED LPO

3.1 Mechanisms of LPO

The free-radical-mediated LPO proceeds by a chain mechanism, that is, one initiating free radical can

oxidize many lipid molecules. It was confirmed experimentally that chain reactions proceed in the oxidation of biological membranes³⁷ and LDL³⁸ *in vitro* with considerably long kinetic chain length, but it is difficult to measure the kinetic chain length of LPO *in vivo*. The mechanism of chain initiation and the responsible initiating free radicals *in vivo* have been argued extensively, but the details are not fully elucidated yet. Different types of active species may be involved under different conditions. The relevant free radicals and their kinetic parameters are summarized in Table 2. Hydroxyl radical may be formed by the reaction of hydrogen peroxide and ferrous ion (Fe^{2+}) (Fenton reaction) or cuprous ion (Cu^+), from peroxyxynitrite, or high energy irradiation. Alkoxyl radical may be formed in the decomposition of hydroperoxides by metal ions such as heme proteins and copper (Haber–Weiss reaction). Metals may contribute in the chain initiation step directly as well. Superoxide and nitric oxide (NO) are produced from enzymes such as NADPH oxidase, xanthine oxidase, and nitric oxide synthase. Neither superoxide nor NO is active enough *per se* to initiate LPO directly, but they react quite rapidly at diffusion controlled rate to give peroxyxynitrite, which may initiate LPO chain reaction.^{39,40} Superoxide is not reactive as a radical, but it may contribute to free radical generation by reducing transition metal ions to more reactive lower valency state, for example, Fe(III) to Fe(II). Nitrogen dioxide may be formed from NO or inhaled from cigarette smoke or polluted air. It is not a reactive free radical, but may add to the double bond of unsaturated lipids and initiate chain reaction. As shown above, free radicals may also be formed by MPO. It may be noted that even α -tocopheroxyl radical, a radical produced from vitamin E, a major antioxidant *in vivo*, can

Table 2 Order of magnitude of rate constant ($\text{M}^{-1} \text{s}^{-1}$) for hydrogen atom abstraction from methylene (CH_2) group of saturated, monounsaturated, and polyunsaturated fatty acids (LH) by free radicals.

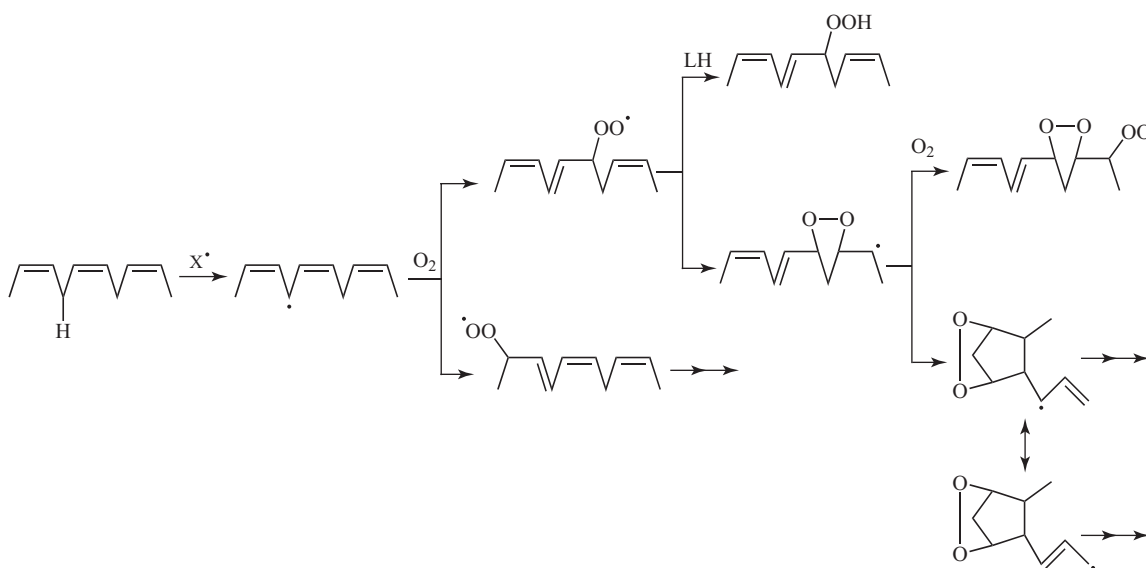
Radical X	BDE(X–H)	Saturated	Monounsaturated	Polyunsaturated
	BDE(L–H)	95	85	75
Hydroxyl, $\text{HO}^\bullet$	119	10^8	10^9	10^9
Alkoxyl, $\text{LO}^\bullet$	104	10^5	10^6	10^7
Peroxyl, $\text{LOO}^\bullet$	88	10^{-2}	1	10^2
α -Tocopheroxyl	78	0	0	10^{-2}
Nitrogen dioxide, $\text{NO}_2^\bullet$	78	0	0	na (not available)
Nitric oxide, $^\bullet\text{NO}$	50	0	0	0

BDE, bond dissociation energy in kcal mol^{-1} .

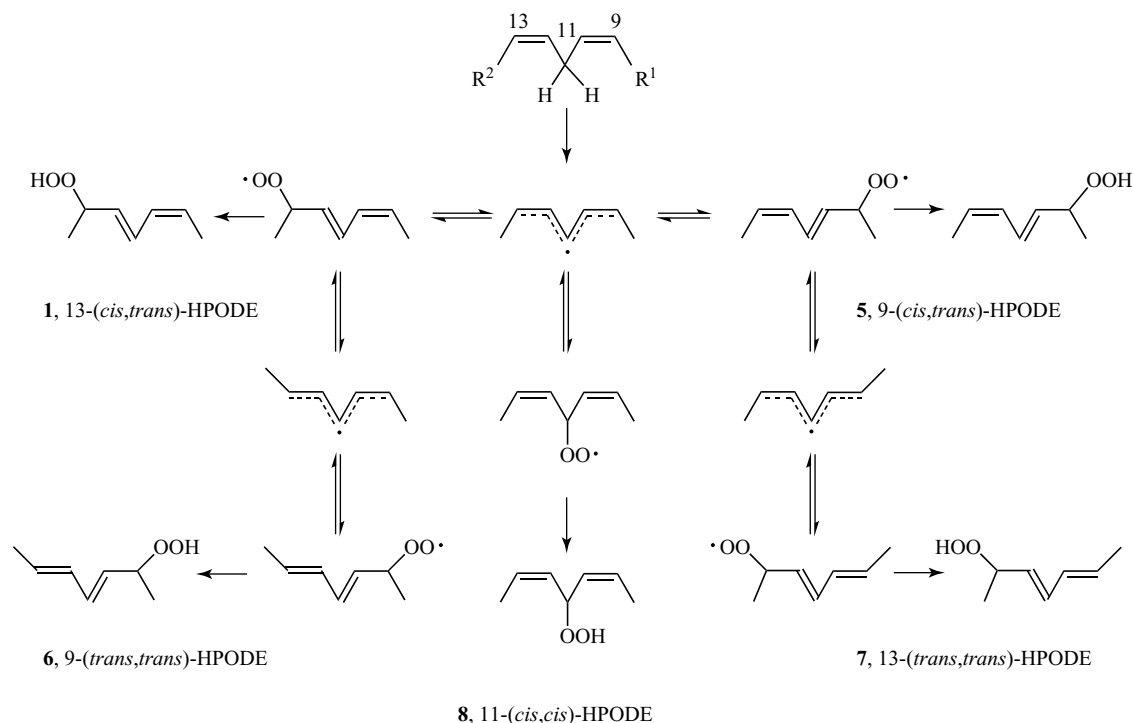
abstract hydrogen atom from PUFAs at appreciable rate constant (Table 2).⁴¹ It should be emphasized that the chain propagation is carried by lipid peroxy radicals independent of the type of chain-initiating free radicals.

The mechanism of free-radical-mediated LPO has been studied extensively, most notably by Porter and his colleagues.^{7,8} The major reactions include (i) abstraction of bisallylic hydrogen from PUFAs to give carbon-centered radical, which is highly delocalized and rearranges to more stable *cis*,*trans*-pentadienyl radical, (ii) addition of oxygen to the pentadienyl radical to give lipid peroxy radical, (iii) release of oxygen from the peroxy radical to give oxygen and pentadienyl radical, (iv) rapid reaction of the pentadienyl radical with oxygen to give thermodynamically more stable *trans*,*trans*-form preferentially than *cis*,*trans*-form, and (v) intramolecular addition of the peroxy radical to the double bond to yield bicyclic prostaglandin-type products (Scheme 2). The important chain propagation step is the abstraction of bisallylic hydrogen from polyunsaturated lipids by lipid peroxy radical to give conjugated diene lipid hydroperoxide and new lipid radical, which continues another chain propagation sequence. The product distribution is determined by the relative importance of these many competing reactions of different types of free radicals.

The LPO of linoleic acid and its esters has been studied extensively, since they are the most abundant polyunsaturated lipids *in vivo* and their oxidation proceeds by a straightforward mechanism to give much simpler products with high selectivity than arachidonates and other more highly unsaturated fatty acids. The free-radical-mediated oxidation of linoleates proceeds by the steps 1–4 mentioned above to give four conjugated diene hydroperoxides **1**, **5**, **6**, and **7** quantitatively (Scheme 3). LPO of linoleates is initiated by the abstraction of hydrogen at C11 to yield a pentadienyl radical. Unlike specific hydrogen abstraction by LOX, both C11 bisallylic hydrogens are abstracted equally. Nonconjugated C11-hydroperoxide **8** is obtained from linoleates only in the presence of high concentration of potent hydrogen donor such as α -tocopherol.⁴² Oxygen adds to the pentadienyl radical at either C9 or C13 to give the corresponding *cis*,*trans*-peroxy radical. The kinetic products, 9-10-*trans*,12-*cis*-HPODE **5** and 13-9-*cis*,11-*trans*-HPODE **1**, are formed by hydrogen abstraction, but under such conditions that potent hydrogen donor is not present, the *trans*,*cis*-peroxy radical at C9 or C13 can undergo β -fragmentation to yield original *cis*oid-pentadienyl radical or *trans*oid-pentadienyl radical if bond rotation precedes β -fragmentation. The process of β -fragmentation was studied in detail using



Scheme 2 Pathways of free-radical-mediated lipid peroxidation.



Scheme 3 Mechanisms of peroxidation of linoleic acid. R^1 : $-(\text{CH}_2)_7\text{COOH}$, R^2 : $-(\text{CH}_2)_4\text{CH}_3$.

^{18}O labeled methyl linoleate hydroperoxide.⁴³ The rate constant for β -fragmentation of dienyloperoxyl radicals leading to transoid centers was found to be 16 times larger than that leading to cisoid centers, 430 and 27 s^{-1} , respectively.⁴⁴ The thermodynamic products, 9-*trans,trans*- and 13-*trans,trans*-HPODE, **6** and **7** respectively, can be obtained by oxygen addition to *trans,trans*-radical followed by hydrogen abstraction. It was found that in the oxidation of methyl linoleate under air in acetonitrile solution induced by a constant flux of free radicals generated from azo initiator, the amounts of methyl linoleate consumed, oxygen uptaken, conjugated diene formed, and hydroperoxide formed agreed well,⁴⁵ suggesting that methyl linoleate was oxidized by a straightforward mechanism to give methyl esters of four conjugated diene HPODE quantitatively. It is noted that the amounts of HPODE **1** and **5** are equal and **6** and **7** are equal and that they are racemic, that is, equal amounts of *R* and *S* forms are formed.

Compared with linoleic acid, the oxidation of more highly unsaturated fatty acids having more than three double bonds such as linolenic acid

(18:3), arachidonic acid (20:4), eicosapentaenoic acid (EPA) (20:5), and docosahexaenoic acid (DHA) (22:6) proceeds by more complicated mechanisms including intramolecular addition reaction to give numerous products such as prostaglandin-type cyclic peroxides as well as hydroperoxides. Serial cyclic peroxides as well as monocyclic peroxides have been identified in the oxidation of arachidonates.⁸ Nonetheless, the oxidation proceeds by a combination of the elementary reactions mentioned above. The importance of intramolecular addition reaction relative to hydrogen abstraction is determined by the concentrations of reactive hydrogen and oxygen (Scheme 2).

Arachidonates have three centers at C7, C10, and C13 that have carbons flanked by two double bonds. The six bisallylic hydrogens on these carbons are attacked similarly by peroxy radicals to form three pentadienyl radicals. Oxygen adds to either end of the radicals giving 5-, 8-, 9-, 11-, 12-, and 15-eicosatetraenylperoxyl radicals, having *trans*-*cis* diene geometry. Hydrogen atom abstraction by these peroxy radicals gives the corresponding six regioisomers of *trans,cis*-HPETEs. The 8-, 9-, 11-, and

Table 3 Distribution of HPETE regioisomers formed in the oxidation of 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine, PC(16:0/20:4).

HETE	In methanol		In liposomes	
	Antioxidant: none		α -Tocopherol	Trolox
5-HETE	31.3	39.6	23.1	37.1
8-HETE	7.3	4.3	11.1	5.1
9-HETE	8.6	7.8	16.6	7.1
11-HETE	8.9	5.9	12.0	6.2
12-HETE	10.4	9.6	14.8	8.2
15-HETE	33.0	32.6	22.5	36.3

Source: Reproduced from the data in Ref. 46.

^aThe oxidation of PC(16:0/20:4) liposome was performed at 30 °C in tris-HCl buffer (pH 7.4) for 3 h and HETEs were analyzed after treatment with triphenylphosphine. Values are mean percentage of several experiments ($n > 5$). For simplicity, standard deviation is not shown.

12-peroxyl radicals have isolated double bonds placed such that a 5-exo-cyclization can occur and the intramolecular cyclization of these four peroxyl radicals proceeds faster than β -fragmentation and therefore few *trans,trans*-HPETE is formed from these peroxyl radicals. On the other hand, 5- and 15-peroxyl radicals cannot undergo intramolecular cyclization and may give the corresponding *trans,trans*-HPETEs.

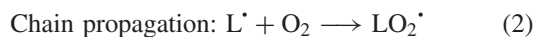
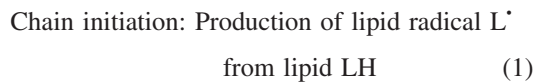
The distribution of HPETEs obtained in the oxidation of 1-palmitoyl-2-arachidonoyl PC liposomes in aqueous dispersions induced by free radicals is shown in Table 3.⁴⁶ The products were treated with triphenylphosphine to convert HPETEs to the corresponding HETEs. The results in Table 3 support the above statements that 5- and 15-HETEs yields are higher than those of 8-, 9-, 11-, and 12-HETEs, which are formed similarly. The addition of hydrogen-donating antioxidant α -tocopherol, but not Trolox, increased relative amounts of 8-, 9-, 11-, and 12-HETEs by scavenging peroxyl radicals before they undergo intramolecular addition reaction. Hydrophilic antioxidant Trolox localized in the aqueous phase cannot scavenge peroxyl radicals within the lipophilic compartment efficiently and its effect on regioisomer distribution of HETEs was small (see **Antioxidants in Chemistry and Biology**).

3.2 Dynamics of LPO

Fatty acids are present *in vivo* mainly in ester forms such as phospholipids, glycerides, and cholesteryl esters as well as in free form. They are present in cellular membranes and lipoproteins.

The biological membranes and lipoproteins have characteristic structure and properties, but the free-radical-mediated LPO in the membranes and lipoproteins are assumed to proceed by substantially the same mechanisms and to give the same products as in homogeneous solution. The fatty acid distribution in membranes and lipoproteins depends on the type of tissues and also diets. Furthermore, cholesteryl esters and triacylglycerols contain relatively more linoleate and oleate, respectively. It has been observed that the LPO proceeds similarly in isolated LDL,⁴⁷ plasma,⁴⁸ erythrocytes,⁴⁹ whole blood,⁵⁰ tissues,⁵¹ and whole body.⁵² It may be noted, however, that the rate of and relative susceptibility to oxidation of lipids may change depending on the environmental characteristics such as heterogeneous distribution, fluidity, rigidity, and packing in the membranes and lipoproteins. For example, fatty acid moieties of cholesteryl esters present in the core of LDL particles are more readily oxidized than those in phospholipids localized in the outer surface of LDL particles, because LDL core is less rigid than the outer membrane.⁴⁷ It is known that the oxidizability of unsaturated fatty acids increases with increasing number of double bonds. However, it is also known that EPA and DHA reduce the oxidizability of micelles.⁵³

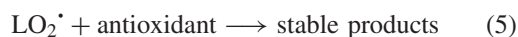
The chain reaction of LPO is expressed by a very simplified scheme shown below in sequence of equations from (1) to (5):





Chain termination: $2 \text{LO}_2^\bullet \longrightarrow \text{non-radical}$

products (4)



In the chain initiation step, a lipid radical is formed from the lipid (1). The lipid radical reacts with oxygen to give lipid peroxy radical (2). This reaction is a radical–radical coupling process, which proceeds rapidly at or near diffusion controlled rate with a rate constant of approximately $10^9 \text{ M}^{-1} \text{ s}^{-1}$. The resultant peroxy radical abstracts bisallylic hydrogen from PUFA (3) to yield lipid hydroperoxide and a new lipid radical, the rate constant being approximately $30 \text{ M}^{-1} \text{ s}^{-1}$ per active hydrogen. In the chain termination step, two lipid peroxy radicals react (4) or lipid peroxy radical is scavenged by an antioxidant (5) to give stable products.

In the absence of an antioxidant, the rate of LPO is given by (6):

$$\frac{-d[\text{O}_2]}{dt} = \frac{k_p[\text{LH}]R_i^{1/2}}{(2k_t)^{1/2}} \quad (6)$$

where k_p and k_t are the rate constants for chain propagation reaction (3) and chain termination reaction (4), respectively and R_i is the rate of chain initiation. LPO of phospholipids in lipid bilayers follows the same kinetic rate law as in homogeneous solution.⁵⁴

As described above, the hydrogen abstraction from PUFA by *trans,cis*-peroxy radicals from linoleates leading to *trans,cis*-HPODE and β -fragmentation of the peroxy radicals leading to *trans,trans*-HPODE compete and this competition has been used to “clock” the bimolecular atom transfer reaction,⁵⁵ that is, the rate constant for chain propagation step, k_p , is estimated from the ratio of *trans,cis*-H(P)ODE/*trans,trans*-H(P)ODE and the absolute rate constant k_p for linoleic acid measured by rotating sector method.⁵⁶ The rate constants k_p for PUFA and cholesterol obtained by this method are summarized in Table 4.⁵⁷ The estimated rate constants for hydrogen atom abstraction by peroxy and alkoxy radicals are also included in Table 4. It can be seen that the rate constants, that is, the reactivity toward

Table 4 Absolute rate constants ($\text{M}^{-1} \text{ s}^{-1}$) for hydrogen atom abstraction from PUFA and cholesterol by peroxy and alkoxy radicals.

Oxygen radical Lipid	Peroxy ^a	Peroxy ^b	Alkoxy ^b
Stearic (18:0)	—	10^{-3} – 10^{-4}	2.3×10^6
Oleic (18:1)	—	0.1–1	3.3×10^6
Linoleic (18:2)	62 ^c	60	8.8×10^6
Linolenic (18:3)	—	120	1.3×10^7
Arachidonic (20:4)	197	180	2.0×10^7
Eicosapentaenoic (20:5)	249	—	—
Docosahexaenoic (22:6)	334	—	—
Cholesterol	11	—	—

^aReference 57.

^bReference 58.

^cReference 56.

lipid peroxy radicals, increase with an increase in parallel with the number of double bonds and that cholesterol having no bisallylic hydrogen has much lower reactivity than PUFA. Application of this clock method to the oxidation of PC liposomal membranes gave relative chain propagation rate constants of arachidonate, eicosapentaenoate, and docosahexaenoate to be 115, 145, and 172, respectively, that parallels one in solution. Interestingly, it has been observed that linoleate peroxy radicals at different positions on the 18-carbon chain have different kinetic properties and C9-peroxy radical gives more *trans,cis*-HPODE or less *trans,trans*-HPODE than does the C13-peroxy radical.⁵⁷

3.3 Products of LPO

3.3.1 Lipid Hydroperoxides and Hydroxides

Lipid hydroperoxides are formed in LPO as the primary product. Above all, the oxidation of linoleates gives HPODE **1**, **5**, **6**, and **7** quantitatively, whereas the oxidation of fatty acids and esters having more than three double bonds gives cyclic peroxides in addition to hydroperoxides since intramolecular addition reaction of peroxy radical competes with the hydrogen atom abstraction. In the presence of potent hydrogen donor such as vitamin E, the yield of hydroperoxide becomes relatively higher. Lipid hydroperoxides are reduced *in vivo* by glutathione peroxidases (GPx) and selenoprotein P

to yield the corresponding hydroxides. Also lipid hydroperoxides may undergo secondary reactions to form various secondary products. As described above, LOX also oxidizes PUFA to give hydroperoxides and CYP gives hydroxides.

3.3.2 Aldehydes

Various small molecular weight aldehydes such as acrolein, malondialdehyde (MDA), and 4-hydroxy-2-nonenal (HNE) are formed during LPO as secondary or decomposition products.⁵⁹ More than 20 saturated and unsaturated aldehydes were identified and found in biological samples by a method based on the use of *O*-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride to form the oxime, followed by trimethylsilylation of the hydroxyl group to trimethylsilyl ethers.^{60,61} Among them, HNE produced in the oxidation of *n*-6 PUFA has been studied most extensively,⁶² while 4-hydroxy-2-hexenal is an oxidation product of *n*-3 PUFA and may be important in tissues such as brain and retina.⁶³ The formation of aldehydes by MPO–hydrogen peroxide–chloride ion system may also be an important pathway *in vivo*.⁶⁴ It should be added that aldehydes are not only toxic end products and remnants of LPO but may also act as signaling mediator.

3.3.3 Epoxides

Epoxides are formed by both free-radical-mediated LPO and by CYP enzyme oxidation. Peroxyl radicals add to the double bond to yield an adduct, which undergoes β -scission to produce epoxide and alkoxyl radical (7).



As expected, the yield of epoxide increases with decreasing oxygen concentration.

The generation of EETs from arachidonic acid by *P*450 enzymes has been known well.⁶⁵ Arachidonic acid has four double bonds and 5,6-, 8,9-, 11,12-, and 14,15-EET are formed. Recently, the epoxidation of EPA and DHA has also received attention.⁶⁶

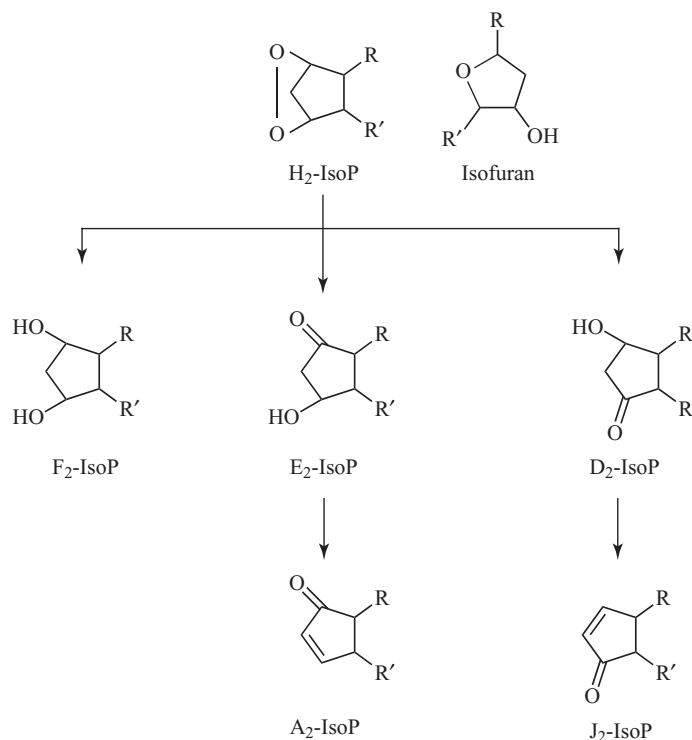
3.3.4 Ketones

Oxo-derivatives are also one of the major oxidation products of PUFA. They may be produced in the decomposition of hydroperoxides or directly in the biomolecular interactions of lipid peroxyl radicals (4). For example, 9- and 13-oxooctadecadienoic acids are formed in the oxidation of linoleic acid. Both *cis,trans*- and *trans,trans*-forms are formed.⁶⁷

3.3.5 Isoprostane (IsoP)

Since the discovery in 1990 by a group of Morrow and Roberts that isoprostanes (IsoPs) are formed by a free-radical-mediated oxidation of arachidonic acid independent of COX,⁶⁸ numerous studies have been performed on these interesting LPO products. IsoPs are a series of prostaglandin-like compounds (Scheme 4), of which F₂-IsoPs containing F-type prostane ring have been studied most extensively.⁶⁹ The 8-, 9-, 11-, and 12-peroxyl radicals, but not 5- and 15-peroxyl radicals, derived from arachidonic acid undergo two consecutive intramolecular cyclizations, oxygen addition (Scheme 2), and hydrogen abstraction to form PGG₂-like compounds, which are reduced by ketoreductase to give F₂-IsoPs. Compounds are denoted as 5-, 8-, 12-, and 15-series regioisomers depending on the carbon atom to which the side-chain hydroxyl is attached.⁷⁰ A total of 64 isomers of F₂-IsoPs can be formed from arachidonic acid. An important structural distinction between IsoP and COX-derived PGs is that the former contain side chains that are predominantly oriented *cis* to the prostane ring, whereas the latter possess exclusively *trans* side chain.⁶⁸ The prostaglandin H₂-like bicyclic endoperoxide intermediates isomerizes to yield D₂- and E₂-IsoP, which are unstable and spontaneously dehydrate to yield J₂- and A₂-IsoPs,⁷¹ chemically reactive electrophilic cyclopentenones. The oxidation of EPA and DHA by similar mechanisms gives F₃-IsoPs and F₄-neuroprostanes, respectively.⁷²

The product distribution is determined by the relative importance of many competing reactions. The 8-, 9-, 11-, and 12-peroxyl radicals derived from arachidonates may abstract hydrogen to give HPETE or undergo intramolecular cyclization to give cyclic peroxide containing carbon-centered



Scheme 4 Isoprostanes and isofurans.

radical, which may react with oxygen to give peroxyl radical or undergo exocyclization to form the bicyclic endoperoxide, which leads to the formation of IsoP. Therefore, with increasing concentrations of hydrogen donor and oxygen, the formation of IsoPs becomes disfavored. In agreement with this, it was found that isofurans having a substituted tetrahydrofuran ring structure becomes more favored with increasing oxygen concentration.⁷³

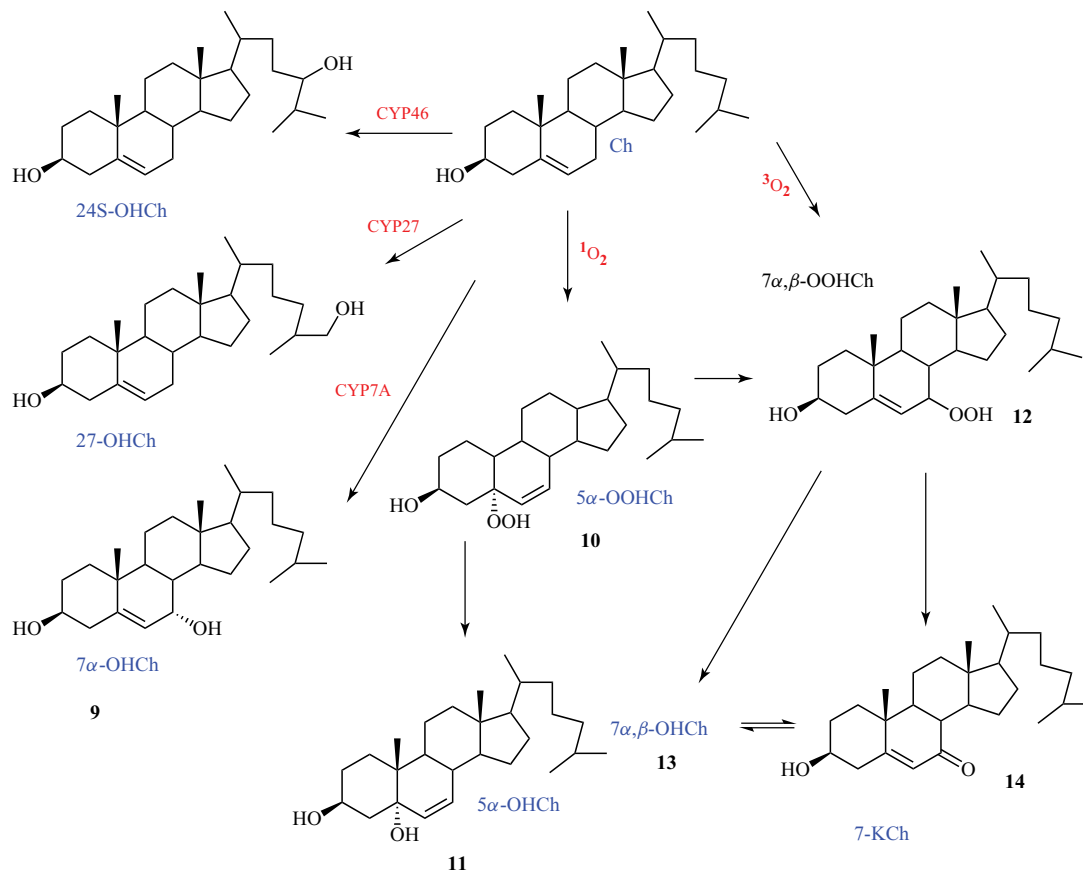
3.3.6 Nitro-Fatty Acids

Nitro-fatty acids are another class of interesting product.⁷⁴ Two allylic nitro derivatives of linoleic acid were found in human erythrocytes and plasma as both free and ester forms.⁷⁵ They were identified as 10-nitro-9-*cis*,12-*cis*-octadecadienoic acid and 12-nitro-9-*cis*,12-*cis*-octadecadienoic acid. Nitrated derivatives of all principal unsaturated fatty acids were detected in human plasma and urine.⁷⁶ More nitrated oleic acids were observed than nitrated linoleic acids.⁷⁶ A nitrated derivative of cholesteryl

linoleate was detected also in human plasma and lipoproteins.⁷⁷ Nitro-fatty acids are assumed to be formed by the initial addition of nitrogen dioxide radical and/or nitronium ion, NO₂⁺, to the double bond. Peroxynitrite and peroxynitrous acid may be involved as well.

3.4 Oxidation of Cholesterol

Cholesterol is another important constituent of biological membranes and exerts biological functions. Cholesterol physically stabilizes membrane and increases membrane rigidity, which makes the membrane more resistant to free radical attack from an external aqueous phase. Cholesterol is also an important substrate of oxidation and oxidized similarly as PUFA by three mechanisms mentioned above (Scheme 5).^{78–81} The oxidation products of cholesterol are named *oxysterols*. The free-radical-mediated oxidation of cholesterol gives 7-hydroperoxycholesterol (**12**, 7-OOHCh) as the primary product together with 7-hydroxycholesterol



Scheme 5 Major pathways and products of cholesterol oxidation.

(**13**, 7-OHCh), 7-ketocholesterol (**14**, 7-KCh), cholesterol-5,6-epoxide (5,6-epoxyCh), and cholestane-3 β ,5 α ,6 β -triol as major products. Both α and β forms of **12**, **13**, and 5,6-epoxyCh are formed. Although cholesterol does not have bisallylic hydrogen, it is oxidized significantly within cells to give hydroperoxide.⁸²

Singlet oxygen oxidizes cholesterol to give 5-HOOCh **10** as a major primary product. The oxidation of cholesterol by ozone has received attention, since it was reported that ozonolysis products of cholesterol were found in atherosclerotic plaques,²⁰ although there is some controversy about this finding.^{16,19} The ozonolysis products such as 5,6-secoesterol (3 β -hydroxy-5-oxo-5,6-secocholestan-6-al) (atheronal-A), its aldolization product (atheronal-B), and 5,6-epoxyCh have been found as major products from cholesterol.⁸³ It was reported recently that 5,6-secoesterol was formed by

Hock cleavage of 5 α -hydroperoxycholesterol **10**²¹ or from the MPO—hydrogen peroxide—chloride system,²³ not by ozonolysis. It was also reported that the reaction of cholesterol with singlet oxygen formed by photodynamic action of thermal decomposition of 1,4-dimethylnaphthalene endoperoxide gives atheronal-B.²² The oxidation of cholesterol by hypochlorite gives chlorohydrins and 5,6-dichlorocholesterol as major products.⁸⁴

Various enzymes oxidize cholesterol to give specific hydroxycholesterols.^{85,86} Many of the enzymes belong to the CYP family and are present in hepatocytes, but 24-hydroxylase, CYP46A1, is found exclusively in neuronal cells in brain and retina and gives 24(*S*)-OHCh as a specific product.⁸⁷ 7 α -Hydroxycholesterol **9**, an important intermediate in bile acid biosynthesis, is formed by cholesterol 7 α -hydroxylase (CYP7A1) as well as free radical oxidation. The drug-metabolizing

enzyme CYP3A4 oxidizes cholesterol to give 4 β -hydroxycholesterol. The mitochondrial enzyme CYP27A1 gives 27-hydroxycholesterol. 25-Hydroxycholesterol is formed by cholesterol 25-hydroxylase which is not a CYP enzyme.⁸⁸

It is assumed that 7 β -OHCh and 7-KCh are characteristic products formed by free-radical-mediated oxidation, but it should be noted that the interconversion between oxysterols has been found.⁸⁹ for example, the interconversion of 7 β -OHCh and 7-KCh by 11 β -hydroxysteroid dehydrogenase type 1 was confirmed to take place in humans.⁹⁰

3.5 Reactions of LPO Products

Many LPO products are not stable end products but they undergo various secondary reactions and react with proteins and DNA bases. Lipid hydroperoxides, the primary product of LPO, may be decomposed by transition metal ions and modify proteins by reacting with lysine residue.⁹¹ Cholesteryl hydroperoxide has been reported to induce DNA strand break and base modification.⁹² The α,β -unsaturated aldehydes such as HNE are highly reactive and readily react with proteins, DNA, and phospholipids to cause deleterious effects. Modification of amino acids of proteins and peptides by these aldehydes occurs mainly at cysteine, lysine and, to a lesser extent, histidine to form stable covalent-bonded adducts by Michael addition reaction across its carbon-carbon double bond.⁹³ Carbonyl groups of aldehydes may alternatively react with the amino groups to form Schiff bases. HNE can undergo both a Michael addition and a Schiff base formation with phospholipids such as phosphatidylethanolamine and phosphatidylserine. HNE- and acrolein-protein adducts are considered to be a good biomarker of LPO and protein modification *in vivo* and they have been applied widely by using antibodies directed against these adducts.^{93,94}

4 LIPID PEROXIDATION IN BIOLOGICAL SAMPLES

4.1 LPO of Low Density Lipoprotein

With increasing evidence showing the involvement of LPO in the pathogenesis of various diseases,

the LPO in biological samples have received much attention. Especially, the oxidation hypothesis presented by Steinberg and his colleagues⁶ that oxidative modification of LDL is the key initial event of atherosclerosis triggered extensive studies on the oxidation of LDL.

Human LDL is a spherical particle with a diameter of about 22 nm and an average molecular weight of 2.5 million. Neutral lipids such as cholesteryl esters and triglycerides form a hydrophobic core, whereas amphipathic phospholipids and free cholesterol form a surface monolayer and surround a core. The approximate number of molecules of phospholipids, free cholesterol, cholesteryl esters, and triglycerides are 700, 600, 1600, and 100, respectively, per LDL particle.⁹⁵ On average, 2700 molecules of fatty acids are bound in the different classes of lipids, of which about half are PUFA, linoleic acid being the major PUFA with smaller amount of arachidonic acid. Linoleic acid is predominantly bound in cholesteryl esters, whereas more arachidonic acid is bound in phospholipids than in cholesteryl esters. PC is the major phospholipid in human LDL particle.

The oxidation of LDL *in vitro* has been studied quite extensively using metal ions such as iron and copper, cells, azo free radical initiators, and enzymes such as LOX and CYP. The LPO in LDL particles proceeds by substantially the same mechanisms as in homogeneous solution described above. The free-radical-mediated oxidation of human LDL isolated from plasma gives cholesteryl ester hydroperoxides and PC hydroperoxides as major primary products. More cholesteryl ester hydroperoxides are formed than PC hydroperoxides. The relative susceptibility of fatty acid esters increases with increasing number of double bond. Cholesterol is oxidized appreciably only at the later stage. On the other hand, various secondary oxidation products of phospholipids and cholesterol are found in human LDL.⁹⁶ LPO products, above all reactive α,β -unsaturated aldehydes, modify apolipoprotein B100 covering LDL particle and make oxidized LDL pro-atherogenic.

HDL is capable of inhibiting oxidation of LDL and reducing cholesterol level, but HDL is oxidized similarly, resulting in loss of its anti-atherogenic function.⁹⁷

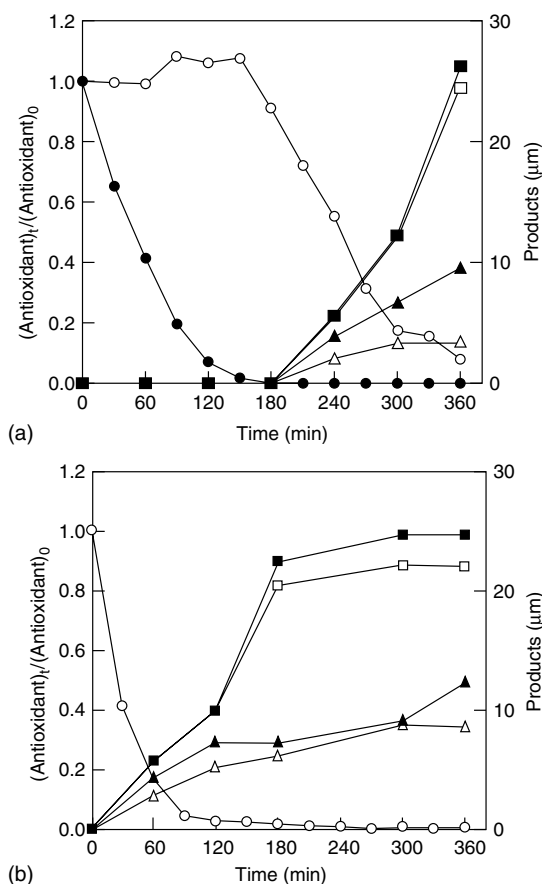


Figure 1 Oxidation of rat plasma (a) before and (b) after dialysis in PBS (1:1 by volume) at 37°C. Open circle: α -tocopherol, solid circle: ascorbic acid, solid square: CEOOH + CEOH, open square: CEOOH, solid triangle: PCOOH + PCOH, open triangle, PCOOH. [From Ref. 98. © 2004, Elsevier B.V.]

4.2 Oxidation of Plasma

Plasma is a suitable substrate for investigating the mechanisms, dynamics, and inhibition of LPO in biological settings. Lipids are present predominantly within lipoproteins in plasma together with various proteins, enzymes, and antioxidants. The free-radical-mediated oxidation of human plasma gives cholesteryl ester hydroperoxides as a major product together with minor amounts of cholesteryl ester hydroxides, PC hydroperoxides, and hydroxides. An example of plasma oxidation is shown in Figure 1.⁹⁸ Lipid hydroperoxides are reduced to the corresponding hydroxides by GPx. PC hydroperoxides are reduced faster than cholesteryl ester

hydroperoxides. The amounts of oxysterols are small.

The oxidation of plasma is a convenient system to elucidate the action mechanisms and protective effects of antioxidants in biologically relevant settings.^{98–100} The efficacy of both hydrophilic and lipophilic antioxidants and their interaction against LPO may be assessed in the oxidation of plasma induced by either hydrophilic or lipophilic azo initiator.

4.3 Lipid Peroxidation in Erythrocytes

Erythrocyte membrane is composed of cholesterol and various phospholipids. PUFA contained in the phospholipids are oxidized similarly to form various LPO products. The LPO of erythrocytes induces membrane damage and leakage of potassium ion, lactate dehydrogenase (LDH), and hemoglobin, eventually resulting in hemolysis.¹⁰¹ The radical-scavenging antioxidants such as vitamin E inhibit LPO and hemolysis.

4.4 Lipid Peroxidation in Experimental Animals

Animals have been used extensively to elucidate the mechanisms and products of LPO *in vivo* and also the biological effects of antioxidants against LPO. The LPO has been induced by γ -ray irradiation, photo-oxidation, hyperbaric oxygen, and administration of metal, carbon tetrachloride, or azo-compound. It was reported that administration of carbon tetrachloride to a rat induced a pronounced increase in the trans,trans-conjugated diene, a footprint of radical-mediated LPO, in microsomal lipid extracts and that the formation of trans,trans-isomers was strongly suppressed by prior administration of vitamin E.¹⁰² The administration of azo radical initiator to mouse induces oxidative stress¹⁰³ and increases the levels of LPO products such as hydroxyoctadecadienoic acid (HODE), HETE, and 8-IsoPs in plasma and tissues,¹⁰⁴ which are suppressed by radical-scavenging antioxidants.

5 PHYSIOLOGICAL LEVELS OF LPO PRODUCTS IN HUMAN

As shown above, LPO produces vast variety of products by different mechanisms and it is quite difficult to identify and quantify all of them. Furthermore, these products undergo secondary reactions and they are readily metabolized and excreted by efficient defense mechanisms *in vivo*. Therefore, the levels of LPO products measured in biological fluids and tissues reflect the balance between formation, metabolism, clearance, and excretion. Further, the diet contains various LPO products and the measurement of LPO levels in biological samples, especially plasma, may be confounded by the diet unless the subjects are fasted.¹⁰⁵ The measurement of the levels of LPO products in biological fluids and tissues is important to assess the extent of oxidative stress *in vivo*, to understand their physiological effects, and to evaluate the effect of antioxidants.

Lipid hydroperoxides, the primary products of LPO, are substrate of GPx¹⁰⁶ and selenoprotein P,¹⁰⁷ which reduce hydroperoxides to the corresponding hydroxides. GPx isotypes exhibit striking differences in peroxide reactivity.¹⁰⁸ Classical cellular GPx, GPx1, reduces hydrogen peroxide and free fatty acid hydroperoxides, but it does not reduce ester forms of lipid hydroperoxides nor cholesterol hydroperoxide. The type 4 GPx, also known as phospholipid hydroperoxide glutathione peroxidase (PHGPx) can catalyze the direct reduction of phospholipid hydroperoxides, cholesteryl ester hydroperoxides, and cholesteryl hydroperoxide. Recent study showed 25-fold greater activity of phospholipid hydroperoxides toward GPx4 than 7 α -OOHCh.¹⁰⁹

Metabolism and excretion are important factors that determine physiological levels of LPO products *in vivo*. They are not as extensively studied nor elucidated as the formation of LPO products. Incubation of PCOOH in human plasma gave the corresponding PCOH with minor amounts of the corresponding cholesteryl ester hydroperoxides and hydroxides, which were formed by the action of lecithin cholesterol acyltransferase (LCAT) present in HDL.¹¹⁰ Disposition, biotransformation, and clearance of exogenously prepared, radiolabeled LPO products have been studied in animal experiments.¹¹¹ Although it has to be taken into consideration that the metabolic pattern of exogenously

administered LPO products may be different from that of endogenously formed products, such studies must be useful to shed light on the fate of LPO products *in vivo*. The major metabolic pathways involve hydrolysis by phospholipases, conjugation by glutathione *S*-transferases, and β -oxidation, in addition to the reduction mentioned above.

LPO products in human fluids and tissues have been measured by diverse methods and techniques.¹⁰⁵ Recently, the LPO products have been analyzed extensively by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS), which enabled analyses with high sensitivity and specificity, although it is labor intensive and high expenditure.¹¹² One advantage of LC-MS/MS methods is that the sample preparation for analysis is simpler than that for GC-MS because no derivatization is required. In some cases, the biological samples are treated with triphenylphosphine to reduce peroxides and/or hydrolyzed to convert fatty acid esters and cholesteryl esters to free fatty acid and free cholesterol forms, respectively. Recently, the levels of LPO products in biological fluids and tissues have been measured extensively as potential biomarkers for oxidative stress *in vivo*.^{105,113,114}

5.1 Lipid Hydroperoxides

Hydroperoxides are the major primary products of free-radical-mediated LPO of PUFAs and cholesterol and their levels in human blood have been measured in many studies by several methods including high performance liquid chromatography (HPLC)-chemiluminescence and LC-MS. The reported levels of phosphatidylcholine hydroperoxides (PCOOH) in healthy human plasma range from nil to 220 nM, while cholesteryl ester hydroperoxides (CEOOH) from nil to 12 nM,¹ except one report in which 497 nM was detected by HPLC-chemiluminescence method.¹¹⁵ Lipid hydroperoxides measured by FOX2 assay have been reported to be much higher, for example, 2.8 μ M in plasma of healthy subjects.¹¹⁶ It has been reported that lipid hydroperoxides levels are elevated in diseased patients, such as hyperlipidemia, atherosclerosis, diabetes mellitus, hemodialysis, stroke, multiple sclerosis, subarachnoid hemorrhage, and alcoholic patients.

5.2 Thiobarbituric Acid Reactive Substances (TBARS)

Thiobarbituric acid reactive substances (TBARS) and MDA have been used as a biomarker of LPO for more than 30 years.¹¹⁷ Although these markers are frequently used in many laboratories due to simplicity and low cost, the validity of these markers has been criticized often for a lack of specificity and problems with post-sampling formation. TBARS was measured originally by spectrophotometric detection, but recently MDA–TBA adducts are measured by HPLC with UV/Vis or fluorescence detection and MDA is measured also by GC-MS after derivatization. The reported values for MDA in human plasma are often higher than 1 μM .¹¹⁷

5.3 Isoprostane (IsoP)

As described above, IsoPs are a series of prostaglandin-like compounds produced by the free-radical-mediated oxidation of arachidonic acid independent of COX.⁶⁸ IsoPs are accepted as the most reliable biomarker of oxidative stress *in vivo* and many studies show that the levels of IsoPs in human plasma and urine are increased in a number of diseases.^{118,119} The physiological level of IsoPs in human plasma is around 1 nM, which is much lower than those of HETE and HODE.

5.4 Aldehydes

Many types of aldehydes have been detected in human fluids and tissues. The HNE levels in human samples have been measured by various methods in free and adduct forms.⁶⁹ HNE was measured as a trimethylsilyl ether of pentafluorobenzyl oxime by gas chromatography negative ion chemical ionization mass spectrometry using selected-ion monitoring in 194 healthy men and women and it was 74 nM, increasing with age.⁶⁰ Some studies reported higher values such as 660 nM in plasma of healthy adults¹²⁰ and 300 nM in umbilical cord plasma of full-term healthy neonates.¹²¹ The HNE levels in plasma and cerebrospinal fluid of Alzheimer's disease patients¹²²

and plasma of major depression patients¹²³ were reported to be higher than those of controls. As mentioned above, the levels of MDA in human plasma are reported to be higher than 1 μM ,¹¹⁸ but these values may not reflect the LPO level accurately.

5.5 Nitro-Fatty Acids

Nitro-fatty acids have been found in human plasma. The basal plasma concentrations of 9- and 10-nitro-oleic acids in healthy subjects were reported by Baker *et al.*⁷⁵ as 619 nM (free forms) and 302 nM (ester forms) as measured by LC-MS/MS and those in erythrocytes were 50 and 199 nM, respectively. The levels of nitro-linoleic acids were lower than nitro-oleic acids.^{75,76} On the other hand, much lower levels of nitro-oleic acids were reported, at a mean concentration of 1 nM measured by GC-MS/MS.¹²⁴

5.6 Oxysterols

Ring- and side-chain oxidation products of cholesterol in human plasma have been measured in many studies. Hydroperoxide is the primary product of cholesterol oxidation by free radicals and singlet oxygen. 7-Hydroperoxycholesterol **12** has been detected in human atherosclerotic lesions,¹²⁵ erythrocytes,^{126,127} lung and kidney,¹²⁸ and alcoholic fatty liver, but not in control and alcoholic cirrhotic liver.¹²⁹ It was reported that **12** was the major oxidation product in the early stage but readily metabolized and only trace amounts could be detected in human atherosclerotic plaque.¹³⁰ 5-Hydroperoxycholesterol **10**, a specific product of singlet oxygen oxidation, was detected in human and rat skin and found to increase with sunlight exposure.^{131,132}

More data are available for 7-oxygenated oxysterols. 7 α -Hydroxycholesterol **9** is formed by both enzymatic and nonenzymatic mechanisms, whereas 7 β -OHCh and 7-KCh **14** are formed mainly by free-radical-mediated oxidation. The sum of 7 β -OHCh and 7-KCh **14** ranges between 26 and 63 nM and higher levels have been observed in many diseased patients.^{1,130,133–136}

Table 5 Hydroxyoctadecadienoic acid (HODE) and 7-hydroxycholesterol (7-OHCh) in human blood.

	HODE (nM)	18:2 (mM)	7-OHCh (nM)	Ch (mM)	HODE/18:2 ($\mu\text{mol mol}^{-1}$)	7-OHCh/Ch ($\mu\text{mol mol}^{-1}$)	(HODE/18:2)/ (7-OHCh/Ch)
Plasma	203	1.28	243	6.87	194	40.9	4.74
RBC	1919	0.66	5226	11.0	3519	686	5.13
Plasma/RBC	1/9.4	—	1/21.5	—	1/18.1	1/16.8	

Source: Adapted from Ref. 133.

^aThe levels are the average values obtained for plasma and erythrocytes (RBC) from 44 healthy human subjects after reduction and saponification. HODE is a sum of free and ester forms of four isomeric hydroxyoctadecadienoic acid. 7-OHCh is a sum of free and ester forms of 7α - and 7β -hydroxycholesterol. 18:2 and Ch are the sum of free and ester forms of linoleic acid and cholesterol, respectively.

5.7 Oxidation Product/Parent Lipid Ratio

The ratio of oxidation product to parent lipid is another biomarker to show the level of oxidative stress *in vivo*. In some studies, the biological fluids were reduced by sodium borohydride or triphenylphosphine and saponified with potassium hydroxide to convert hydroperoxides and ketones as well as hydroxides of free and ester forms of fatty acids and cholesterol to hydroxyfatty acids and hydroxycholesterol, respectively. The levels of HODE and 7-OHCh thus obtained for human plasma and erythrocytes are summarized in Table 5 together with the total concentrations of linoleic acids and cholesterol.¹³³ The relative extent of oxidation of linoleates to that of cholesterol as estimated from the ratio (HODE/18:2)/(7-OHCh/Ch) is calculated to be 4.7 and 5.1 for plasma and erythrocytes, respectively. The relative extent of LPO in plasma to that in erythrocytes is estimated to be 1/9.4, 1/21.5, 1/18.1, and 1/16.8 from HODE, 7-OHCh, HODE/18:2, and 7-OHCh/Ch, respectively, suggesting that both linoleates and cholesterol are relatively more oxidized in erythrocytes than in plasma of healthy humans.

The ratios of 7-oxygenated oxysterols to cholesterol calculated from the reported literature values range from 7.6 to 41 μmol for healthy human plasma, while higher ratio for normal artery and much higher ratio for atherosclerotic lesion, but not exceeding 1% of cholesterol, were observed.^{126,134–136} It was also reported that the levels of 7-KCh **14** were 99.4 and 383 nM in plasma and erythrocytes, respectively, from healthy human subjects.¹³⁷

The oxidation status of LDL isolated from healthy human plasma was assessed by HODE, 7-OHCh, and 8-IsoP after fractionation with anion-exchange HPLC.¹³⁸ Human LDL was subfractionated as

LDL-1, LDL-2, and LDL-3 in the order of increasing anion charge of LDL particles. Each fraction accounted for 75.1, 19.3, and 5.6% of total LDL respectively. The levels of HODE, 8-IsoP, and 7-OHCh in each LDL fraction are summarized in Table 6, together with the ratio to the respective parent lipids. It clearly shows that the levels of HODE, 8-IsoP, and 7-OHCh and their ratio to parent lipids all increased with an increase in anion charge of LDL particles, the highest ratio being 3.67 molecules HODE/1000 molecules linoleates, 0.367%. The smaller ratio of 8-IsoP/20:4 is ascribed to the fact that 8-IsoP is one of the many products of arachidonate oxidation. It also shows that linoleates and arachidonates are relatively more oxidized than cholesterol with increasing oxidation of LDL. In addition, the LPO in HDL has received attention in connection with atherosclerosis.¹³⁹

Although numerous studies have reported the levels of LPO products in human subjects, only a few papers measured products from linoleates, arachidonates, and cholesterol simultaneously from the same samples.^{113,133} It is difficult to define the reference levels of LPO products, partly because the reported values vary considerably, which is not surprising since they are affected by many factors such as lifestyle including diet, drinking, smoking, and exercise. In Table 7, the levels

Table 6 Lipid peroxidation products in human LDL fractions.

LDL fraction	HODE	8-IsoP	7-OHCh
LDL1	1935 (227)	5.8 (8.7)	2100 (116)
LDL2	4657 (782)	33.1 (18.3)	5703 (181)
LDL3	36434 (3670)	162.1 (66.6)	18314 (344)

Source: Adapted from Ref. 138.

^aThe concentrations in pmol/mg apo B. The numbers in parentheses are the ratio of products to the corresponding parent lipid, in $\mu\text{mol product/mol}$ parent lipid.

Table 7 Estimated levels of free-radical-mediated LPO products in human plasma.^a

LPO products	nM	μM/M parent lipid
F ₂ -isoprostanes	1	10
Total HETE ^b	100	450
9- and 13-(<i>trans,trans</i>)-HODE	130	100
7β-OHCh	10–20	2–4
7-KCh	20–30	6

^a Adapted from Ref. 1. © 2009, Elsevier B.V.^b Enzyme-mediated oxidation products may be involved.

of free-radical-mediated LPO products in healthy human plasma estimated from literatures are summarized. Among them, the level of HETE may contain those produced by enzyme oxidation. It may be said that the level of LPO products in the plasma of healthy human subjects is below 1 μM and 0.1% of parent lipids.

One of the interesting points is the unexpectedly high levels of oxysterols observed in human plasma, LDL, and erythrocytes. In contrast to PUFAs, cholesterol does not contain bisallylic hydrogen and the reactivity of allylic hydrogen toward peroxy radical, a chain-carrying species in LPO, is about 100 times smaller than that of bisallylic hydrogen (Table 2). In fact, it was found that little oxidation of cholesterol proceeded in the oxidation of isolated LDL *in vitro* and it was oxidized after substantially all PUFAs were consumed.⁴⁷ It may be noted that cholesterol was relatively more oxidized than linoleates in the cultured cells under oxidative stress induced by selenium deficiency and free radical attack.⁸² The high level of 7-oxygenated oxysterols observed in healthy human blood may be ascribed to slower metabolism and/or excretion and to enzymatic oxidation by 7α-hydroxylase, CYP7A1.

Finally, it should be noted that, as often pointed out, accurate determination of LPO products in human samples is not easy and great care should be taken in the measurement and interpretation of the data. A potential generation or loss of LPO products during sampling, storage, extraction, isolation, and analysis may take place. The plasma contains several millimoles of reactive lipids and the oxidation of 0.01% gives several hundreds of nanomoles, suggesting the difficulty of accurate measurement. Sodium borohydride used as a reducing agent may induce *ex vivo* oxidation, especially in the presence of metals such as iron contained

in blood and tissues, which is avoided by using triphenylphosphine as a reducing agent.¹⁴⁰ The use of appropriate internal standard is recommended. Furthermore, as mentioned above, blood should be withdrawn after sufficient fasting.

6 BIOLOGICAL EFFECTS OF LPO PRODUCTS

6.1 Cytotoxic and Cytoprotective Effects of LPO Products

It has been shown that LPO products exert various biological effects either directly by reacting with proteins, enzymes, and nucleic acids or indirectly through receptor-mediated pathways.^{12–14,62,80,141–143} LPO alters chemical characteristics and physical organization of cellular membranes to induce functional loss and modifies lipoproteins to pro-atherogenic and pro-inflammatory forms. LPO products are assumed to be pathogenic and contribute to the etiology of various diseases, including neurodegenerative diseases.¹⁴⁴ Aldehydes react with nucleic acid bases to give exocyclic adducts with a five-membered ring (etheno adducts) and a six-membered ring (propane adducts), which are accepted to contribute to the mutagenic and carcinogenic effects associated with oxidative stress.^{145,146} Oxidative modification of nucleic acids has also been implicated in neurodegeneration.^{147–149}

It is known that LPO products, both chemically reactive and stable compounds, exert cytotoxic effects. Unsaturated carbonyl compounds, lipid hydroperoxides, hydroxyl-fatty acids, hydroxy-cholesterols, ketocholesterol, epoxycholesterol, and lyso PC all induce cell death.¹⁵⁰ At the same time, it has been shown over recent years that LPO products at low concentrations activate the cellular cytoprotective signaling pathways and increase antioxidant defense capacity.¹⁵¹ It is becoming increasingly clear that the pretreatment of cells with LPO products such as PCOOH, lyso PC, hydroxycholesterol, epoxy cholesterol, HNE, and 15 d-PGJ₂ at sublethal level enhances the cell tolerance against forthcoming oxidative stress induced by ROS/RNS and LPO products.^{152–155} Another example is the effect of oxidized LDL. The association of oxidative modification of LDL and development of atherosclerosis has been recognized in many *in vitro* and

in vivo studies, but it has also been observed that low levels of oxidized LDL are cytoprotective and anti-atherogenic.^{14,156}

It may be said that the adaptive response induced by ROS/RNS, LPO products, and physical stimuli is a general phenomenon endowed inherently to aerobic organisms during evolution to cope with oxidative stress. The adaptive response to low levels of radiation has been known for many years as hormetic effects.¹⁵⁷ A human being is prepared to respond to the oxidative stress and capable of coping with it by inducing adaptive response to maintain homeostasis or even to stimulate ourselves to promote healthy state, both physically and emotionally.

6.2 LPO Products as Signaling Messenger

Many data show that ROS/RNS are used in physiological settings in a regulated manner.^{158,159} It is also assumed that LPO products modulate cell signaling and gene expression.¹ However, the experimental evidence was obtained mainly in the studies using cultured cells and the physiological significance of the action and role of free-radical-mediated LPO and its products as cellular signaling messenger *in vivo* is not clear. It should be added that, in order to exert physiologically important function as a regulator of gene expression and mediator of cellular signaling, the formation of LPO products must be tightly controlled and programmed. It may be possible to regulate the formation of superoxide, hydrogen peroxide, and NO and also enzymatic LPO,¹⁶⁰ but it seems difficult to program and control the time, site, and amount of free radical formation, the selectivity and specificity of free-radical-mediated LPO reactions, and the formation of LPO products.

7 CONCLUDING REMARKS

There is no doubt that free radicals induce LPO *in vivo* and that LPO and its products exert deleterious effects, although LPO products may play a role as a cellular regulator and signaling messenger under certain cases. Numerous studies show the cytotoxicity of LPO products, and an association between the increase in the levels of LPO products

and the progress of oxidative stress-related diseases, although it is not clear whether LPO is important as a cause or it is simply a consequence.

In any case, it is surmised that the aerobic organisms have created a fine defense network and sophisticated response system during the course of evolution to cope with, or even utilize, the moderate level of LPO, but that excessive unregulated LPO leads to degenerative and pathological consequences and, in such cases, the radical-scavenging antioxidants should exert beneficial effects. Many issues have been elucidated on LPO in the last three decades, but as many issues still remain unanswered or emerged and await to be addressed in the future studies.

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Lipid Isomerization

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1 INTRODUCTION

Free radical chemistry of lipid molecules is very well known in the field of oxidative processes. This subject is fully addressed in the article **Lipid Peroxidation**. Only in the end of twentieth century free radical reactivity involving directly the double bonds of unsaturated fatty acids started to attract interest with the process of lipid isomerization. Actually, the cis–trans isomerization of double bonds was known in free radical chemistry much earlier by the work of Walling in 1957,¹ but never applied to unsaturated fatty acids in an aqueous environment.^{2–4}

The interest in lipid isomerization resulted very timely in the development of chemical biology. In fact, considering that in eukaryotic cells the natural fatty acids have mainly the cis configuration, the formation of trans isomers can be studied not only as a free radical-mediated chemical conversion but also as an important structural change in connection with a cellular stress or signal. Fatty acid residues are present in several biologically important lipid molecules, such as triglycerides and phospholipids. Fatty acids are carboxylic acids having a long hydrocarbon chain (up to 26 carbon atoms), which can be saturated or unsaturated with up to six double bonds. They have important roles in biology, in particular for the regulation of the structure and functions of the cell membrane compartment, including permeability and fluidity properties. The geometry of the double bonds in naturally occurring

mono- and polyunsaturated fatty acid (MUFA and PUFA) residues is crucial for this regulation.

Examples of MUFA and PUFA structures and also of some trans isomers are shown in Figure 1, with the common names and the abbreviations describing the position and geometry of the double bonds (e.g., 9*cis* or 9*trans*) as well as the notation of the carbon chain length and total number of unsaturations (e.g., C18:1).⁵

The cis geometry is strictly controlled by the regiospecific and stereoselective enzymatic activity of desaturases during MUFA and PUFA biosynthesis.⁶ This choice of nature is interesting, considering the different stability of the two geometrical isomers and the fact that the thermodynamically less stable cis form is the ubiquitous one. Therefore, the role of geometry in living system is an interesting research subject, and in particular, the isomerization by free radical species can be studied not only from the chemical point of view but also more in general as the loss of a structural information needed for biological activities.

It is also worth noting that the discovery of the lipid isomerization process gave a different perspective to the previously known detection of trans fatty acid isomers in humans, thought to derive only from dietary sources. In fact, in the past years, a series of panels made in several countries determined that the increase in trans fatty acid isomers in humans derives from the consumption of deodorized and partially hydrogenated fats and oils contained in foods.^{7,8} Chemically speaking, these processes can cause the formation of different products, either

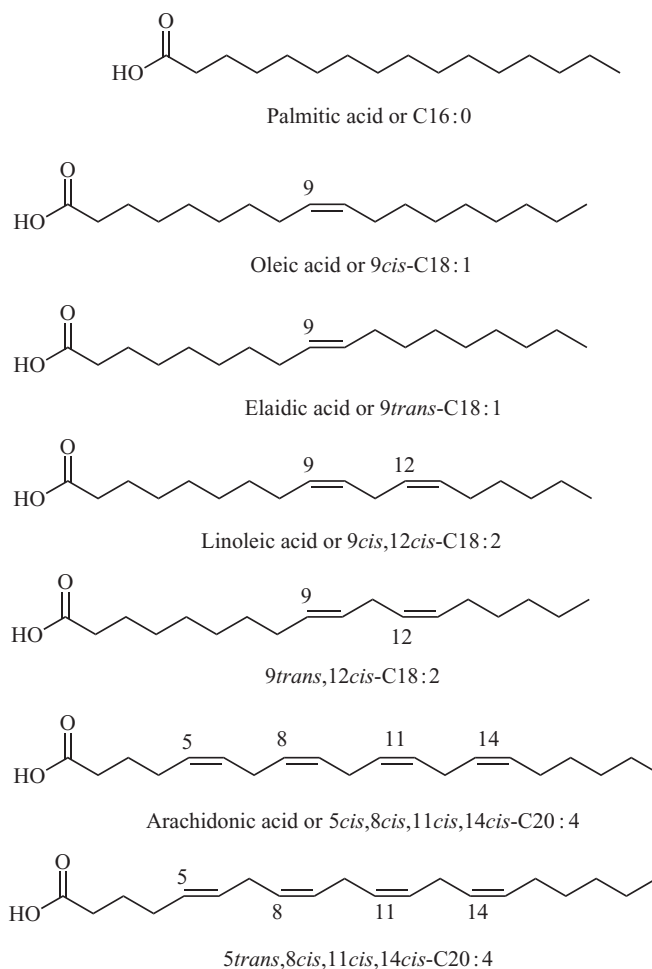


Figure 1 Examples of natural fatty acids and some trans isomers.

geometrical and positional isomers of the natural substrate. Public concern arose due to the harmful effects of trans fatty acids on health, involving risk factors of heart attack and coronary artery disease, impairment of fetal and infant growth, and inhibition of lipid metabolic pathways.^{9–12} Nowadays, different molecular libraries can assist either the dietary and the endogenous trans fatty acid isomer detection, thus distinguishing among different contributions.

The lipid isomerization offers a beautiful example of a cross-disciplinary research subject, involving several life science disciplines with the centrality of free radical chemistry. The multiple aspects of these subjects have been time to time summarized in articles and reviews.^{13–18} This article aims at

offering an overview, starting from the chemical mechanisms and applications of supramolecular systems such as liposomes, and including the meaning of lipid isomerization as a free radical signal or damage in a biological environment. The readers will appreciate the various fields where the isomerization process has been applied and its future perspectives.

2 FREE RADICAL MECHANISM OF LIPID ISOMERIZATION

The reactivity of the double bond toward free radicals is well known, being many free radicals

(e.g., $\text{RS}^\bullet$, $\text{RSe}^\bullet$, $\text{RSO}_2^\bullet$, $\text{NO}_2^\bullet$, $\text{R}_3\text{Sn}^\bullet$, $(\text{Me}_3\text{Si})_3\text{Si}^\bullet$, etc.) and atoms (e.g., $\text{Br}^\bullet$, $\text{I}^\bullet$, etc.) able to add reversibly to this functionality. Among them, the potential of S- and N-centered radicals emerged for their biological significance in the propagation of free radical stress.

Scheme 1 shows the process where the radical species $\text{X}^\bullet$ adds to the cis or trans double bonds, thus forming a radical adduct that ejects the radical and reconstitutes the double bond.^{1–4,19}

During this process, the isomeric purity is lost since the unsaturated substrate becomes a mixture, reaching about an 80:20 trans:cis ratio, regulated by thermodynamical factors. The efficiency of the isomerization process strongly depends on the characteristics of the attacking radicals, and it was noted that thiyl radicals ($\text{RS}^\bullet$) are very effective in this transformation.²⁰

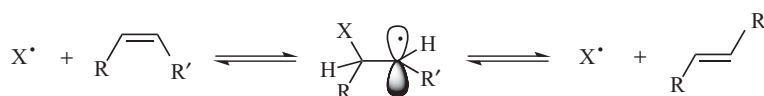
There are two features of the free radical isomerization that should be evidenced also for their relationships with the biological process: (i) all steps are reversible and the overall process is catalytic; provided that the free radical intermediate is not trapped before the β -elimination, one radical is able to sustain the catalytic chain, isomerizing a number of molecules before going to the termination step. This results in an amplification of the damaging potential at low levels of radical generation; (ii) only geometrical isomers can be obtained after isomerization, since no positional shift of the double bond can occur during the addition–elimination process. This is a very important feature for building molecular libraries related to geometrical isomers as free radical stress biomarkers, also in view of the fact that different trans isomers (positional) can derive from dietary sources.

Among the radical species, S-centered radicals are most specific and efficient to sustain catalytic cycles of lipid geometrical isomerization; therefore, they can be proposed as the real culprits of the biologically occurring process,²¹ whereas for N-centered radicals, there are some confounding aspects that are further detailed.

2.1 Thiyl Radicals as Isomerizing Agents

Lipid isomerization is successfully obtained by S-centered radicals, which can be generated from a variety of compounds including thiols, disulfides, and, under certain conditions, thioethers. Using thiols as the starting reagent, the “classical” free radical initiation by azocompounds in alcoholic solutions was used to study MUFA residues in alcohol solution, thus obtaining basic chemical and kinetic information. Under catalytic thiol concentrations (<50 mol% equiv relative to the fatty acids), the isomerization process is easily achieved in quantitative yield, leading to the formation of >80% of trans isomers. The process is independent from the position of the double bond and is equally efficient for different MUFA.²²

The MUFA experiments allowed the rate constants of each step to be obtained, using different initiation procedures including photolysis.^{23,24} The addition rate constants k_a to cis and trans isomers were almost similar ($k_a^{\text{cis}}/k_a^{\text{trans}} = 1.8$), whereas the unimolecular β -elimination rate constant (k_f) for the formation of the trans isomer was one order of magnitude faster ($k_f^{\text{cis}}/k_f^{\text{trans}} = 9.4$). The large preference of fragmentation to the trans isomer was attributed to different energy barriers for the formation of the two transition states.²³ These data allowed to define that the formation of trans isomers is favored not only by thermodynamic reasons but also by kinetic factors of the fragmentation step; moreover, the fragmentation step results to be very fast ($k_f^{\text{trans}} = 1.6 \times 10^8 \text{ s}^{-1}$), and this can be important in the estimation of competitive processes. In fact, the intermediate radical in Scheme 1 can be trapped either by oxygen or H-donors. Both these reactions can occur in a biological environment and the kinetic data of the β -elimination step are necessary to estimate the occurrence of alternative pathways. It is also worth adding that thiols are also well known in biology as “repairing” agents for free radical damage, due to their good H-donor ability. Therefore, the fate of the thiol reactivity and the



Scheme 1 The addition–elimination steps of free radical-catalyzed cis–trans isomerization of double bonds.

extent of the isomerization process make part of a wide scenario where several possibilities have to be evaluated.

The kinetic data allowed a realistic context of the lipid isomerization to be formulated. In Section 4, the role of oxygen and antioxidants is considered in the whole process. By these preliminary evaluations, lipid isomerization appeared to be a feasible conversion to occur in a biological environment.

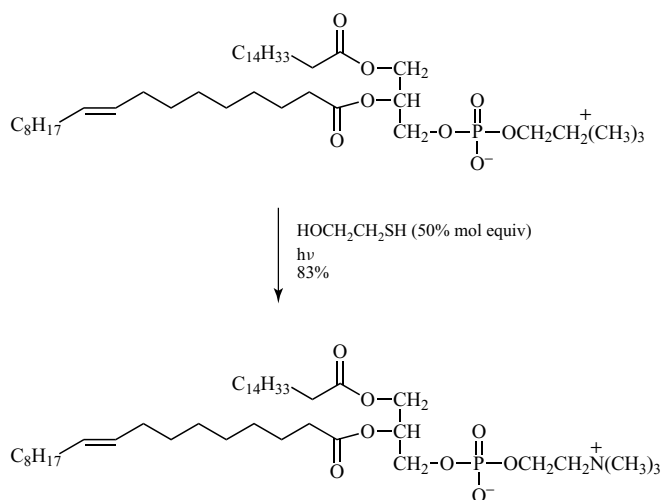
The isomerization was tested also as a synthetic access to trans phospholipids. 1-Palmitoyl-2-oleoyl phosphatidyl choline (POPC) was converted to a 17:83 mixture of POPC:1-palmitoyl-2-elaidoyl phosphatidyl choline (PEPC) in 99% yield in the presence of catalytic amount of 2-mercaptoethanol under photolytic conditions, as shown in Scheme 2.²⁵

It is worth mentioning that this synthesis also allowed to gather data for the first time on the behavior of trans lipids in the spontaneous formation of liposome vesicles and the role of trans lipids in membrane behavior.^{25,26} This is a very interesting subject also for the field of archeobiology, studying early life on Earth and the formation of the first cellular entity. Provided that lipids gave the membrane aggregation for the birth of the first cell, it is worth underlining that the cis geometry should have not been prevalent in the environment that accompanied the early life development, due to high radiations and temperatures. Therefore, the experimental protocols related to the studies

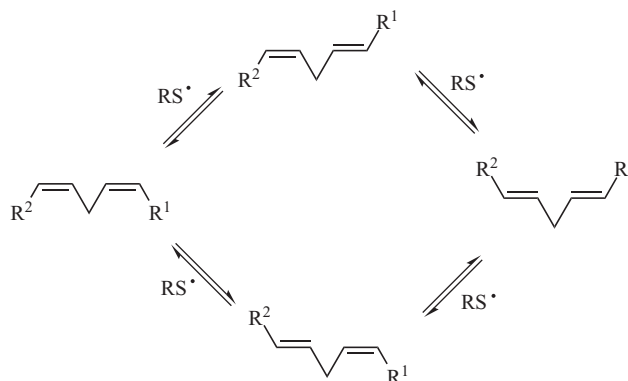
of the behavior of proto-cells should take into account the trans geometrical features. Interestingly, comparison of different vesicles generated spontaneously from phospholipids having saturated, cis-monounsaturated, and trans-monounsaturated residues evidenced that the dimension of the resulting cell compartment goes from smaller to larger following the order: saturated < *trans*-MUFA < *cis*-MUFA.²⁵ The cis geometry was highlighted as an important element for obtaining size of compartments larger than 100 nm. As a matter of fact, the dimension theory has recently proven that protein synthesis can start in 100-nm POPC vesicles enclosing an ensemble of enzymes, ribosomes, tRNA, and low molecular weight molecules.²⁷ The easy synthetic access to trans phospholipids can be useful for a thorough study on mixtures of different geometrical fatty acid structures in the biological membranes.

In case of PUFA residues, the isomerization leads to several isomers calculated as 2^n , n being the number of double bonds. The process occurs by a step-by-step procedure depicted in Scheme 3 with the mono-trans isomers as the first products.²⁸

The formation of di-trans isomers can occur in a subsequent step, in particular, when the mono-trans isomer concentration increases in the medium. This leads to the possibility of stopping the isomerization procedure at different stages, with enrichment of the desired isomer fraction for an easy isolation procedure. Therefore, the thiol radical-catalyzed process can be suggested as the best synthetic way



Scheme 2 The conversion of POPC (1-palmitoyl-2-oleoyl phosphatidyl choline) to PEPC.



Scheme 3 The step-by-step isomerization of polyunsaturated substrates.

to build-up a library of geometrical isomers to be used in the recognition of the trans isomer presence in naturally occurring materials. Instead, other lipid isomerization procedures, such as heating^{29–31} or acid/base treatment,³² can afford geometrical and positional isomers, which are complicated to resolve especially in case of PUFA substrates. The recognition of trans lipids will be further treated in Section 3.2.

In PUFAs, the exhaustive isomerization of the double bonds brings to the formation of all-trans compounds, which can be used for the study on the biological consequences of the total loss of the cis geometry, thus representing an anti-sense strategy. In fact, biological activities are linked to all-cis PUFA structures and the synthesis of all-trans arachidonic acid (AA), linolelaidic acid, all-trans arachidonoyl ethanolamide (all-trans anandamide), and linolelaidoyl ethanolamide allowed the effects given by the change in the geometrical asset to be studied for the first time.^{33,34} The structures are shown in Figure 2.

Some interesting observations can result. For example, the isomer of AA gave a dual effect on platelets.³³ At high concentrations ($>10^{-4}$ M), all-trans AA caused aggregation, while the respective natural isomer have similar effect at approximately 10 times lower concentration. On the other hand, at lower concentrations, all-trans AA inhibited the aggregation induced by the strong platelet agonist, platelet activating factor, PAF (4×10^{-10} M) with an $IC_{50} \sim 6 \mu\text{M}$ but not that induced by thrombin. Similar results were obtained with all-trans isomer of linoleic acid.

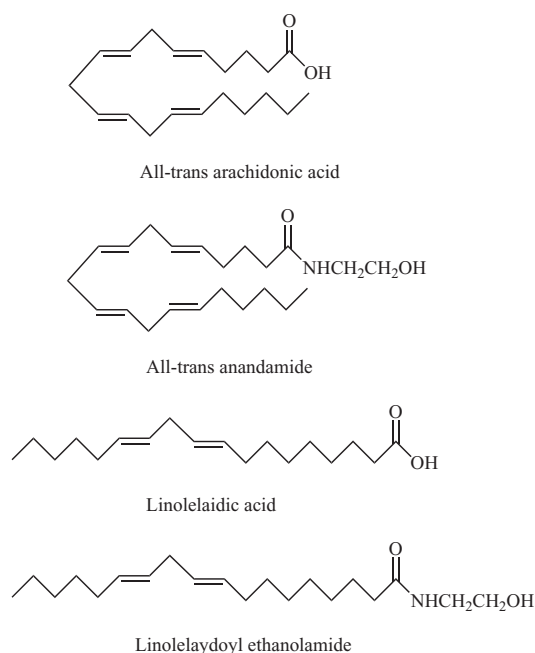


Figure 2 All trans lipid strategy with all-trans arachidonic acid, all-trans anandamide, linolelaidic acid, and linolelaidoyl ethanolamide.

The anti-sense strategy carried with all-trans lipids indicated that the effects obtained by such structural change are not completely adverse with the pathways followed by their (natural) cis counterparts, although the interaction with the enzymatic cascades can be much weaker.

The synthetic isomerization procedure was also applied to natural triglycerides that make part of the trans lipid library.³⁵ In Table 1, the treatment

Table 1 Fatty acid composition of rice and borage oils before and after the thiyl radical-catalyzed procedure followed by winterization procedure.

Fatty acid	Rice		Borage	
	Before	After	Before	After
16:0	17.0	20.6	11.8	20.0
18:0	1.8	4.5	3.8	6.6
18:1, <i>trans</i> 9	—	43.0	—	20.2
18:1, <i>trans</i> 11	—	—	—	0.4
18:1, <i>cis</i> 9	42.5	9.7	16.4	4.5
18:1, <i>cis</i> 11	1.2	—	0.6	—
18:2, <i>trans</i> 9,12	—	15.3	—	23.3
18:2 <i>cis/trans</i>	—	6.9	—	7.6
18:2n-6	36.8	—	39.7	1.5
18:3n-6 <i>trans</i>	—	—	—	7
18:3n-6 <i>cis/trans</i>	—	—	—	3.3
18:3n-6	0.7	—	23.6	—
20:1, <i>trans</i> 11	—	—	—	4.8
20:1, <i>cis</i> 11	—	—	4.1	0.8

of oils containing MUFA and PUFA residues with the isomerization procedure is shown. The enrichment of trans isomers is obtained after applying the winterization procedure, which consists of the low temperature (-20°C) crystallization in a suitable solvent. In this work, the effect of lipase-catalyzed transesterification procedures was also tested (*Candida antarctica* lipase), realizing that hydrolytic enzymes can function with cis and trans substrates without distinction. This raises an interesting question on specific enzymatic systems able to recognize the presence of trans isomers in eukaryotes, which still waits for an answer. In Section 4.3, it will be shown that the enzymatic cis–trans conversion in prokaryotes is an important subject of research. The oil isomerization is relevant for the biotechnological area of food industries, which has been extensively treated in books and papers addressing the quality and quantity of trans isomers produced in the oil processing.^{7,8,36–39}

As far as S-containing compounds used for thiyl radical generation are concerned, most of the synthetic procedures and kinetic studies were carried out with 2-mercaptoethanol as the thiol. This is an amphiphilic thiol, highly soluble in hydrophobic and hydrophilic solvents, which is also useful for the efficiency and flexibility of the reaction. The synthetic procedure works with a variety of free radical conditions and thiols, as well as S-containing compounds, including sulfonfyl species.⁴⁰ Being sulfur-containing compounds

relevant in biological systems, the chemical/kinetic observations should be easily transferred from a synthetic to a biomimetic model. In this respect, 2-mercaptoethanol turned out to be very useful for exchanging information from one system to another.

In heterogeneous systems such as liposomes, further treated in this article, an additional role is played by the partition coefficient of the reactive species in the medium, making differences among the different biologically relevant S-containing compounds.

2.2 Nitrogen-Centered Radicals as Isomerizing Agents

Other radicals and atoms are able to induce cis–trans isomerization following the mechanism reported in Scheme 1. $\text{NO}_2^{\bullet}$ radicals are known isomerizing agents from the work by Titov in 1963.⁴¹ From a biological point of view, N-centered radicals can be interesting since they make part of the nitrosative stress with damaging potential to biomolecules.^{42–44} There are a few kinetic data for the reaction of $\text{NO}_2^{\bullet}$ radicals with olefins, indicating that both the addition and the hydrogen abstraction steps are slow processes.⁴⁵ For the addition of $\text{NO}_2^{\bullet}$ radicals to 2-pentene, the addition rate constants are slow ($k_a^{\text{cis}} = 0.18$ and $k_a^{\text{trans}} = 0.038 \text{ M}^{-1} \text{ s}^{-1}$) and the fragmentation step occurs with $k_f = 8 \times 10^4 \text{ s}^{-1}$ for both isomers. Moreover, the H-abstraction from bisallylic position also showed to be competitive with addition in solution.⁴⁵ Therefore, the result of $\text{NO}_2^{\bullet}$ radical reactivity can be a mixture among addition, isomerization, and oxidation depending on the reaction conditions. The reaction with methyl linoleate has been studied in detail,⁴⁶ individuating that $\text{NO}_2^{\bullet}$ radicals can initiate lipid autoxidation due to the bisallylic H abstraction. A small yield of trans isomers can also derive from the reversible addition but only in the absence of oxygen. It can be estimated that in the presence of 0.1 mM oxygen, the isomerization becomes unimportant due to the trapping of the adduct radical and formation of peroxy derivatives, which evolve toward oxidation products.⁴⁷

$\text{NO}_2^{\bullet}$ radical isomerization has been proposed as a process occurring in the biological environment, envisaging its involvement in the formation of

trans AA in platelets⁴⁸ as well as in the general vascular stress.⁴⁹ Although the direct reaction of NO₂[•] radicals with methyl arachidonate can give rise to some trans isomers, this process has to be contextualized in an *in vivo* situation where all competitive pathways can occur. As a premise to any reactivity evaluation, it must be underlined that the prediction of a free radical biological pathway is possible by a careful evaluation of the rate constants of all possible processes and the relative concentration of all reaction partners. As it will be further detailed in the sections dedicated to biomimetic studies, free radical chemistry is quite predictable based on the known kinetic and thermodynamic data, but in the biological environment, other factors must be taken into account: the system is heterogeneous, and the partition coefficient as well as other parameters, such as the diffusibility of the reaction partners, are all important for the reaction outcomes.

In case of NO₂[•] radicals, it is well known that they react quite fast at physiological pH with thiols, such as glutathione ($k = 3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$), also being a moderate one-electron oxidant $E^0(\text{NO}_2^{\bullet}/\text{NO}_2^-) = 1.04 \text{ V}$ (vs NHE). Both thiyl and NO₂[•] radicals react with urate at a similar rate ($k \approx 10^7 \text{ M}^{-1} \text{ s}^{-1}$).^{50,51} By taking into account the relative concentrations in different compartments, it can be estimated that the lifetime of NO₂[•] radicals in cytosol is <10 μs and that thiols are the dominant sink for NO₂[•] radicals in cells and tissues, whereas urate is the main scavenger in plasma. This reactivity is obviously influenced by the pK_a of the different thiol compounds, but it can be generally said that thiols act as anti-nitrosative agents.⁵²

As a result of all these considerations, thiyl radicals emerge as the main isomerizing agent in a biological system and the role of N-centered radicals is more likely to mediate thiyl radical formation rather than cause directly a cis–trans lipid isomerization.

2.3 Degradative Processes Involving Sulfur-Containing Compounds

Lipid isomerization became an interesting subject of chemical biology due to its relationship with the free radical reactivity of biologically relevant S-containing compounds. They can produce thiyl

radicals by two main pathways: (i) the H-atom donation from thiol compounds as well as the bond breakage from disulfides, both making part of important protective and redox systems in the cell⁵³ and (ii) desulfurization (elimination) processes from reactive intermediates during stress.^{4,21} In both cases after generation of thiyl radicals, lipid isomerization can occur, the two processes making part of a tandem damage, as described in Sections 2.3.1 and 2.3.2. This was also thought to be the mechanistic scheme followed by lipid isomerization *in vivo*.

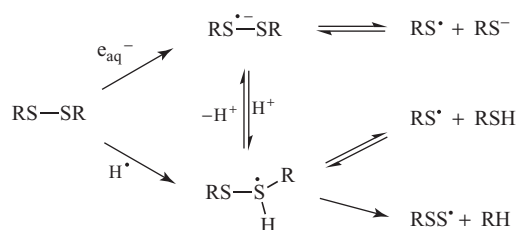
Before lipid isomerization came into play, the scenario of the damage to cysteine (CySH), cystine (CySSCy), and methionine (Met)^{54,55} was connected mainly to a direct oxidative stress. The reactivity of these biologically relevant sulfur compounds under free radical conditions is treated in the article **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**. Here, it is important to underline that in biology, thiols are mostly perceived as protecting agents for free radical stress, being glutathione one of the most important free radical trapping agents, and the role of disulfides connected with the equilibrium between the oxidized and the reduced forms.^{51,53} In fact, thiols and disulfides are not perceived as possible damaging agents to biomolecules, although mechanisms of thiyl radical generation and reactivity have been proposed.^{56–58} This is an example of information gap between chemistry and biology, which has to be addressed by improving interdisciplinarity.

Lipid isomerization can be utilized as a nice example of a chemical mechanism transferred to biology for a better understanding of the puzzling scenario of free radical stress and the related products.

2.3.1 The Case of S-Containing Amino Acids and Peptides

H-atom abstraction from thiols is very well known as “repair reaction,” which is quite important for protection of living systems. In this respect, protective agents can be either small molecules, such as glutathione,⁵⁹ or large structures, such as albumin.⁶⁰

Considering that biological environment is a heterogeneous system, it is worth recalling that thiyl radicals from CySH residues reside in the hydrophilic part, whereas CyS[•] radicals generated



Scheme 4 Pathways of formation of thiyl radicals from disulfides.

in peptides or proteins can instead be close to hydrophobic compartments, such as membrane lipid bilayers. The localization of sulfur residues is quite important in heterogeneous systems, and it will be more appreciated in liposomes, described in Section 3.

Disulfides can lead to the formation of thiyl radicals by different pathways shown in Scheme 4.⁶¹ It is worth mentioning that when disulfides are present in macromolecular structures, such as disulfide bridges in proteins, the corresponding thiyl radicals cannot behave as in small molecules (such as cystine or oxidized glutathione) and their localization, as well as partition, is restricted. This can also affect the reactivity toward lipid isomerization.

Several biomimetic studies in the field of amino acid damage and lipid isomerization have been performed using ionizing radiations. In water, the effect of ionizing sources such as ⁶⁰Co is to generate the primary water radicals and solvated electrons according to Figure 3.⁶²

Provided that a cobalt source is available, this initiation can be suggested as a simple protocol to simulate the effect of stress in the biological environment. Indeed, the initiation compartment is water and highly reactive species such as hydrated electrons (e_{aq}^-) and $\cdot\text{OH}$ radicals are produced in the system with several advantages: (i) the production of $\cdot\text{OH}$ radicals can occur without the presence of metals or oxidizing agents, which are instead needed in other protocols, such as the Fenton reaction; (ii) the selection of the reactive species

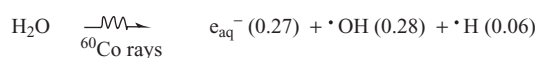


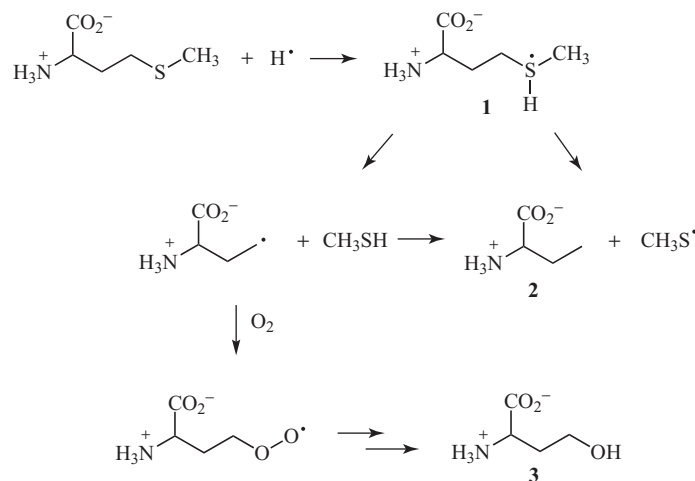
Figure 3 Formation of reactive species from the irradiation of water (radiation chemical yield).

can be simply affected, that is, by flushing of gases in the reaction medium: for example, e_{aq}^- can be quenched by flushing N_2O in the medium, leaving $\cdot\text{OH}$ radicals and $\text{H}^{\cdot}$ atoms as reactive species in a 90 and 10% relative distribution. N_2O efficiently reacts with electrons ($k = 9.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$); alternatively, hydrated electrons can be chosen as the main reactive species, mainly quenching $\cdot\text{OH}$ radicals by alcohols (i.e., by *t*-BuOH with $k = 6 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$); the reactivity of $\text{H}^{\cdot}$ atoms can be further selected, either by eliminating $\cdot\text{OH}$ radicals and using phosphate buffer as the solvent, which reacts with hydrated electrons in deaerated solution increasing the $\text{H}^{\cdot}$ atom yield ($k = 1.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$); (iii) finally, the quantitative radical generation can be estimated using the radiation chemical yield (G) in $\mu\text{mol J}^{-1}$ units.^{63,64} The use of radiations turned out to be very important in order to envisage novel pathways of amino acid degradation by desulfurization processes and to establish their relationship with the lipid isomerization.

In case of methionine, this amino acid was already individuated for its role in oxidative stress with the formation of the corresponding sulfoxides.^{65–68} Also irradiation conditions were described to produce methionine oxidation, thought to be induced by $\cdot\text{OH}$ radical attack. More recently, novel mechanistic pathways have been described under anaerobic and aerobic conditions,⁶⁹ which can cause desulfurization according to Scheme 5.

It can be seen that the attack of hydrogen atoms occurs mainly to S centers with the formation of a sulfuranyl type radical **1**, which undergoes a β -fragmentation with the ejection of the MeSH moiety and formation of a C-centered radical. The fate of these species under anaerobic conditions is to give α -amino butyric acid **2** and $\text{MeS}^{\cdot}$ radical; under aerobic conditions, the C-centered radical can be trapped by oxygen and the corresponding peroxy radical can fragment and generate homoserine **3** together with $\text{MeS}^{\cdot}$ radicals. In both cases, $\text{MeS}^{\cdot}$ species have a very high diffusibility and can induce lipid isomerization.

It is worth underlining that this desulfurization process leads to a chemical mutation of a naturally coded amino acid into not genetically coded amino acids. In particular, methionine also plays an important role in the protein synthesis being a methionine-containing triplet often at the start of this process. The consequences of this mutation have not yet been addressed. In this view, libraries of



Scheme 5 Transformation of methionine via sulfuranyl radicals **1** into α -amino butyric acid **2** and homoserine **3**.

desulfurated sequences can be useful references in proteomic analyses to identify the occurrence of such transformations in complex mixtures. A similar process can occur to CySH residues and can lead to the formation of alanine residues. This process was identified in the 60–70s under radiation conditions, but never combined with a tandem damage in the biological environment.^{70–73}

Details of the free radical mechanisms involving S-containing compounds are given in article **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**. The applications to a biomimetic model of tandem damage in liposomes will be described in the following sections.

2.3.2 Lipid Isomerization as a Tool for Individuating Protein Damage: the Tandem Protein–Lipid Damage

In case of peptide and protein structures, the radical attack can occur to various amino acids of the sequence. Proteomic analyses are useful for mapping the damages, and the individuation of sequence alterations at very low level of damage can suffer from low resolution. It turned out that lipid isomerization can function as a very sensitive detection system for the damage to S-containing residues. In fact, after formation of thiyl radicals by the mechanisms described in the previous section, the catalytic cycle of cis to trans conversion can start, involving an unsaturated fatty acid present in the medium.

The combination of desulfurization–isomerization represented an interesting hypothesis to be assayed by biomimetic chemistry, in order to propose a novel pathway of tandem damage by free radical stress. Unlike the standard double lesions that are produced by two separate attacks by radical species, the concept of a tandem lesion includes the occurrence of a first damage by a single attack that generates reactive species able to migrate and react with other molecules, producing a second damage. The tandem process can involve two different cell compartments, and a precedent example of this kind of damage was described in case of lipid and DNA molecules, which give rise to adducts thus connecting two apparently separated environments such as membranes and nucleus.⁷⁴

The model chosen for biomimetic chemistry was composed of a lipid substrate containing a cis double bond (i.e., phospholipids such as POPC) in the presence of a sulfur-containing amino acid, or a peptide/protein sequence, as shown in Figure 4.

In case of aqueous systems, lipids are hydrophobic molecules that spontaneously organize themselves in aggregates. The details of this organization will be treated in Section 3. To this system, a radical stress was applied and the reaction products were analyzed in order to check the occurrence of the cis–trans isomerization of the lipid partner together with the desulfurization of the amino acid counterpart.

The tandem desulfurization–isomerization process highlighted the occurrence of a reductive

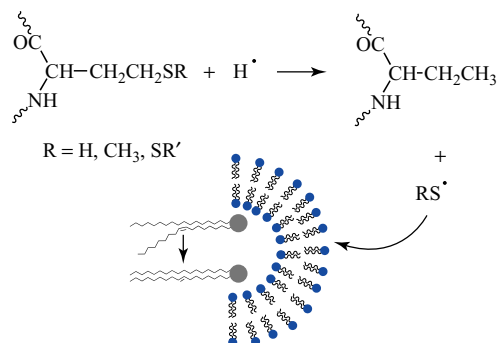


Figure 4 Tandem protein-lipid damage by reductive stress to S-containing residues with formation of a diffusible thiyl radical which migrates into the lipid bilayer and causes the cis–trans isomerization.

radical stress, which is certainly less studied than the oxidative damage.^{75–78} Indeed, using ionizing radiations in aqueous systems, the formation of primary radicals from water occurs (Figure 3) and hydrogen atoms can be selected. These reactive species were already known for their specificity toward sulfur moieties,^{70–73} but the behavior examined in radiation chemistry was not extrapolated to a possible path in the biological environment. It is worth underlining that the occurrence of a reductive stress is still underestimated, although hydrogen atoms can be produced by reaction of dihydrogen phosphate anions with electrons ($k = 1.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).^{63,64} This process waits for more attention among the radical stress pathways.

Free radical conditions can affect sulfur-containing residues, either under anaerobic or aerobic conditions, and the result is the transformation of natural amino acids in other amino acids, which are natural but not genetically encoded. These transformations are quite different from those already evidenced under oxidative stress. In fact, methionine is known to be transformed into methionine sulfoxides (the two *R* and *S* sulfoxide epimers), and this is actually considered an antioxidant system also balanced by enzymatic redox complexes.⁷⁹

Novel mechanistic pathways were individuated using ionizing radiations, as described for the simple amino acids, and the fate of S-containing residues belongs to a scenario with different possibilities. Peptide and protein sequences were studied in this respect, such as amyloid β -peptide, bovine pancreatic RNase A, and human serum albumin,

among others. Amyloid β -peptide is an interesting substrate involved in the damage caused by radical stress to the nervous system, which induces formation of fibrils disturbing the neuronal membrane structure and functions.⁸⁰

Reductive radical stress was applied to the 40 amino acid sequence of the amyloid β -peptide and the transformation of Met residues into α -amino butyric acid occurred, as identified by high performance liquid chromatography (HPLC) separation and matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) analysis. The experiment was also carried out in the biomimetic model of liposomes to ascertain the occurrence of a tandem lipid damage induced by the reductive desulfurization of the peptide with the formation of a diffusible radical species ($\text{MeS}^\bullet$), which penetrates the liposome bilayer and induces trans lipid formation (Figure 4).⁸¹

In the case of RNase A and albumin, both disulfide bridges and Met residues were found to be involved in the damage and the corresponding lipid isomerization. The secondary and tertiary structures of the protein render some residues more exposed than others to the attack of free radicals and also the diffusibility of small reactive species such as hydrogen atoms plays a role in the amino acid involvement. For RNase A, a complete proteomic analysis was carried out, showing that desulfurization selectively affected Met79, Cys110, Cys58, and Cys72 during first stages of reaction.⁸²

In an overview of the sulfur-containing substrates involved in lipid isomerization, the reactivity of metallothioneins is intriguing, because these proteins are S-rich sequences containing methionine and also metal-thiolate clusters created by complexation of metals with CySH residues and inorganic sulfur (Figure 5). The effect of reductive conditions (H atoms and solvated electrons) on these sequences, containing zinc or cadmium as the metals, was examined together with the identification of a tandem lipid isomerization and the proteomic analysis.⁸³ In Figure 5, the possible S-centered radical generation from Met, CySH, and S-containing clusters is indicated.

Preliminary indications that Cd and Zn proteins behave differently have been obtained, highlighting the influence of the two different protein structures on the reactivity outcome. Coupling the radiation with the detection of the spectral changes by Raman spectroscopy, it was possible to envisage that

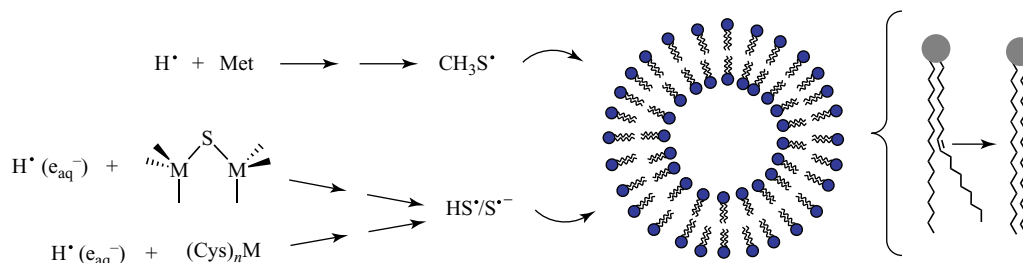


Figure 5 Pathways of free radical generation on Met, CySH, and S-metal clusters belonging to metallothioneins.

Cd-containing protein appears to respond with the S-metal cluster, whereas for Zn-metallothionein, the CyS-metal clusters is more reactive.⁸³ In both cases, liberation of $\text{HS}^\bullet/\text{S}^{\bullet-}$ species occurs (Figure 5). These diffusible species are effective lipid isomerizing agents, which are able to migrate in the lipid compartment and cause the trans isomer formation. This result adds other chemical information to the already known role of metallothionein as antioxidants⁸⁴ and suggests that the liberation of sulfur species could represent a signal in the biological environment, which triggers other responses and endogenous cellular defenses.

The reactivity of S-containing residues reinterpreted as a tandem process with lipid isomerization offers several hints for novel chemical pathways occurring in aqueous systems, thus expanding the scenario of the possible changes that occur under free radical stress.

3 LIPID ISOMERIZATION IN ORGANIZED SYSTEMS

Liposomes such as multilamellar vesicles (MLVs) and small or large unilamellar vesicles are widely accepted as models of membrane lipid assembly. In Figure 6, an example is shown with the phospholipid dioleoyl phosphatidyl choline (DOPC).

After an initial use of MLVs, the choice was oriented to large unilamellar vesicles obtained by the extrusion technique. These models are much closer to cell membranes, due to the presence of a single bilayer.⁸⁵ Depending on the polycarbonate filter size used for the extrusion, vesicles of circa 90-nm diameter can be prepared and form an almost transparent suspension, which is also suitable for studies under photolytic conditions.^{25,26} Aqueous and lipid phases are the two distinct compartments

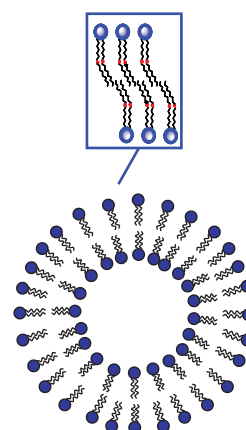


Figure 6 Unilamellar vesicle or liposome formed by DOPC (dioleoyl phosphatidyl choline).

of this nonhomogeneous system; therefore, several characteristics should be taken into account for the reactivity toward free radicals. First of all, where is the location of the initiation step, that is, where does the formation of an initial radical species occur. When a vesicle system is used to model free radical processes, it is important to establish which method of radical generation to be used, because it influences the reactivity. For example, radical processes can be initiated by diazocompounds of general formula $\text{R}-\text{N}=\text{N}-\text{R}$, which are homolytically cleaved at the appropriate temperature thus giving $\text{R}^\bullet$ with the evolution of N_2 .⁸⁶ These azoinitiators can be either hydrophilic, the generation of radicals occurring in the aqueous compartment, or hydrophobic, generating radicals within the lipid compartment. On the other hand, if generation of radicals is obtained by irradiation, the radiation source is important. In fact, using continuous radiolysis (^{60}Co source) in aqueous

liposome suspensions, the initiation occurs by the water compartment due to the interaction of γ -rays with water that generates primary reactive species (Figure 3).⁶²

Another factor to take into account is the orientation given by the supramolecular arrangement of the lipid assembly, with the fatty acid chains of phospholipid molecules that form the hydrophobic core of the model membrane and the polar heads that face the aqueous internal and external phases. In liposomes, there is a precise arrangement of the hydrophobic core, which can influence the position of the double bonds in the bilayer and the subsequent radical reactivity. A similar effect was also shown for ionic processes in organized systems.⁸⁷ Therefore, the reactivity of the fatty acid double bonds to the radical attack in suspensions is not equal to solution. Finally, the distribution of substrates added to liposome system in the two compartments depends on their partition coefficient.

3.1 Supramolecular Organization and Positional Isomer Preference

Lipid organization is a very important factor for the reactivity. It must be underlined that the most feasible membrane model is represented by mono-lamellar vesicles that have a single lipid bilayer simulating the natural cell membrane. In the mono-lamellar system, the process of the lipid isomerization was studied, and for the first time, the regioselectivity of this process with a positional preference was shown. This was studied using an amphiphilic thiol, 2-mercaptoethanol, as well as with other thiols, such as H_2S ,⁸⁸ which are highly diffusible species, able to move without restriction from the aqueous phase to the lipid bilayer and vice versa.

The model of liposomes made of egg yolk lecithin contained different fatty acid residues, as shown in Figure 7, with a mean fatty acid composition of palmitic acid (C16:0) 32%, stearic acid (C18:0) 14.1%, oleic acid (9*cis*-C18:1) 27%, vaccenic acid (11*cis*-C18:1) 1.2%, linoleic acid (9*cis*,12*cis*-C18:2) 20%, AA (5*cis*,8*cis*,11*cis*,14*cis*-C20:4) 4.8%. Lecithin can simulate much closer the various types of fatty acids present in the natural membranes.

In the presence of thiols and free radical conditions, it was demonstrated that the double bonds

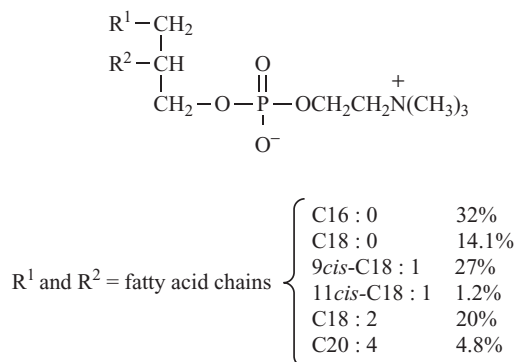


Figure 7 Composition of phosphatidyl choline (lecithin) from egg yolk.

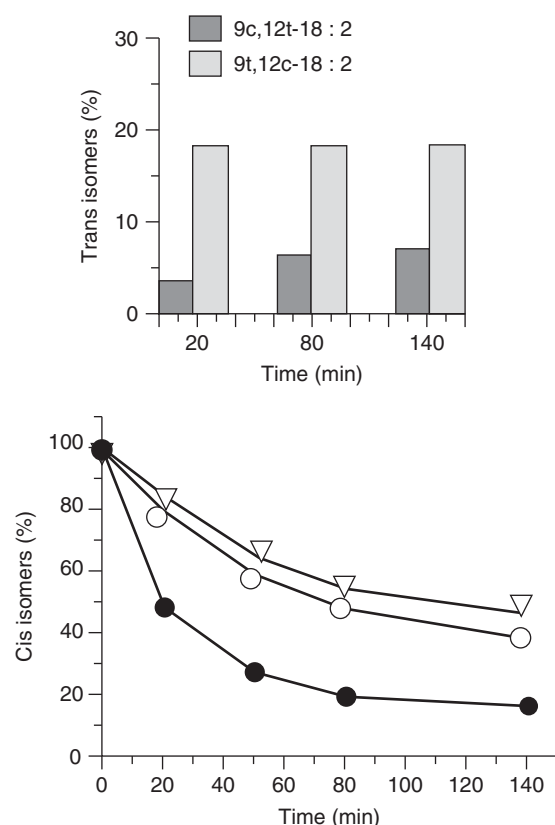


Figure 8 Isomerization of the fatty acid residues in liposomes made of egg lecithin by diffusible thiol radicals. Normalizing the fatty acid content according to the double bonds, arachidonic acid (∇) is faster than linoleic acid (○) and oleic acid (●). The bar diagram indicates the different amounts of mono-trans isomers of linoleic acid found in liposomes at different irradiation times.

located closest to the membrane polar region are the most reactive toward the attack of diffusing radicals.^{28,89} In fact, linoleic acid residues in vesicles have the double bond in position 9 more reactive than that in position 12, and the mono-9-trans isomer was formed preferentially (Figure 8).

Looking at the composition of egg lecithin reported in Figure 7, the normalization of the fatty acid content according to double bonds showed that AA residues are the most reactive in vesicles compared to oleic and linoleic acids (Figure 8, bar diagram). This was due to the fact that the two double bonds in 5 and 8 are the first ones available to free radicals diffusing in the layer, therefore, the first to be isomerized by diffusible thiyl radicals.

Several information were obtained from this biomimetic study to be extrapolated to the lipid isomerization process occurring in a biological environment: (i) among different fatty acid residues, AA residues as very relevant markers of thiyl radical reactivity in membrane phospholipids. This fact can lead to the hypothesis that tissues with a high polyunsaturated content can be more exposed to the isomerization process. The vulnerability of tissues containing PUFA residues is well known in oxidative processes and described by the parameters of peroxidation index or oxidizability.^{90,91} Also in the case of isomerization, PUFA content can be evaluated and it is likely that different tissues can have an indicative isomerization index or isomerizability which could be calculated. (ii) The isomerization of PUFAs occurs by a step-by-step mechanism (as shown in Scheme 3); therefore, the first isomers to be formed are mono-trans isomers of AA. Actually, in the liposome models, it was suggested that the mono-5-trans and 8-trans isomers are the first isomers to be formed by an endogenous process by diffusible free radicals penetrating the bilayer, since these positions are the first encountered during diffusion. The isolation and characterization of the mono-trans isomers of AA was carried out, gathering data on the chromatographic conditions (thin layer chromatography and gas chromatography (GC)) and spectroscopic (nuclear magnetic resonance, NMR) measurements that allowed to distinguish the four mono-trans isomers (Figure 9).⁸⁹ (iii) considering the biochemical pathways of AA formation from linoleic acid (in Section 3.2), it turned out that the positions 5 and 8 are those most involved *in vivo* in the activity of the desaturase enzymes; therefore, they are significant to highlight

the occurrence of an endogenous isomerization with conversion of the natural cis isomers into trans. (iv) The experiments in liposomes suggested that lipid isomerization in natural membranes should lead mainly to mono-trans isomers, the second step (i.e., formation of di-trans isomers) being less probable at the low radical production expected *in vivo*. This is a very important indication for building the library of cis and trans lipid isomers in order to effect the recognition in biological samples. Moreover, the endogenously formed mono-trans isomers turned out to be distinguishable from the exogenous trans isomers derived from dietary contribution, as it is explained in Section 3.2.^{89,92–94} The extended library can involve other PUFA residues, such as the fatty acids of the ω -3 series (eicosapentaenoic acid and docosahexaenoic acid) and lipid substrates not only related to membranes. Attention should be given to geometrical isomers that are the only products of a free radical-catalyzed isomerization and it is particularly important to consider the regioselectivity of the isomerization process, which helps in individuating the double bond positions that can be involved.

Important factors examined in the liposome model were the partition coefficient of sulfur-containing compounds and the compartment of the radical initiation step, which have a role in the isomerization outcome. Hydrophilic, lipophilic, and amphiphilic compounds have a different behavior and the combination between the S-containing compound and the radical initiator can be a crucial step. In biomimetic models, a variety of biologically relevant sulfur-containing compounds, such as cysteine, glutathione, methionine, lipoic, and dihydro lipoic acids,²² were examined under different radical initiating conditions.

Radical initiation can be obtained in the aqueous compartment by several methodologies: (i) thermal decomposition of a hydrophilic azocompound, which can also simulate a biological situation, such as the repair reaction given by hydrogen-donation from cysteine and glutathione toward carbon-centered radicals; (ii) ionizing radiations, such as γ -irradiation of aqueous systems which gives e_{aq}^- , $HO^\bullet$, and $H^\bullet$ atoms as reactive species, and the possibility of selection of the reactive species under appropriate conditions (Figure 3)⁶²; direct photolysis that can mimic the irradiation effects of light.

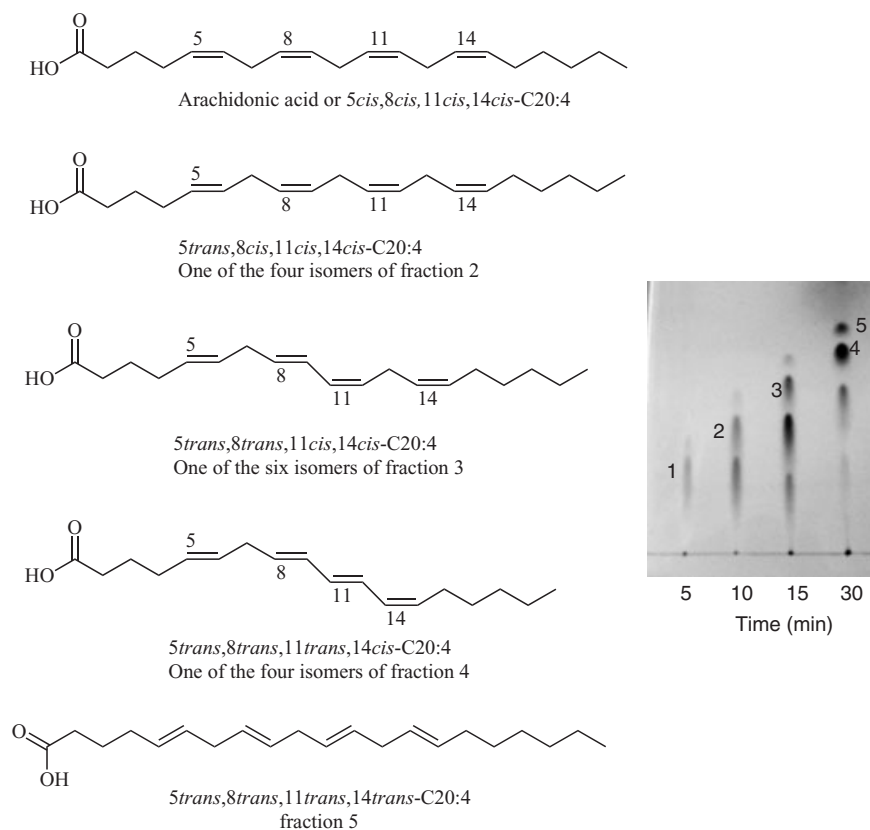


Figure 9 Time course of the photolytical isomerization of methyl arachidonate by Ag-TLC and structures of some of the trans isomers.

By examining different combinations of thiols and initiators, it was established that hydrophilic compounds, such as cysteine, combined with a hydrophilic thermal initiator, did not give any isomerization of the lipid bilayer.²⁸ This behavior was easily explained by the fact that hydrophilic thiol radicals are not able to enter the lipid bilayer and therefore cannot reach the lipid double bonds. On the other hand, under γ -radiolysis conditions, lipid isomerization with cysteine occurred. The radical damage was found to be caused by hydrogen atoms ($H^\bullet$) able to attack the sulfur moiety of the amino acid, and produce a desulfurization reaction,^{76,82,95} as previously described in the tandem lipid–protein damage. It cannot be excluded that CySH residues in a different context would be able to interact with membrane lipids. In fact, these residues are also present in membrane proteins, such as the mitochondrial respiratory chain enzymes. However, by

comparing different thiols, it was evident that the more hydrophobic the thiol, the higher the ability of inducing the cis–trans lipid isomerization. It must be underlined that the evaluation of lipid isomerization in the membrane compartment does not exclude that isomerization could occur in other cellular compartments where lipids are present. In this case, it could be expected that regioselectivity changes; however, lipids are organized in any case, for example, in micelles, and the organization mode has to be properly addressed.

3.2 Lipidomics and Recognition of trans Lipids in Biological Samples

Transferring chemical and reactivity information to a biological context is the task of chemical biology. Lipid isomerization is an interesting process to

be connected with the occurrence of free radical stress in cells. In order to evaluate the impact of this process in cellular stress, two main issues have to be addressed: (i) the analytical protocols for the identification of cis and trans lipids and (ii) the biological significance of the geometrical isomerization.

Nowadays, the follow-up of the lipid transformations belongs to the field of lipidomics, a discipline that brought a renovation of the methodologies and biological interpretation of lipid structures and metabolism. Trends and opportunities opened by lipidomics have been discussed in different contexts.^{96,97}

Lipidomic follow-up of free radical stress includes several indicators: (i) polyunsaturated fatty acids, which are sensitive substrates to free radical conditions and are well known to be transformed or consumed by oxidative stress. Oxidation and degradation products of PUFA are stress biomarkers to be found as metabolites, together with the changes of PUFA content in comparison with normal conditions; (ii) trans isomers obtained by lipid isomerization, which have been recently introduced as biomarker of free radical stress. They can be important *per se*, as well as give an indirect information on other degradation processes, such as the desulfurization of S-containing substrates; (iii) the overall content of the different families of fatty acids (PUFA, monounsaturated, and saturated fatty acids), which can change under stress, which have several consequences for the organization of membrane compartment and its functioning.

These lipid indicators can be estimated by an analysis of all fatty acid types and isomers present in a tissue in comparison with known normal compositions. Owing to the enormous relevance of free radical processes for health, it is clear that lipidomic analyses and the identification of important fatty acid biomarkers can also help envisage protective and integrative strategies of intervention. In this way, lipidomics of free radical stress provides a beautiful example of a straightforward application of chemical knowledge to health and medicine, which is expected to develop in several directions in the future.⁹⁸

As mentioned in Section 1, trans fatty acids are subject of nutrition research, due to the fact that isomerization can occur during fat manipulation in food industries. Several papers appeared on the intake of trans isomers through the diet and

the correspondent detection of trans fatty acids in tissues.^{7,11,12,99–101} From these results, it is clear that trans isomers can be enzymatically processed *in vivo* and the unnatural trans geometry is incorporated in biological structures, thus, resulting in an alteration of the cis geometry of natural lipids. Up to now, it is not known whether the presence of trans isomers in eukaryotic cells can be detected and recognized by specific enzymes, which can remove this alteration *in vivo*. Certainly, their presence can produce a signaling activity at various levels; in particular, trans isomers can be sensed in membrane lipids influencing, for example, membrane properties, channel and protein functioning.^{102–105}

The hypothesis of trans fatty acids formed directly in tissues by an endogenous free radical process was formulated after the chemical studies in biomimetic models. Studies on *in vitro* and *in vivo* trans-free systems, such as cell cultures⁹⁴ and animals,^{106,107} gave information on the endogenous trans fatty acid formation. The first report described THP-1 cell lines (human leukemia cell line) analyzed for the membrane fatty acid content under different conditions. A basal content of trans lipids was found in controls (circa 2.7%, indicated as the relative percentage on the total fatty acid residues detected by GC) under normal incubation condition. The addition of the amphiphilic thiol 2-mercaptoethanol to the cultures caused a slight increase in trans isomers (circa 3.8%). On the other hand, glutathione was not able to induce a significant increase in trans isomers during normal incubation, indicating the different fate of thiols in cells. When these thiols are used under radical stress produced artificially in the cell cultures by γ -irradiation, trans lipid formation increased up to 15.5% of the total fatty acid content. According to the biomimetic chemistry assayed in liposomes, lipid isomerization can likely occur by diffusible thiyl radical species, either produced under normal metabolism or under radical stress, entering the membrane compartment from the aqueous phase and attacking the double bonds. Fatty acid analysis indicated that the most prominent residue in this transformation was AA, confirming the indications derived from liposome experiments. In fact, the supramolecular membrane organization renders the double bonds of different fatty acids nonequivalent, therefore, favoring the reactivity of AA and in particular the formation of mono-trans isomers of this fatty acid at positions 5 and 8.⁹⁴

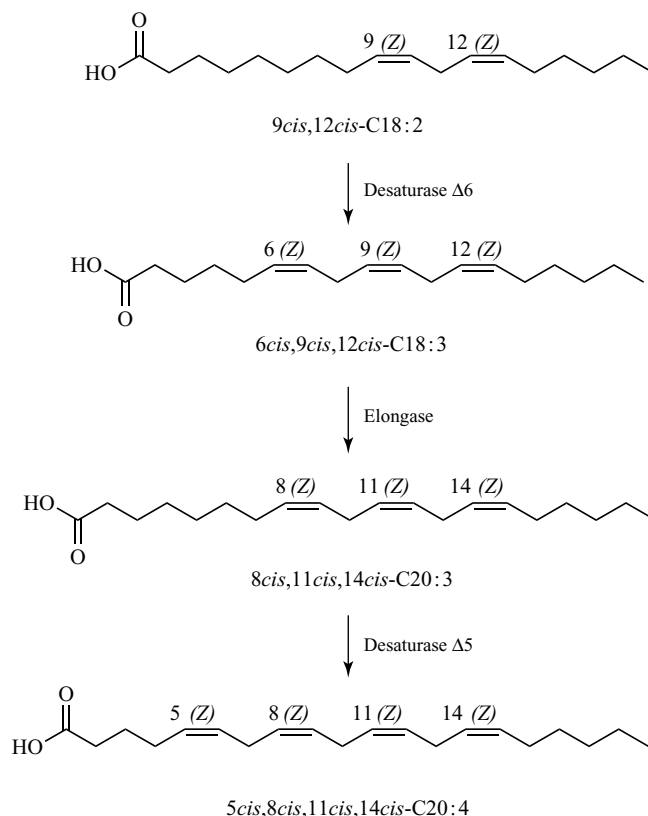


Figure 10 Biosynthetic pathway from linoleic acid ($9cis,12cis\text{-}C18:2$) to arachidonic acid ($5cis,8cis,11cis,14cis\text{-}C20:4$).

As mentioned in Section 3.1, the reactivity of AA can be successfully applied to distinguish the trans isomer dietary contribution from the trans isomer formation by free radicals. Taking into account that ω -6 and ω -3 are essential fatty acids, in the former series, the intake of linoleic acid ($9cis,12cis\text{-}18:2$) provides the precursor for AA ($5cis,8cis,11cis,14cis\text{-}20:4$) (Figure 10). The two double bonds of linoleic acid taken from the diet can be cis or trans, depending on whether the ingestion of partially hydrogenated oils occurs. On the other hand, tracing the biosynthetic transformation of linoleic acid to AA, other two double bonds are formed by desaturase enzymes at positions 5 and 8 of AA, which can be only cis, unless subsequently modified endogenously by free radical attack.

The identification of the 5-mono-trans and 8-mono-trans isomers of AA started the library of trans lipid isomers,^{89,92,94} to be used as markers of endogenous isomerization in biological samples.^{91,93}

As far as analytical methodologies for recognition of trans lipids are concerned, the total trans content can be identified by infrared spectroscopy through the absorbance of the trans double bond at a wave number of 966 cm^{-1} .^{108,109} However, for a lipidomic study, the identification of each isomer is crucially important, GC being the most effective and sensitive methodology to apply under appropriate conditions. Optimal resolution can be achieved as reported in case of ω -6 and ω -3 derivatives.^{89,94,110} Figure 11 shows an example of GC runs of the fatty acid methyl esters obtained by processing egg lecithin, before (A) and after (B) the isomerization catalyzed by thiyl radicals. The good resolution of cis and trans isomers can be appreciated.

Mass spectrometry, even with soft techniques, are not yet so efficient for the specific geometrical isomer distinction. Indeed, up to now, small differences are reported, which cannot be useful for complex mixtures, consisting of intensity differences in the mass peaks in the fast atom

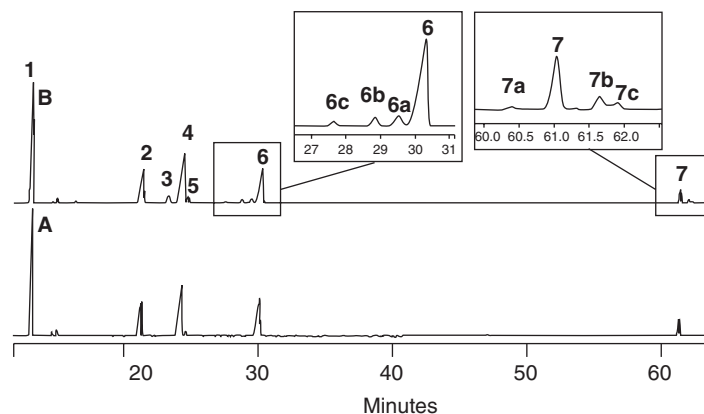


Figure 11 GC chromatograms of the cis and trans fatty acids found in egg lecithins (after transesterification of phospholipids): (A) before irradiation and (B) after irradiation in the presence of 2-mercaptoethanol. Fatty acid methyl esters: (1)-C16:0; (2)-C18:0; (3)-9-*trans*,C18:1; (4)-9-*cis*,C18:1; (5)-11-*cis*,C18:1; (6)-C18:2; (7)-C20:4. In the insets, the enlargements of the regions referred to trans isomers of linoleic acid (6a, 6b, and 6c) and arachidonic acid (7a, 7b, and 7c).

bomb mass spectrometry (FAB-MS) or chemical ionization mass spectrometry (CI-MS) spectra.¹¹¹ Trans isomers identification still rely on “classical” techniques, such as GC (coupled with flame ionization or mass spectrometry detection),¹⁰⁹ and on the “old” separation procedure by chromatography on silver nitrate-impregnated silica gel plates.¹¹² Lipids have to be extracted from the sample by known methodologies and then transformed into fatty acid methyl esters for the GC analysis.¹¹³

The detection of trans lipids have also been performed in humans, using blood as source of plasma or cell membranes. Obviously, other tissues can be used, but blood can be useful for routine analyses. Trans fatty acids have been detected in the plasma of smokers,¹¹⁴ in erythrocyte and lymphocyte membranes of children affected by atopic dermatitis⁹³ and in erythrocyte membrane phospholipids of centenarian offspring,^{91,115} in all cases being significantly different from healthy controls. It is remarkable that all these conditions can imply the increase in free radical stress and impaired defense.

4 FACTORS AFFECTING LIPID ISOMERIZATION

Biomimetic chemistry also allowed for a thorough examination of the factors that influence the cis–trans isomerization process of lipid double

bonds. The context of lipid isomerization can be correlated with the biological occurrence of an endogenous process; therefore, the models have to take into account the main factors present in a cellular environment: in particular, oxygen and free radical scavengers. Free radical reactivity can be studied in a competitive manner, taking into account the rate constant of each process and the relative concentrations of substrates at the reaction site. In this way, the evaluation of free radical reactivity leads to a predictable scenario, which is important to propose mechanistic views of biological processes. It is worth underlining that the chemical knowledge is the basis of the study on free radicals in biology and medicine.

4.1 The Role of Oxygen

The first factor to be considered in the biological environment is oxygen. The role of oxygen is very well known for PUFA causing the lipid peroxidation, a process that indeed occurs at the expense of fatty acids containing bisallylic positions. This field was first approached by chemists,^{1,116} which then motivated, and still it does, a huge amount of research in life sciences,¹¹⁷ as described in the articles **Lipid Peroxidation**. This topic can be certainly considered as a successful example of the fruitful relationship between chemical and biological investigations.

The steps that are interesting in the autooxidation process are the atom abstraction from the bisallylic position and the trapping by oxygen. Both steps can be involved in the protective action of thiol compounds. The peroxy radical can be quenched by H-donation from a thiol.¹¹⁸ It is also worth recalling that thiols react very fast with $\cdot\text{OH}$ radicals ($k = 1.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-163}$), therefore, quenching of initiation species can also occur. From all these reactions, thiyl radicals are generated, which can start the catalytic cycle of double bond isomerization with the rate constants described in Section 2.2. In the reactivity scenario, it should also be considered that thiyl radicals can add reversibly to oxygen (see **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**) (Figure 12).

It is likely that the formation of thiyl radicals even from a biological repair in the presence of oxygen can be connected with lipid isomerization, whereas the presence of thiol may inhibit the occurrence of lipid peroxidation. The first model experiments showed that the $\text{HOCH}_2\text{CH}_2\text{S}^\cdot$ radical induced cis–trans isomerization of methyl oleate or methyl linoleate in *t*-BuOH solutions saturated with 10% oxygen (corresponding to 0.23 mM, which is more than that of a well-oxygenated tissue, i.e., $40 \mu\text{M}$ ¹¹⁹), without loss of PUFA as estimated by quantitative analysis.¹⁹

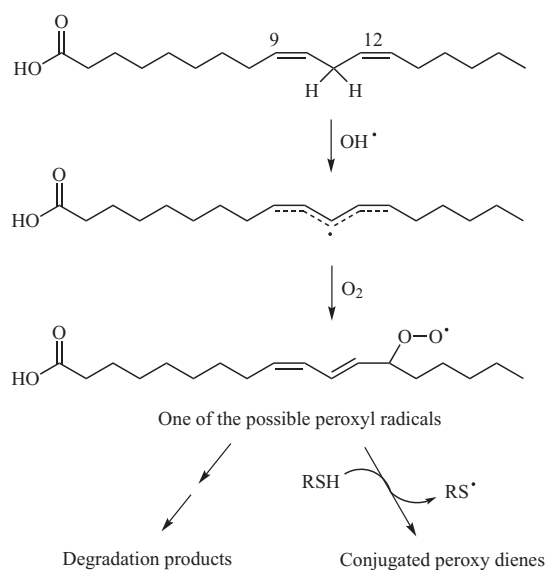


Figure 12 Initial steps of linoleic acid autooxidation and the intervention of thiol with formation of thiyl radicals.

It is worth mentioning that the study on oxidation of liposomes by hydroxyl and glutathyl radicals by γ -irradiation showed that degradation was prevented by adding the suspension with protein substrates. The competition with the multiple reactive sites present in the protein sequence was able to protect lipid oxidation initiated by thiyl radicals.¹²⁰ On the other hand, taking into account the protein desulfurization induced by radical damage described in Section 2.3.2, the scenario of thiyl radical formation and reactivity becomes more intriguing and worth further investigations in the model system of liposomes.

A recent competitive model of autooxidation/isomerization using micelles of linoleic acid, prepared by addition of a nonionic surfactant (TWEEN®-20) and 2-mercaptoethanol as the amphiphilic thiol, was assayed by ionizing radiation up to 400 Gy under various conditions. In air-equilibrated solutions, the cis–trans isomerization process was observed with a catalytic cycle of 370 together with a substantial amount of hydroperoxides. For the first time, peroxidation and isomerization processes supported by thiol compounds were compared, showing that the two processes can occur site by site and a 1:2 peroxidation:isomerization ratio was also estimated in the micelle model.¹²¹

4.2 Isomerization Inhibitors

As mentioned in Section 3.2, up to now there is no enzymatic system in eukaryotes able to recognize specifically trans fatty acids and process them, for example, by reconvert the cis double bond or eliminating the trans geometry. Evidently, alternative mechanisms provide protection to the cis double bond geometry of natural lipids. The molecular line of endogenous defense against free radicals comes from antioxidant vitamins and cofactors. Therefore, models were studied on the effectiveness of cis–trans isomerization in the presence of the most common antioxidants.²²

It should also be pointed out that the location of the antioxidants with respect to the various steps of the isomerization reaction is important. In fact, there is no doubt that the fatty acid double bond is located in a hydrophobic environment, especially considering the membrane bilayer compartment. On the other hand, if an initial generation of radicals

occurs in the aqueous compartment, hydrophilic antioxidants can also have a role in the quenching of isomerizing agents.

This different behavior suggests to perform experiments in homogeneous and heterogeneous systems in order to get a comprehensive scenario of the reactivity.

It is also important to assess the mechanism for the best inhibition of the lipid isomerization. For example, the RS[•] radical's ability to add to all-*trans* retinol ($1.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for GS[•]) and β -carotene ($2.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for HOCH₂CH₂S[•]) suggested that retinoid and carotenoid derivatives can be the best inhibitors of the cis–trans isomerization.^{122,123} Indeed, in *t*-BuOH solution of methyl oleate (0.15M), the isomerization catalyzed by the radiolytically generated HOCH₂CH₂S[•] radicals (75 mM 2-mercaptoethanol) showed an initial strong inhibition in the presence of 1 mM all-*trans* retinol acetate, the cis:trans isomeric ratio reaching the same equilibration point at a longer time.²² This lag time was due to the efficient scavenging of thiyl radicals from the conjugated diene until it is consumed.

The inhibition mechanism of α -tocopherol against thiyl radicals is based on the H-donation; this is a reversible process shifted to the right ($k_1 = 1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$; limit value of $k_{-1} < 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for the reaction of cysteinyl radical with Trolox¹²³). This behavior renders vitamin E not very efficient in the inhibition of the isomerization of methyl oleate, in the above described conditions, which showed only a little delay in reaching the same cis:trans mixture without antioxidant.

On the other hand, the reaction of thiyl radicals with ascorbate anion occurs with a high efficiency (10^8 – $10^9 \text{ M}^{-1} \text{ s}^{-1}$) by electron transfer.^{22,119} Since ascorbate is present at micromolar levels in blood serum (50 μM ¹²⁴) and increases up to 10-fold levels in tissues,¹²⁵ it becomes the most natural sink of thiyl radicals in the body. Using ascorbic acid 6-*O*-palmitate, which is soluble in lipophilic environment, the efficiency of this compound was tested, finding the inhibition of the isomerization process by five to six times compared with the uninhibited reaction. It was quite easy to predict, and to demonstrate in liposome vesicles using the amphiphilic 2-mercaptoethanol, that the inhibition order is α -tocopherol $\ll$ ascorbic acid 6-*O*-palmitate $<$ all-*trans* retinol acetate. As previously mentioned, vitamin C radical anion also

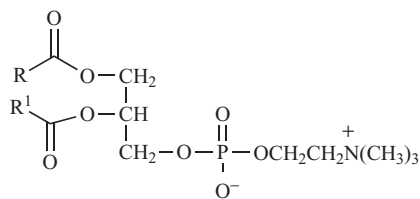
acts in the aqueous phase by electron transfer with the isomerizing species.

Focusing on the importance of the cis geometrical integrity in eukaryotic cells, the role of different compounds and their synergies against lipid isomerization are expected to be further addressed, also expanding the application in medicine and health. The anti-isomerizing activity can parallel the well-known antioxidant activity, which is a very active field of research with the discovery of a huge amount of molecules having this inhibiting effect. However, caution must be taken in order to distinguish the effectiveness of a simple chemical inhibition from the activity in a biological system; therefore, models and protocols must be chosen appropriately.

4.3 Environmental Factors: Bacterial Isomerization

In living organisms, the membrane compartment is a central point of regulation through the so-called homeoviscous adaptation, which represents the ability of modulating membrane functioning and properties, such as permeability and “fluidity,” to the various environmental conditions, without changing consistently the final metabolic responses.¹²⁶ There are different mechanisms to effect the necessary modification, one of the most important relying on the phospholipids, in particular changing saturated/unsaturated ratio, as well as the chain length or branching of the fatty acid residues. One of the reasons is a physical characteristic, since saturated, cis, and trans-unsaturated phospholipids display very different values of phase transition temperatures (T_m), that is, the temperature at which the transition between gel and liquid crystal phases occurs. For example, in the case of phosphatidyl cholines (Figure 13), where the R¹ fatty acid substituent is fixed as C16:0, and the R² varies through the series C18:0, 9*trans*-C18:1 and 9*cis*-C18:1, T_m values are 41.5, 35, and -3°C , respectively.¹²⁷

Also, the molecular shapes of saturated and cis-unsaturated lipids are quite different, since the cis geometry confers a kink in the lipid hydrocarbon chain, with an angle of circa 30° in the acyl chain. It is interesting to note that the lipid isomerization corresponds to a “cancellation” of the bending,



R = C16:0

R¹ = C18:0, or 9*trans*-C18:1, or 9*cis*-C18:1

Figure 13 Phosphatidyl cholines with different fatty acids in position 2 of glycerol.

because *trans* isomers also have a straight molecular shape, more similar to that of saturated compounds (Figure 14).

The packing of a lipid assembly follows the order: saturated > *trans*-unsaturated > *cis*-unsaturated, whereas the gross membrane property of “fluidity,” as well as permeability, follows the inverted order, so that at a physiological temperature, the *cis*-unsaturated residue ensures the most “fluid” state to the lipid assembly.

Membranes are the most sensitive cellular site to a stress. The fastest adaptive response occurs in membranes and is affected through the variation of the fatty acid composition of membrane lipids. In particular, the degree of phospholipid saturation is well known in animals and plants: at low temperatures, adaptation is afforded by enrichment of polyunsaturated lipids, whereas at high temperatures, the saturated fatty acid residues play the most important role for keeping the right properties of the lipid assembly.^{128–130}

With this premise, it is surprising that the *cis* and *trans* lipid geometry makes part of the regulation and adaptation responses only for prokaryotes.^{131–133} As a matter of fact, *trans* fatty acids were detected

as phospholipid residues in membranes of bacteria, and they were not dependent on growth, so that they did not derive from the *de novo* synthesis. In fact, they were also present in nongrowing cells, when lipid biosynthesis is absent and the total saturated and unsaturated fatty acid content cannot vary. Extending the analyses to other bacteria, it was shown that in obligate aerobic and anaerobic bacteria, biosynthesis provides oleic or palmitoleic acid, respectively, but formation of *trans* double bonds was not related to biosynthetic routes. The *trans* formation increased proportionally to the chemical or environmental stress applied to the bacterial cultures. *Trans* isomers were only geometrical isomers, in particular 9*trans*-C16:1 was found in anaerobic bacteria, such as *Pseudomonas* and *Vibrio* strains, as determined by GC analyses. It is worth noting that microbiologists apply a protocol in order to check the structure of the *trans* isomers present in bacterial lipids and the double bond position along the hydrocarbon chain, by preparing the corresponding methylthio derivatives by dimethyl disulfide addition, which have typical GC/MS spectra.¹³⁴

By adding a monounsaturated fatty acid, such as 9*cis*-C18:1, that is not present in *Pseudomonas putida* P8, it was incorporated in the membrane and, under addition of toxic compounds, also converted to the corresponding *trans* isomer.¹³⁵ The total amount of monounsaturated fatty acid remained constant, but the *cis/trans* ratio changed according to the stress conditions. This was the proof of a biological path carried out by a specific enzyme, which worked without changing the position of the double bond, but only its geometry. The existence of a *cis*–*trans* isomerase (Cti) was first hypothesized and then proved by cloning the Cti gene from *Pseudomonas* strains, followed by purification and

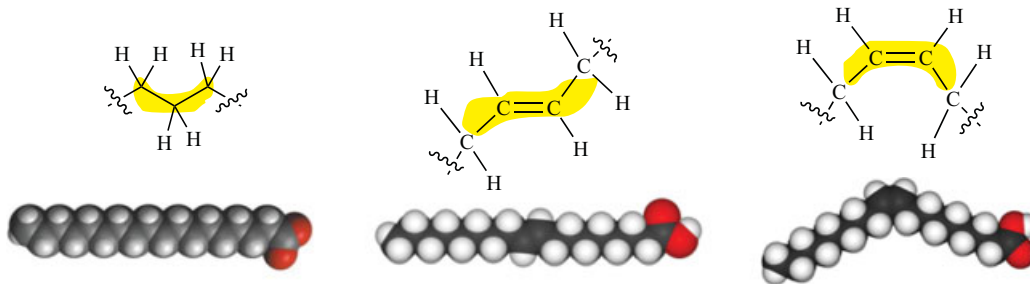


Figure 14 The molecular shapes of saturated, *trans* and *cis* fatty acids.

characterization of the enzyme.¹³⁶ Cti also work under anoxic conditions as well as in the presence of chelating agents, but the activity was strongly inhibited by 1 mM catecholic antioxidants, such as α -tocopherol and nordihydroguaric acid.¹³⁷ Some hypotheses of the enzyme activity have been forwarded, but the mechanism is far from being fully understood. In a study on *Pseudomonas* sp. strain E-3, the similarity between Cti and LOX was hypothesized on the basis of the common inhibition given by antioxidants.¹³⁷ However, chelating agents, which instead do not affect the isomerization, also inhibit LOX. A second mechanistic hypothesis was then formulated, consisting of the hydration–dehydration mechanism, similar to the formation of 3-*trans*-enoyl-CoA from the corresponding *cis* isomer.¹³⁸ Another mechanism based on the analysis of the carbon isotope fractionation experiment of the *cis*–*trans* isomerization proposed that the enzyme forms with the unsaturated substrate a complex as an intermediate, which allows the rotation of the carbon–carbon double bond to occur.¹³⁹ The involvement of free radicals during the enzymatic isomerization process is still to be demonstrated. It is also worth underlining that the lipid isomerization highlights its role as an evolutionary symbol, as already mentioned in the Section 2.1, since it means survival and adaptation for prokaryotes, whereas it means damage and loss of natural structural feature for eukaryotic organisms.

5 CONCLUSIONS

In the past years, lipid isomerization has been the subject of research in an interdisciplinary manner:

- in biomimetic chemistry showing the importance of liposomes to study the *trans* fatty acid formation and all factors influencing the reactivity; these studies also addressed the synthesis of molecular libraries made of *trans* lipids useful to biological and medical studies as well the role of S-containing compounds under free radical conditions;
- in biology, for a thorough understanding of membrane lipid characteristics and properties and the fatty acid behavior, as well as of the reactivity of S-containing compounds either as repairing and damaging agents in free radical stress;
- in lipidomics, applying the knowledge gathered from the models for studying physiological and pathological conditions, where a free radical stress can be linked to a change in the membrane lipids asset and the geometrical configuration.

In all these fields, the lipid isomerization will continue to be studied in order to get a complete picture of the role of geometry in life sciences. Owing to the relationships with lipid oxidative processes, lipid isomerization is also expected to gain more and more consideration either in the field of biomarker discovery and in the applications to medicine and health, thus contributing to a better definition of the scenario of the free radical consequences in living systems.

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Antioxidants in Chemistry and Biology

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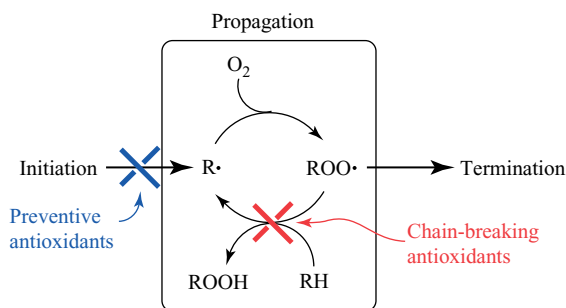
1 ANTIOXIDANTS

Antioxidants can be broadly defined as compounds capable of slowing the overall rate of hydrocarbon oxidation. Antioxidants comprise an incredibly vast and heterogeneous family of small organic and inorganic molecules, as well as macromolecules and enzymes. This topic can hardly be addressed as a whole without focusing on a specific process, substrate, or environment. Here, we will focus primarily on processes occurring in biological systems or in solutions of organic compounds, wherein antioxidants often operate by inhibiting the free-radical chain oxidation (autoxidation) of organic substrates by lowering the steady concentration of chain-carrying radicals. In biological systems, the most relevant substrates for autoxidation lipids, and most often polyunsaturated fatty acids are found either as triglycerides or cholesterol esters in cellular membranes or circulating lipoproteins. The autoxidation of lipids is a process exemplified by the rancidification of edible fats and which parallels the oxidative degradation of motor oils and polymers. The process can be generalized for a substrate R–H (i.e., lipid or hydrocarbon) as in Scheme 1. The reaction is initiated by a radical species which, regardless of origin (e.g., photochemical, mitochondrial) or structure, abstracts a H atom from the substrate to form an alkyl radical R[•]. This radical then reacts with O₂ at essentially diffusion-controlled rates to form a peroxy radical (ROO[•]) which can propagate the chain reaction

Lipid Peroxidation.

Antioxidants capable of directly impairing this radical chain reaction are divided into two groups depending on their mechanism of interference. *Preventive antioxidants* interfere with the initiation process; that is, they retard or stop the initial formation of radical species. Examples of such are the enzyme catalase, metal chelators such as ethylenediaminetetraacetic acid (EDTA), and UV filters such as 2-hydroxybenzophenone. *Chain-breaking antioxidants* slow down autoxidation by competing with the propagation reactions; that is, they react with peroxy radicals faster than the oxidizable substrate to form species that do not propagate the oxidation chain. Representative examples include vitamins E and C as well as plant-derived flavonoids. In addition to these direct antioxidants, compounds that do not themselves possess antioxidant activity in solution or in model systems (i.e., micelles, liposomes, etc.), but can stimulate and increase the efficacy of the endogenous antioxidant defenses in biological systems, are usually classified as *indirect antioxidants*.

In the interest of space and given the context of this article as part of a comprehensive ensemble dealing with the most important aspects of free radicals in chemistry and biology, we will focus on radical-trapping, chain-breaking antioxidants in the following sections, while the discussion on preventive as well as on indirect antioxidants



Scheme 1 Mechanisms by which antioxidants can directly interfere with the free-radical autoxidation (peroxidation) process.

will be limited to some of the most relevant examples.

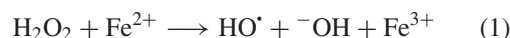
1.1 Preventive Antioxidants

1.1.1 Small Molecules

The autoxidative degradation of hydrocarbons is often initiated by light, either through Norrish-type carbonyl photochemistry that results in alkyl (or acyl) radicals which subsequently react with O_2 to yield chain-propagating peroxy radicals, or through the direct photolysis of labile (hydro)peroxide $O-O$ bonds to yield chain-initiating alkoxy radicals. This is the case for organic materials ranging from plastics¹ to human skin.² Therefore, UV filters, such as endogenous melanin or zinc oxide and benzophenone derivatives, which are able to absorb ultraviolet radiation (chemical filters, e.g., benzophenone) or reflect it (physical filters, e.g., zinc oxide), are among the most important preventive antioxidants. UV filters have long been employed for the protection of polymeric materials³

and are routinely incorporated in the formulation of protective paints and coatings for a variety of materials exposed to both air and light, as well as in the formulation of pharmaceuticals and cosmetics for the protection of human skin.⁴

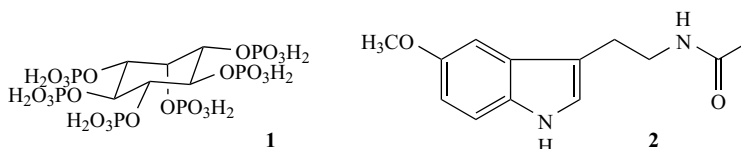
Hydrogen peroxide and organic hydroperoxides can also give rise to chain-initiating hydroxyl and/or alkoxy radicals through their reduction by low-valent transition-metal ions (e.g., Fe^{2+} , Cu^{1+}). The best known example is the Fenton reaction (1), which involves the formation of a hydroxyl radical via a dissociative electron transfer from $Fe(II)$ to H_2O_2 .



As such, transition-metal chelating agents are important preventive antioxidants, acting to remove such ions from solution or maintain them in a higher oxidation state. EDTA is an example of a powerful chelating agent for transition metals and has been widely employed as an antioxidant in the food and cosmetic industries. Diethylenetriaminepentaacetic acid (DTPA) and other polyaminopolycarboxylic acids share similar chelating and antioxidant properties.

Likewise, desferrioxamine, produced by *Streptomyces pilosus*, and other natural and synthetic hydroxamic acid-containing siderophores⁵ with high affinity for iron ions, have been used to treat iron-poisoning and hemochromatosis and to decrease oxidative stress associated with the accumulation of redox-active iron in blood and tissues.^{6,7} Phytic acid (inositol hexakisphosphate, **1**), a natural component of many fruits and vegetables, also has good iron-chelating ability, which is responsible for its antioxidant properties and has stimulated interest in its use as a health-promoting nutrient.⁸

Melatonin (**2**), a pineal hormone well known for its activity as a regulator of circadian rhythm, has been ascribed several biological properties



associated with its antioxidant activity. While it has been shown to possess no relevant chain-breaking antioxidant behavior, it is an effective inhibitor of transition-metal-initiated lipid peroxidation.⁹

In addition to possessing moderate chain-breaking antioxidant behavior, curcumin, the compound believed to be responsible for the medicinal activity of the spice cumin (*Curcuma longa*), has $\log K_f = 5.2$ and 5.1 for Cu^{2+} and Fe^{2+} ,¹⁰ respectively, which has prompted its study in the therapy of Alzheimer's disease. Similar affinity has been recorded for synthetic bis-tacrine anti-Alzheimer drugs.¹¹ Indeed, transition-metal chelation and the prevention of increased oxidative stress associated with Fenton-type chemistry are currently seen as part of the therapeutic strategy for neurological disorders.

Compounds capable of decomposing hydroperoxides and hydrogen peroxide to nonradical products, either stoichiometrically or catalytically, are among the most important preventive antioxidants. Organophosphines such as triphenylphosphine (Ph_3P) and organophosphites $((\text{RO})_3\text{P})$ react in a 1:1 stoichiometry with hydroperoxides to yield the corresponding alcohols and phosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) or organophosphate $((\text{RO})_3\text{P}=\text{O})$, respectively. Both phosphines and phosphites also react with chain-carrying peroxy radicals; however, the product of the reaction is the corresponding alkoxy radical, which is able to initiate a new oxidation chain. Thus, phosphines and phosphites are preventive antioxidants, but do not act as chain-breaking antioxidants.¹² Aryl and alkyl sulfides react with 1 equiv of hydroperoxides to form the corresponding sulfoxide and with a second equivalent to form sulfones, yielding, respectively, 1 or 2 equiv of alcohol.¹² Similarly, disulfides, RSSR , react with hydroperoxides to form thiosulfates,

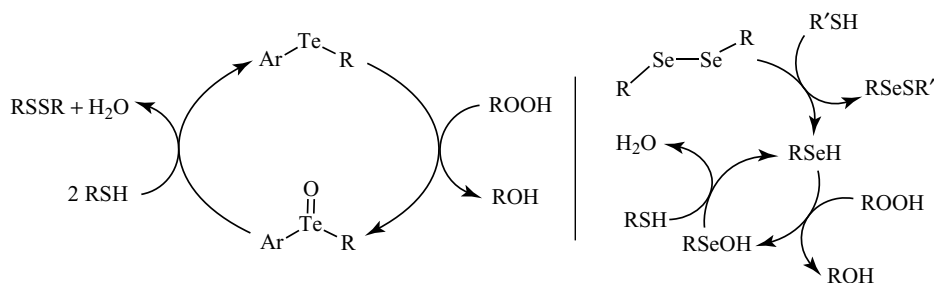
RS(O)SR , which can decompose to yield sulfenic acids RSOH : their chemistry will be discussed in Section 3.

Several Se(II) - and Te(II) -containing organic compounds have been found to catalytically decompose hydrogen peroxide and organic hydroperoxides to water or alcohols respectively, in the presence of a stoichiometric reducing agent, most commonly a thiol, thereby behaving similar to the glutathione peroxidase (GPx) system (see below).^{13,14} Diselenides and ditellurides normally have even better catalytic activity, and in some cases they have been suggested for medicinal applications.¹⁵ Although the mechanisms can be quite complex, they are often exemplified by Scheme 2.

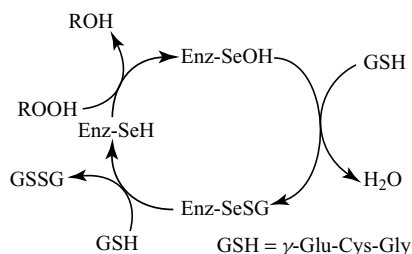
1.1.2 Enzymes and Proteins

Serum proteins, such as transferrin and ceruloplasmin, transport iron and copper ions, respectively, such that they are not free to catalyze Fenton-type chemistry and induce oxidative damage to the cell. These are examples of the so-called metal-deactivating preventive antioxidants.¹⁶ It has been shown that protein glycation can reactivate metal ions (e.g., by reducing protein affinity), thereby modulating their antioxidant activity.¹⁷

GPxs are a superfamily of enzymes containing reduced Se(II) in their active site. Their primary role is the reduction of hydrogen peroxide and organic hydroperoxides to water and alcohols, respectively. To do so, they make use of the tripeptide glutathione (GSH, γ -glutamylcysteinyl glycine) as the stoichiometric reducing agent.¹⁸ The proposed catalytic cycle at is depicted in Scheme 3.

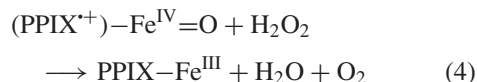
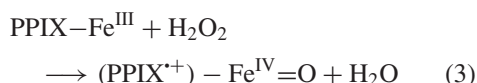
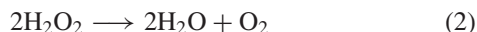


Scheme 2 Hydroperoxide decomposition by organochalcogen species.



Scheme 3 Catalytic cycle of glutathione peroxidase (GPx).

Catalase, an enzyme composed of four protein chains each bringing a protoporphyrin IX (PPIX)-ligated iron, catalyzes the decomposition of hydrogen peroxide to water and molecular oxygen (2). This reaction is known to occur through the intervention of a high-valent iron-oxo complex, called compound I, as exemplified in (3 and 4).¹⁹



Monofunctional heme peroxidases and catalase-peroxidases (KatGs) catalyze the same reaction via a different suggested mechanism; in addition, nonheme Mn-catalases also decompose H_2O_2 to H_2O and O_2 via the intervention of a Mn(III)/Mn(IV) redox couple.²⁰ Catalase and other monofunctional heme peroxidases can catalyze the reduction of hydrogen peroxide at the expense of small molecules such as alcohols, aldehydes, phenols, toxins, or other reducing agents. Thioredoxin peroxidases (TPxs) are a family of nonheme peroxidases, whose active site contains the reduced cysteine residue $-\text{SH}$. TPx reduces hydrogen peroxide using thioredoxin as the stoichiometric reductant.²¹

Superoxide dismutases (SODs) are the primary defense against the damage that can be caused by superoxide ($\text{O}_2^{\bullet-}$) and its reactive progeny, such as its conjugate acid, the hydroperoxyl radical. These enzymes catalyze the dismutation of $\text{O}_2^{\bullet-}$ to

hydrogen peroxide and molecular oxygen (5).



Different types of SOD, inducible and constitutive, found in different biological systems may differ also in the redox-active metal(s) in the catalytic site. For instance, constitutive Fe-SOD and inducible Mn-SOD are found in *Escherichia coli*, while Mn-SOD and Cu,Zn-SOD are found in mammals; in all cases, together with catalases, they strongly contribute to the antioxidant defense machinery, as demonstrated by comparison with knock-out animals.²²

NAD(P)H:quinoneoxidoreductase (NQO) catalyzes the flavin-mediated two-electron reduction of quinones to the corresponding hydroquinones, avoiding the intermediacy of semiquinone radicals (anions), which would react with molecular oxygen to form hydroperoxyl (superoxide). These important antioxidant enzymes act both as preventive antioxidants because they avoid the formation of superoxide and as indirect antioxidants since they increase the amount of chain-breaking hydroquinones, contributing to the cellular antioxidant pool.²³

1.2 Indirect Antioxidants

Indirect antioxidants can act in many ways, but all ultimately enhance the activity of the antioxidant defense machinery, thereby leading to a more effective elimination of reactive-oxygen species (ROS) by balancing their generation and decreasing oxidative stress.²⁴

1.2.1 Enzymes

Glutathione reductase (GR)²⁵ and thioredoxin reductase (TR)²⁶ are examples of indirect antioxidants as they use NAD(P)H to reduce cysteine disulfides in glutathione and thioredoxin, respectively, thereby increasing the pool of cellular antioxidants. Similarly, biliverdin reductase reduces biliverdin to the strong antioxidant bilirubin, and is therefore a major cytoprotectant.²⁷

Inducible heme-oxygenase-1 (HO-1) and constitutive heme-oxygenase-2 (HO-2) are expressed in several mammalian tissues and share the task

of converting pro-oxidant heme into biliverdin, which is subsequently reduced to bilirubin; therefore, both HO-1 and HO-2 can be regarded as indirect antioxidant enzymes.²⁸ Interestingly, HO-1, as well as NQO and other antioxidant enzymes, can be induced through so-called antioxidant responsive elements (AREs), which regulate gene transcription and antioxidant protein overexpression.²⁹

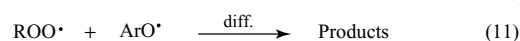
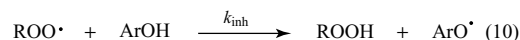
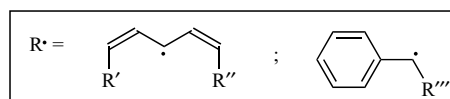
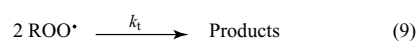
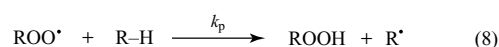
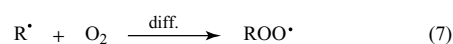
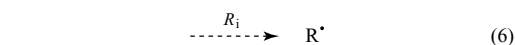
1.2.2 Small Molecules

AREs are sensitive to stimuli from redox-active xenobiotics; particularly quinones, but also hydroquinones and catechols. These compounds and many others (e.g., flavonoids), can act as both chain-breaking antioxidants (see Section 2) and indirect antioxidants as they increase the expression of antioxidant enzymes in the cell.

Isothiocyanates (ITCs) are the breakdown products formed by myrosinase hydrolysis of glucosinolates (GLs) contained in most Brassicaceae vegetables such as broccoli and cauliflower (Scheme 4). They have been attributed a multitude of health-promoting properties associated with their indirect antioxidant and detoxifying activity; indeed, many of them, most notably sulforaphane from *Brassica oleracea* var. *italica*, are potent inducers of antioxidant and phase II enzymes via stimulation of ARE.³⁰

2 CHEMISTRY OF PHENOLIC ANTIOXIDANTS

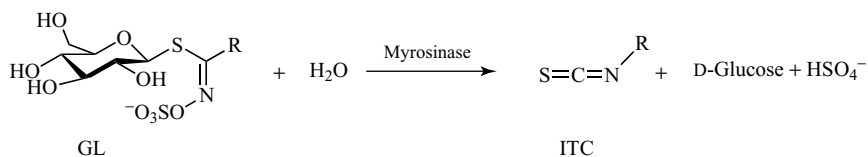
Phenols comprise the archetype of radical-trapping chain-breaking antioxidants. The antioxidant activity of phenols is the result of their rapid reaction with chain-carrying peroxy radicals, which far outpaces the rate at which peroxy radicals propagate hydrocarbon autoxidation. The general mechanism of the free-radical autoxidation of a substrate R-H



Scheme 5 Hydrocarbon autoxidation (6–9) and its inhibition by phenolic antioxidants (10 and 11).

and its inhibition by a phenol ArOH is given in Scheme 5.^{12,31,32}

As mentioned above, and elsewhere in this volume **Lipid Peroxidation**, hydrocarbon autoxidation is a free-radical chain reaction (Scheme 5). The process is initiated via one of the many ways already described, leading to the formation of an alkyl radical (6), which immediately reacts with molecular oxygen to form a peroxy radical (7). In the absence of a suitable inhibitor, the peroxy radical reacts with the oxidizable substrate (normally an unsaturated hydrocarbon) to generate the corresponding hydroperoxide (ROOH) and a new carbon-centered radical (8). The propagation sequence (7 and 8) competes with a number of termination events, most commonly the radical–radical self-quenching of peroxy radicals (9) to yield nonradical products. If propagation is faster than termination, the overall process becomes a chain reaction (autoxidation) and, following any initiation event, several propagation steps can take place before the chain reaction is terminated. The reaction in (7) is extremely fast and nearly diffusion-controlled (k_7 typically ranges from



Scheme 4 Formation of isothiocyanates from glucosinolates.

2×10^9 to $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ in organic solvents at 300 K);³³ therefore the rate-determining step for chain propagation is given in (8) and the autoxidation of a substrate occurs efficiently when $k_p[\text{RH}] \gg 2k_t[\text{ROO}^*]_{\text{ss}}$, where $[\text{ROO}^*]_{\text{ss}}$ is the steady-state concentration of peroxy radicals. Since the rate of autoxidation depends on the ratio $k_p/(2k_t)^{1/2}$ (see below), this quantity is commonly referred to as the *oxidizability* of the substrate; some examples are given in Table 1 alongside their respective k_p and $2k_t$ values. It is clear from these values that the oxidizability of hydrocarbons can vary considerably, from very low values for unbranched saturated compounds to 1000-fold higher for polyunsaturated fatty acid esters and hydrocarbons.³³

Chain-breaking antioxidants, such as phenols, offer an alternative reaction pathway to propagation and termination, to inhibit or stop the autoxidation. They react with peroxy radicals (10) to yield a stabilized aryloxy radical (ArO^*) that is sufficiently unreactive toward the substrate RH to be unable to further propagate the oxidative chain. Indeed, in solution, phenoxyl radicals do not react with the oxidizable substrate at all; rather, they are sufficiently long-lived to “wait” for a second peroxy radical that is rapidly quenched (11) by adding to the aromatic ring to form a variety of peroxy-cyclohexadienones. For example, the reaction of 2,6-di-*tert*-butyl-4-methylphenol (BHT) with alkylperoxy radicals is illustrated in Scheme 6.

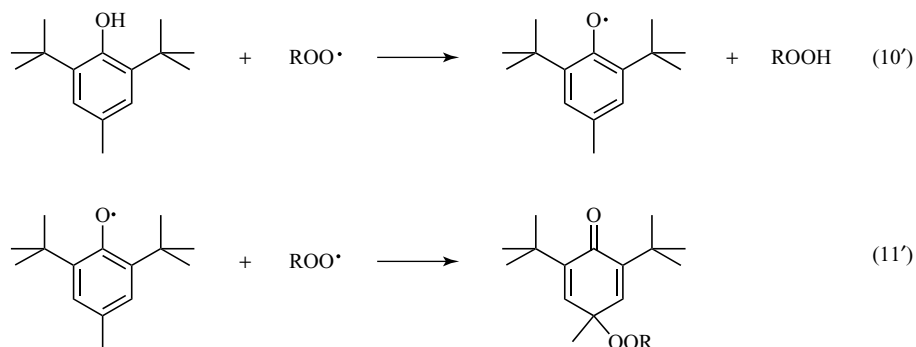
Table 1 Rate constants for the autoxidation of selected organic substrates in chlorobenzene at 303 K.³⁴

Substrate	$k_p \text{ (M}^{-1} \text{ s}^{-1}\text{)}$	$2k_t \text{ (M}^{-1} \text{ s}^{-1}\text{)}$	$k_p/(2k_t)^{1/2} \times 10^5$
Hexadecane ^a	~0.01	~ 1.5×10^6	~0.8
Tetrahydrofuran ³⁵	4.4	3.0×10^6	254.0
Toluene ³⁶	0.24	~ 3×10^8	1.4
<i>n</i> -Butylbenzene ³⁶	0.57	5.0×10^7	8.1
Cumene ³⁷	0.34	4.5×10^4	160.0
Styrene ³⁸	41.0	4.2×10^7	890.0
Methyl methacrylate ^{b,39}	2.96 ^c	2.0×10^6	209.0
Acrylic acid ^{b,39}	2.77	1.4×10^7	75.8
1,4-Cyclohexadiene ³⁶	1400.0	1.3×10^9	3900.0
Methyl oleate ³⁶	0.89	1.0×10^6	89.0
Methyl linoleate ³⁶	62.0	8.8×10^6	2100.0
Methyl linoleate ³⁶	236.0	3.6×10^7	3900.0

^aData were estimated at 30 °C from the rates for H abstraction by $(\text{CH}_3)_3\text{COO}^*$ radical (k_p)⁴⁰ and the self-termination of *sec*-butyl peroxy radicals ($2k_t$).⁴¹

^bValues at 333 K.

^cThe value at 303 K is $k_p = 1.0$, Ref. 34.



Scheme 6 Reactions associated with the chain-breaking antioxidant activity of BHT.

Since reaction (11) is very fast for common phenolic antioxidants⁴² (e.g., $k_{11} = 4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for α -tocopheroxyl in chlorobenzene at 318 K⁴³), according to Scheme 5, each molecule of antioxidant quenches two peroxy radicals (i.e., it blocks two oxidative chains); therefore a phenolic antioxidant is said to have a *stoichiometric factor* of 2. Experimentally, the stoichiometric factor determined for the majority of monophenolic antioxidants in typical inhibited autoxidations at 303–323 K in organic solution is $n = 1.95 \pm 0.15$, which is in excellent agreement with the conventional value $n = 2$.

Despite its obvious relevance, the stoichiometric factor is not the most important parameter to consider in evaluating the performance of a chain-breaking antioxidant. In fact, it is the inhibition rate constant (k_{inh})—the rate constant for reaction (10)—that should be considered most important. Since inhibition competes with propagation, in order for a chain-breaking antioxidant to be effective, reaction (10) should be significantly faster than reaction (8), that is, $k_{\text{inh}}[\text{ArOH}] \gg k_{\text{p}}[\text{RH}]$. Phenolic antioxidants generally have k_{inh} values that fall into the range 10^4 – $10^6 \text{ M}^{-1} \text{ s}^{-1}$, with only very few exceptions. However, while the antioxidant activity of a given phenol will be directly proportional to its k_{inh} , its actual performance depends also on the substrate. For instance, BHT has a $k_{\text{inh}} = 1.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ in chlorobenzene at 303 K;^{37,44} in this solvent and temperature, it gives excellent protection of cumene ($k_{\text{p}} = 0.34 \text{ M}^{-1} \text{ s}^{-1}$) and quite good protection of tetrahydrofuran ($k_{\text{p}} = 4.4 \text{ M}^{-1} \text{ s}^{-1}$) but offers only very modest protection of styrene ($k_{\text{p}} = 41 \text{ M}^{-1} \text{ s}^{-1}$). With styrene, it is normally unable to completely stop the oxidation chain reaction, but it still competes with propagation, slowing down the oxidation of the substrate. For this reason, it might be more appropriate to describe it as a “retarder” of autoxidation in this context rather than an “inhibitor”, although such a description would have no actual chemical meaning. Indeed, any classification based on the antioxidant performance is valid only for a specific substrate and experimental setting (BHT is a retarder for styrene and an inhibitor for cumene) and should be avoided, as it might be misleading. On the other hand, it should be noted that the magnitude of k_{inh} is nearly independent of the oxidizable substrate; that is, it is very similar for different chain-carrying alkylperoxyl radicals,⁴⁴ with

the exception of very electron-poor species such as $\text{Cl}_3\text{COO}^\bullet$ which exhibit much higher reactivity.⁴⁵

2.1 Kinetic Methods

Quantitative measurements of the antioxidant activity of chain-breaking antioxidants, such as phenols, imply knowledge of their reaction kinetics with chain-carrying peroxy radicals. These measurements are normally performed in nonpolar organic solvents because of the good solubility of both the oxidizable substrates and most antioxidants, and also because they reproduce, to some extent, the apolar environment found in the lipid core of biomembranes and low-density lipoproteins (LDLs). Kinetic studies in water or aqueous environments provide complementary information; they often involve hydroperoxyl/superoxide radicals ($\text{HOO}^\bullet/\text{O}_2^{\bullet-}$). Beside these studies, a large body of scientific literature deals with the evaluation of the antioxidant activity, most often of natural compounds or crude natural extracts, by means of a number of rapid assays such as trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbing capacity (ORAC), ferric reducing antioxidant power (FRAP), total radical-trapping antioxidant potential (TRAP), $\text{Cl}_3\text{COO}^\bullet$ assay, DPPH $^\bullet$ quenching assay, carotene-bleaching assay, crocin-bleaching assay, and several variations of these methods. All are based on a single fluorimetric or spectrophotometric reading, after a fixed time, to assess the development or disappearance of absorbance/fluorescence as a consequence of the reaction of the test compound with some radical species or oxidizing agent. In most cases, the radical species used in the assay are not physiological relevant species and have no relation with the actual autoxidation process. Often, results are expressed as the extent of quenching of the oxidizing species or as IC₅₀, which is the concentration of the “antioxidant” that will quench 50% of the oxidant after a fixed time. Therefore, in most cases these assays are different forms of *titration of the reducing ability* of the test compounds or extracts and afford no information on the kinetics of their radical-trapping chain-breaking antioxidant activity. While these measurements can be useful to make a rapid comparison of the antioxidant content of biological samples or extracts of unknown composition,

they should never be regarded as quantitative measurements of the antioxidant activity or be used to draw structure–activity relationships.

2.1.1 Inhibited Autoxidations

Inhibited autoxidation studies are arguably the best established among the quantitative approaches to evaluate the performance of chain-breaking antioxidants. They comprise determining the kinetics of the autoxidation of an appropriately oxidizable substrate under controlled conditions in the presence and absence of variable concentrations of an antioxidant. In order to control the kinetics of the autoxidation, the process is generally initiated by means of a compound that yields radicals at a known rate at a given temperature, so as to ensure a constant and well-defined rate of initiation (R_i , see (6)). The most common radical precursors are azo-alkanes, such as the lipid-soluble 2,2'-azobis(isobutyronitrile) (AIBN), which has a half-life $t_{1/2} = 2660$ hours at 303 K in benzene,⁴⁶ or 2,2'-azobis(2,4-dimethylvaleronitrile) (AMVN), which decomposes about 10 times faster ($t_{1/2} = 320$ hours at 303 K in toluene).⁴⁶ Water-soluble 2,2'-azobis(2-methyl-2-propanimidamide) (ABAP or AAPH) is often employed for studies in aqueous or hydroalcoholic solutions ($t_{1/2} = 330$ hours at 310 K in water, pH 7).⁴⁷ Other radical precursors such as peresters and peroxides are less common.

A general overview of radical initiators for lipid peroxidation has been provided by Niki.⁴⁸

The kinetics of inhibited autoxidation can be determined either by monitoring the disappearance of reactants—most commonly O_2 —or the formation of oxidation products—most commonly hydroperoxides. In the former experiment, the autoxidation is performed in a closed system and the consumption of oxygen is monitored during the reaction by one of several methods. The best established method is based on the use of a differential pressure transducer (Figure 1).^{44,49} Therein two identical reaction vessels placed in a thermostated bath are connected through low-dead-volume, inert teflon (PTFE) high performance liquid chromatography (HPLC) tubing to the opposite sides of a variable reluctance membrane of the differential pressure transducer and the equilibration/isolation of the two channels is allowed by a three-way valve. Both reaction vessels (reference and sample) are loaded with a mixture containing the oxidizable substrate (typically 1–4 M in concentration) and the initiator in a suitable solvent (typically chlorobenzene) having low vapor pressure at the temperature of the experiment (normally 30–50 °C). Solutions are continuously stirred to ensure equilibration with air inside the system. The antioxidant can be injected into the reaction vessels by means of a microsyringe through the opening of a glass tap. Following thermal equilibration, the two vessels are isolated, and any difference in pressure between the two channels is monitored as a function of time, after digitalization of the signal from the transducer.^{50,51}

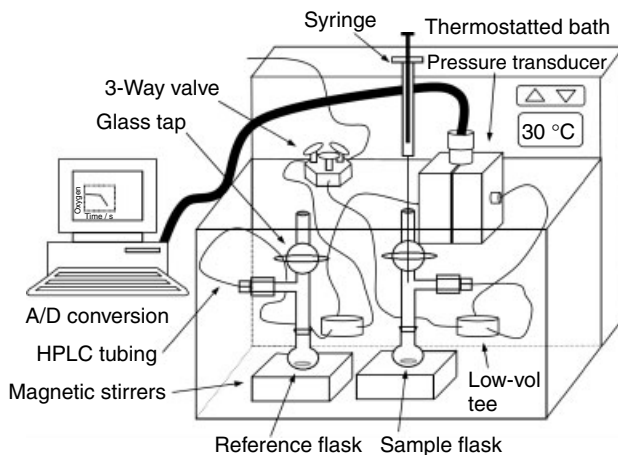
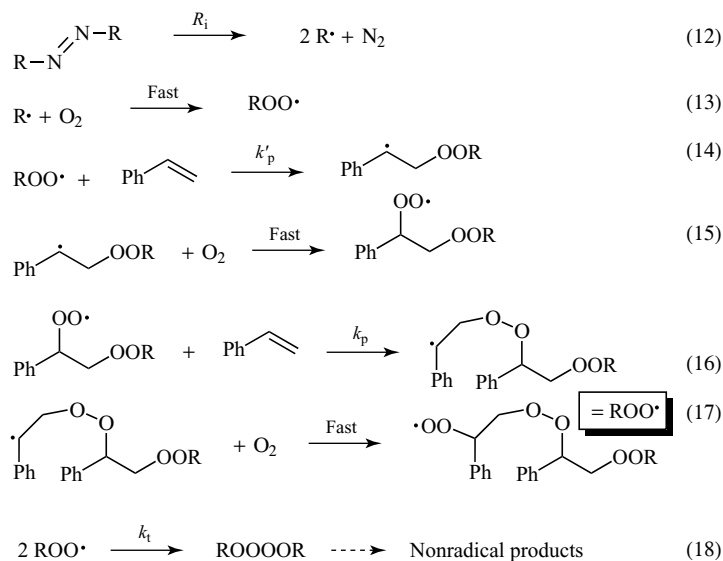


Figure 1 Differential oxygen uptake apparatus for autoxidation kinetics.



Scheme 7 Relevant reactions in the uninhibited autoxidation of styrene.

The reactions occurring in the reference/sample flasks are described by (12)–(18) using styrene as an example of the oxidizable substrate (Scheme 7).

Unlike alkylarenes (e.g., cumene) and polyunsaturated fatty acids/esters (e.g., methyl linoleate), whose propagation proceed by H-atom abstraction by the chain-carrying peroxy radicals (as exemplified by (6)–(9)), styrene and other substrates which possess an activated C=C double (e.g., acrylic acid) propagate by addition of the peroxy radical to the double bond (14 and 16), thereby forming a styrene-dioxygen (or other monomer-dioxygen) copolymer in the autoxidation. Still, the kinetics of the autoxidation are identical to those of nonpolymerizable hydrocarbons and can be subjected to the same kinetic treatment.

Decomposition of the azo-initiator releases N_2 (12), after which the consumption of oxygen begins (13) to form the initial peroxy radicals. Following each initiation event, more O_2 is consumed during the propagation steps (13–16) until termination (17) occurs. Therefore, the pressure balance of the autoxidation depends on the number of propagation cycles occurring after each initiation event—commonly called the *chain length of autoxidation* by analogy with polymerization. Since the same reaction occurs in both the reference and sample chambers, the pressure difference that is recorded should be zero. However, in a typical experiment, a large

excess (1 mM) of a very good antioxidant (often α -tocopherol (α -TOH), $k_{\text{inh}} = 3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$) is injected into the reference flask to completely stop autoxidation (except the initiation step). As a result, the pressure difference recorded between the two channels is due solely to the consumption of oxygen in the sample chamber, where it reflects the extent of propagation. Only the initial stages of autoxidation are monitored, under an excess of azo-initiator, in order to eliminate kinetic complications due to chain transfer reactions and self-initiation phenomena.³⁴ These oxygen consumption plots are therefore linear, as shown in Figure 2, plot A.

If the chain length is sufficiently large, the steady-state approximation can be applied for any transient species, $d[\text{R}^\bullet]/dt = d[\text{ROO}^\bullet]/dt = 0$, and it is possible to obtain the time evolution of the reactants (O_2 and RH) and products (ROOH) as follows:^{12,52,53}

$$\begin{aligned}
 \frac{-d[\text{O}_2]}{dt} &= \frac{-d[\text{RH}]}{dt} = \frac{d[\text{ROOH}]}{dt} \\
 &= \frac{k_p}{\sqrt{2k_t}} \sqrt{R_i} [\text{RH}]_0 + R_i \quad (19)
 \end{aligned}$$

In cases where the chain length is <30 , the last term can be neglected and the expression simplifies to

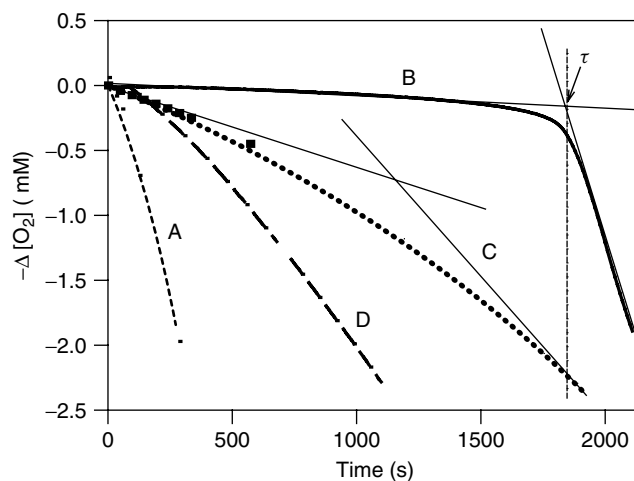
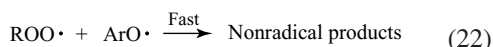
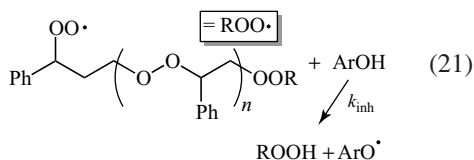


Figure 2 Typical oxygen consumption plots obtained during autoxidation of styrene (A) in the absence of and antioxidant, (B) in the presence of a very good antioxidant, (C) in the presence of an average antioxidant, or (D) in the presence of modest antioxidant.

$$\begin{aligned} \frac{-d[\text{O}_2]}{dt} &= \frac{-d[\text{RH}]}{dt} = \frac{d[\text{ROOH}]}{dt} \\ &= \frac{k_p}{\sqrt{2k_t}} \sqrt{R_i} [\text{RH}]_0 \end{aligned} \quad (20)$$

where $[\text{RH}]_0$ is the initial concentration of oxidizable substrate (since only the initial stages of autoxidation are monitored and actual substrate consumption is negligible), $k_p/(2k_t)^{1/2}$ is the oxidizability of the substrate, which has been previously introduced and has been measured for a variety of compounds.³⁵

If a small amount (1–50 μM) of antioxidant is added to the sample flask, inhibition (21 and 22) competes with propagation and the rate of oxygen consumption decreases, as shown in Figure 2.



A very effective antioxidant will produce an almost complete inhibition of oxygen consumption,

until the antioxidant itself is consumed because peroxy radicals are continuously formed by the initiator (plot B). Once the antioxidant has been completely consumed, the autoxidation proceeds at its uninhibited rate; that is, the rate of oxygen uptake is identical to that recorded without inhibitor. The length of the inhibited period τ provides the best experimental way to determine the stoichiometric factor n , as

$$n = \frac{\tau \times R_i}{[\text{ArOH}]_0} \quad (23)$$

where $[\text{ArOH}]_0$ is the initial concentration of the antioxidant. Alternatively, the same relation provides the simplest way to determine the rate of initiation R_i under the exact experimental settings used for the autoxidation. Thus, a parallel autoxidation is inhibited by a known amount of α -TOH, whose stoichiometric coefficient is 2, and R_i is obtained as

$$R_i = \frac{2\tau}{[\alpha\text{-TOH}]_0} \quad (24)$$

From the initial slope of oxygen uptake during the inhibited period, the inhibition rate constant k_{inh} can be determined according to (25).⁵² Often, the inhibited period is not so clearly identified (plot C) or the initial portion of the plot is not usable to measure the rate of oxygen consumption,

and therefore (25) can be conveniently replaced by its integrated form (26).⁵⁴

$$\frac{-d[\text{O}_2]}{dt} = \frac{k_p[\text{RH}]R_i}{2k_{\text{inh}}[\text{ArOH}]} + R_i \quad (25)$$

$$\Delta[\text{O}_2]_t = \frac{k_p[\text{RH}]R_i}{k_{\text{inh}}} \ln \left(1 - \frac{t}{\tau} \right) \quad (26)$$

It should be noted that (25) and (26) are obtained assuming that the autoxidation is not completely inhibited; that is, the process is still a radical chain reaction and obeys the associated kinetics; otherwise, the slope of the inhibited portion of the oxygen-uptake plots would merely reflect the reaction of the initiator with the antioxidant and the baseline drift of the instrument. Ideally, autoxidation experiments should be designed so that, during the inhibited period, a chain length of 6–12 is maintained, so as to minimize the contribution of k'_{inh} in the measured k_{inh} . This is normally done by adjusting the concentration of the antioxidant, or by selecting an appropriate oxidizable substrate. Indeed, our own experience with the three most common substrates, styrene, cumene, and methyl linoleate (which have largely different oxidizability, see Table 1), indicates that the difference in the measured k_{inh} for the same antioxidant is always less than a factor of two, and most commonly it is less than the experimental error ($\pm 20\%$). As such, the choice of substrate is dictated largely by experimental convenience.

In some cases, the efficiency of the antioxidant is so low that no clear inhibition period is observed and the oxygen consumption is only retarded (plot D). In such cases, k_{inh} can be determined using (27) as developed by Denisov and Khudyakov,⁵⁵ where R_{ox} and $R_{\text{ox},0}$ are the rates of oxygen consumption $-d[\text{O}_2]/dt$ measured in the presence (plot D) and in the absence (plot A) of the antioxidant, respectively, under identical experimental settings.

$$\frac{R_{\text{ox},0}}{R_{\text{ox}}} - \frac{R_{\text{ox}}}{R_{\text{ox},0}} = \frac{nk_{\text{inh}}[\text{ArOH}]_0}{\sqrt{R_i 2k_t}} \quad (27)$$

Alternative mathematical treatments have been developed by Darley-USmar *et al.*⁵⁶ and Roginsky *et al.*⁵⁷ Alternatively, the value of k_{inh} and the time course of changes in reactants/products can be obtained by computational methods, by simulating

the oxygen-uptake trace in accordance with (6)–(11) (or (12–18 and 21, 22)).^{58,59} It should be noted that the stoichiometric factor cannot be obtained from plots C and D, and it has to be assumed as 2 or determined using a substrate with a much lower k_p . It should be pointed out that, in plot C, although the rate of oxygen uptake changes during the autoxidation, the intersection of the linear regressions corresponding to the apparent inhibited and uninhibited portions of the autoxidation does not represent τ . In fact, since the rate of the apparent “uninhibited” portion of the autoxidation is still lower than that of the uninhibited autoxidation (under identical settings), the antioxidant has likely not yet been completely consumed, or an oxidation product may be inhibiting the autoxidation.

The kinetics of oxygen consumption during kinetically controlled autoxidations have also been studied using electron paramagnetic resonance (EPR) spectroscopy. Owing to the paramagnetism of O_2 , the line width in the EPR spectra of radicals obtained in oxygen-containing solutions is broadened by Heisenberg spin exchange. The experimental line width W can be described by (28), where W_{intr} is the intrinsic line width due to unresolved hyperfine splitting and relaxation phenomena and W_{ox} is the line broadening contribution due to oxygen. This depends on $r = 4.5 \times 10^{-8}$ cm,⁶⁰ which is the interaction radius between oxygen and the radical, the probability of spin exchange $p = 1$, and the sum of diffusion coefficients of oxygen (D_{ox}) and the radical (D_{rad}), according to (29).⁶¹ Once simplified to (30), the relationship between the experimental line width and the concentration of oxygen is clear. In practice, it is most convenient to use (31), which relates the oxygen concentration to the intensity I of the EPR spectral line (for a given concentration a radical species in solution).⁶²

$$W = W_{\text{intr}} + W_{\text{ox}} \quad (28)$$

$$W_{\text{ox}} = 4\pi rp(D_{\text{ox}} + D_{\text{rad}})[\text{O}_2] \quad (29)$$

$$W = W_{\text{intr}} + 4\pi rD_{\text{ox}}[\text{O}_2] \quad (30)$$

$$I^{-1/2} \propto W_{\text{intr}} + 4\pi rD_{\text{ox}}[\text{O}_2] \quad (31)$$

Hence, an autoxidation can be run directly inside an EPR sample tube in oxygen- or air-saturated organic or aqueous solution, in the presence of a sufficiently “inert” radical probe, which,

after appropriate calibration, will allow the direct monitoring of oxygen consumption from spectral changes in line width and/or intensity.⁶³ The method has been successfully applied to organic solvents using the persistent nitroxyl radical 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)^{62–64} and in aqueous media, using coal-derived fusinite particles in suspension.^{62,63}

Another popular method to measure the rate of oxygen consumption during an autoxidation is based on its polarographic detection using a Clark-type microelectrode. This approach requires a platinum cathode polarized to approximately +0.8 V with respect to an anode of Ag[°]/AgCl, both immersed in the same KCl solution inside a glass chamber, and separated from a small (~0.6 ml) isolated sample chamber by a polyethylene septum that is porous to oxygen. As oxygen diffuses through the septum, an electrical signal is generated between the electrodes as a result of the reactions in Scheme 8.

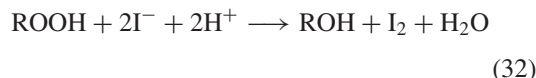
This method is very sensitive, but suffers from limited reproducibility, which often allows only semiquantitative comparison of the kinetics of different antioxidants under identical experimental conditions. Furthermore, it is suitable only for water or aqueous mixtures, where unfortunately the majority of oxidizable substrates are insoluble. However, it has been particularly useful in studies of the autoxidations of lipids in aqueous heterogeneous mixtures, such as liposomes, or micelles (SDS, Triton X-100, etc.), chosen as representative biomimetic models.^{65,66}

Although quantitative kinetic measurements are possible in micelles or liposomes, the kinetic treatment is complicated by the partitioning of the substrate, the initiator, and the antioxidant between the aqueous and lipid phases.^{67,68} Furthermore, the values of k_{inh} measured in these biomimetic systems, for most antioxidants, are orders of magnitude lower than the actual value in a homogeneous solution,^{49,69} since they reflect the rate of exchange of peroxy radicals and/or the antioxidant between micelles or between “compartments”.^{68,70} Such a rate of

exchange, in turn, reflects both the lipophilicity of the reactants and the lifetime of the supramolecular aggregate.⁷¹

The formation of oxidation products in an inhibited autoxidation should, in principle, mirror the consumption of O₂, and can be treated kinetically at the same way. This approach has often been applied to autoxidations of biological samples (e.g., LDLs or tissue extracts), or in models of biological samples (e.g., micelles and liposomes), and therefore has rarely resulted in the actual determination of absolute k_{inh} values. Nonetheless, owing to their widespread use, some relevant examples of this approach will be briefly mentioned here.

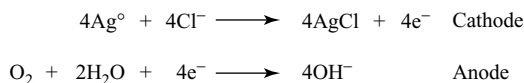
Hydroperoxides originating from the autoxidation of organic substrates have traditionally been determined by iodometric analysis, based on titration with sodium thiosulfate of iodine released upon incubation of the oxidized sample with potassium iodide, according to (32):



Alternative spectrophotometric methods, based on colorimetric redox reactions, have also been proposed.^{72,73} Selective chemiluminescent assays⁷⁴ and enzymatic assays have also been applied to monitor lipid peroxidation in biological samples. A particularly popular method in this context is based on the glutathione oxidase-catalyzed oxidation of GSH to its corresponding disulphide (GSSG), for which hydroperoxides formed during lipid peroxidation can be used as the stoichiometric oxidant. The formation of GSSG can then be monitored via its reduction to GSH by glutathione reductase at the expense of NAD(P)H, which is monitored spectrophotometrically at 340 nm.

Alkyl hydroperoxides originating from autoxidation of saturated hydrocarbons have been sampled during the autoxidation, reduced to the corresponding alcohols with sodium borohydride or triphenylphosphine, and analyzed by gas chromatography (GC) or gas chromatography-mass spectrometry (GC-MS).^{75,76}

The primary products of polyunsaturated fatty acid (PUFA) autoxidation are conjugated diene hydroperoxides, which exhibit UV absorbance around 234 nm.⁷⁷ To avoid interference by other UV-absorbing species, the progress of the reaction



Scheme 8 Electrochemical reactions at the Clark-type electrode for oxygen detection.

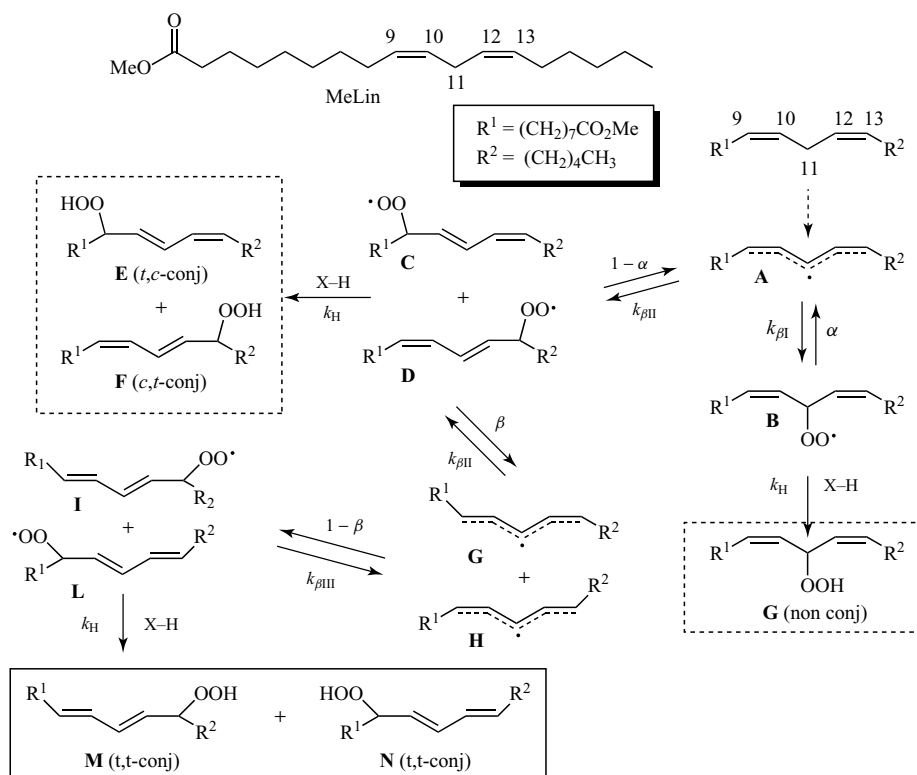
can be monitored at regular time intervals by HPLC-UV analysis of the reaction mixture.^{78,79} Alternatively, HPLC analysis can be performed on samples after reduction of the conjugated diene hydroperoxides to the corresponding alcohols with triphenylphosphine.⁸⁰

Several methods have been developed to monitor the formation of a variety of markers of lipid peroxidation. Malondialdehyde (MDA), a decomposition product of oxidized PUFAs, has been monitored upon reaction with thiobarbituric acid to form a colored adduct with strong absorbance at 532 nm. Other oxidation by-products also give similar reaction and are collectively monitored as thiobarbituric acid reactive species (TBARS), either spectrophotometrically or by HPLC analysis. Indeed, a multitude of assays for the analysis of MDA and 4-hydroxyalkenals, using colorimetric or fluorimetric detection alone or coupled to HPLC, have been described over the years, and in some cases they have been implemented in commercial analytical kits.⁸¹

2.1.2 Peroxyl Radical Clocks

Peroxyl radical clocks offer a convenient approach to measure k_{inh} for most phenolic antioxidants. The basic principle of “radical clocks,” as devised by Griller and Ingold largely for the determination of kinetics of alkyl radical reactions,⁸² is based on the competition between a unimolecular reaction whose kinetics are known and a bimolecular reaction whose kinetics are to be determined (see **Radical Kinetics and Clocks**).

In the case of peroxyl radical kinetics, the clock, that is, the reference unimolecular reaction, was discovered by Porter's group by consideration of the reversibility of the reaction of highly stabilized alkyl radicals with molecular oxygen to yield isomeric peroxyl radicals.^{83–85} In bis-allylic radicals, such as those derived from PUFAs, the regioselectivity of oxygen addition depends strongly on whether the reactions are under kinetic or thermodynamic control. For instance, in oxidations of methyl linoleate (Scheme 9), oxygen partitions



Scheme 9 General mechanism for methyl linoleate (MeLin) oxidation under kinetic or thermodynamic control.

between the central position 11 (to yield peroxy **B**) and the terminal positions 9 or 13 to yield peroxy **C** and **D** with amounts of α and $1 - \alpha$, respectively. However, the initially formed peroxy **B** readily undergoes β -fragmentation to form the original alkyl radical, and this reaction, “the clock,” competes with H-atom transfer from the donor XH, for instance an antioxidant, to form the corresponding hydroperoxides **G**, **E**, and **F**.

Under chain reaction conditions, when the steady-state approximation can be applied to transient species, the ratio of the conjugated (**E** + **F**) to the nonconjugated (**G**) hydroperoxide products can be related to the rate constant for the first β -fragmentation, $k_{\beta I}$ and the rate constant for H transfer (k_{inh} if XH is the antioxidant) according to (33):

$$\text{MeLin}_{\text{fast}} \longrightarrow \frac{[\text{E} + \text{F}]}{[\text{G}]} = \frac{k_{\beta I}}{k_H[\text{XH}]} \left(\frac{1 - \alpha}{\alpha} \right) + \left(\frac{1 - \alpha}{\alpha} \right) \quad (33)$$

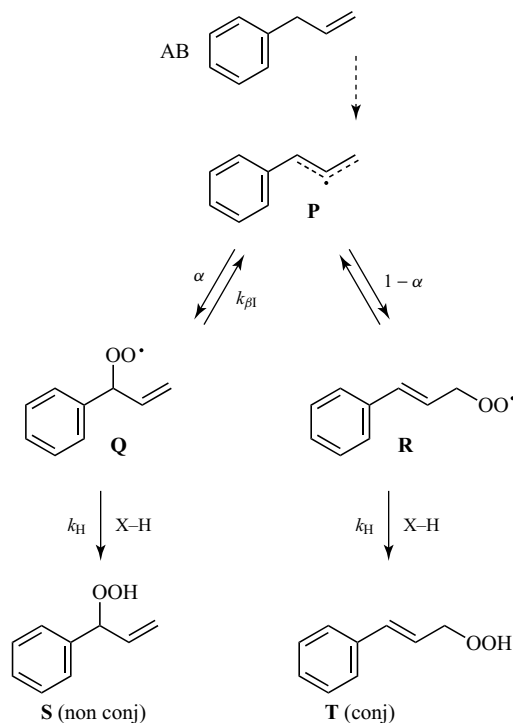
In the absence of a good H atom donor, isomerization of the peroxy **C** and **D** to the more stable *transoid* radicals **H** and **I** has time to occur, via a second β -fragmentation, and again oxygen will partition between the formation of the two *cis*, *trans* peroxy radicals or the two *trans*, *trans* peroxy radicals, which would either fragment back or react with the H donor to give the corresponding hydroperoxides **E** + **F**, as before, or **N** and **R** with *trans*, *trans* geometry. This second β -fragmentation ($k_{\beta II}$) provides a slower unimolecular process with which slower H-atom transfer reactions from less reactive XH can compete and their k_H be determined as detailed in (34):

$$\text{MeLin}_{\text{slow}} \longrightarrow \frac{[\text{E} + \text{F}]}{[\text{N} + \text{R}]} = \frac{k_H[\text{XH}]}{k_{\beta II}[1 - \beta]} + \frac{k_{\beta III}}{k_{\beta II}} \left(\frac{\beta}{1 - \beta} \right) \quad (34)$$

By analyzing the product ratios during methyl linoleate (MeLin) autoxidation in the absence or presence of variable amounts of reference antioxidant α -TOH in benzene at 37 °C, the authors determined $\alpha = 0.45$, $\beta = 0.69$, $k_{\beta I} = 2.6 \times 10^6 \text{ s}^{-1}$, $k_{\beta II} = 690 \text{ s}^{-1}$, and $k_{\beta III} = 50 \text{ s}^{-1}$, suggesting that the methyl linoleate “fast” clock, based upon $k_{\beta I}$,

and “slow” clock, based upon $k_{\beta II}$, are suited to determine k_{inh} for very effective antioxidants (e.g., α -TOH) and very modest inhibitors, respectively. Indeed, since both competing sets of products need to be accurately quantified in the reaction mixture in order to obtain reliable rate constants, it is an intrinsic limitation of the radical clock approach that $0.01 > k_{\beta}/k_H > 100$ (ideally $0.1 > k_{\beta}/k_H > 10$). Furthermore, reaction products need to be formed in relevant amounts to minimize analytical errors, which, in turn, requires that an oxidative chain reaction is maintained even in the presence of good antioxidants: a clear experimental shortcoming in some cases.

The kinetically controlled oxidation of allylbenzene (Scheme 10) offers a similar, albeit simpler, clock to time the reactivity of antioxidants, potentially covering the gap in reactivity of MeLin for most common antioxidants, with k_{inh} in the range 10^4 – $10^6 \text{ M}^{-1} \text{ s}^{-1}$. The kinetic competition shown in (Scheme 10, can be expressed as in (35), which links the ratio of the reaction products to $k_{\beta I}/k_H$: that is, it provides absolute values of $k_H = k_{inh}$ after calibration of the clock as



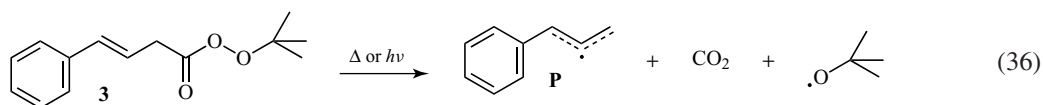
Scheme 10 General mechanism for allylbenzene (AB) oxidation under kinetic or thermodynamic control.

$k_{\beta I} = 2.6 \times 10^5 \text{ s}^{-1}$ and $\alpha = 0.74$ in benzene at 37°C . The main advantage of the AB clock is the ease with which reaction products can be accurately measured by GC.

$$\text{AB} \rightarrow \frac{[\text{T}]}{[\text{S}]} = \frac{k_{\beta I}}{k_{\text{H}}[\text{XH}]} \left(\frac{1-\alpha}{\alpha} \right) + \left(\frac{1-\alpha}{\alpha} \right) \quad (35)$$

In a more recent development, a versatile precursor of allylbenzyl radical **P** was identified as *tert*-butyl styrylperacetate (**3**), which promptly yields radical **P**, either by thermal or photolytic decomposition (36), in the presence of the antioxidant to be tested and in the desired solvent. This approach was determined with the following reference values (in benzene): $\alpha = 0.76$ and $k_{\beta I} = 1.7 \times 10^5$ or $1.4 \times 10^5 \text{ s}^{-1}$, depending on whether thermolysis or photolysis, respectively, is used to decompose the perester **3**.⁸⁶ The perester clock was calibrated in multiple solvents, and it requires only 5–10 mM concentrations of perester to set up the competition kinetics, making the determination of solvent effects on the peroxy radical trapping kinetics of assayed antioxidants possible using this methodology.

Overall, the MeLin and AB radical clocks have provided reliable k_{inh} values for a number of phenol-type antioxidants, often differing by less than a factor of two with respect to values determined by the inhibited autoxidation method. Hence they represent a valuable alternative approach for such measurements—especially for the determination of kinetic solvent effects, which may be investigated using **3**.



2.1.3 Direct Kinetic Measurements

Direct kinetic measurements of the reaction of antioxidants with peroxy radicals are important independent confirmations of k_{inh} values obtained from inhibited autoxidation studies, and provide the essential calibration data for other indirect methods, such as the peroxy radical clock measurements described above.

Laser flash photolysis (LFP) techniques (Figure 3a) would, in principle, be ideally suited to this task given the timescale of most phenol–peroxy radical reactions (microseconds) and the ease with which radicals are usually generated photochemically. However, this approach has been limited by some experimental obstacles. The most significant has been the lack of availability of convenient photochemical precursors to peroxy radicals, since pulsed lasers have fixed wavelengths (e.g., 355 nm for the third harmonic of the most common nanosecond-pulsed source, Nd:YAG) that may not be ideal for the photolysis of common radical precursors. For instance, aliphatic ketones have strong absorbance at around 180 nm ($\pi \rightarrow \pi^*$ transition; $\epsilon \sim 10\,000 \text{ cm}^2 \text{ mmol}^{-1}$), which is unusable for LFP, and a very weak absorbance at around 290 nm ($n \rightarrow \pi^*$ transition; $\epsilon \sim 15 \text{ cm}^2 \text{ mmol}^{-1}$), which is equally difficult to exploit since most antioxidants have higher absorbance at this wavelength. Azo-alkanes have band maxima at around 360 nm, but they are very weak, and radical generation proceeds with low quantum yields.

Another unfavorable feature is the weak UV absorbance of most alkylperoxy radicals.⁸⁷ Monitoring the decay of their UV absorbance is often impossible in a spectral region where all phenolic antioxidants, as well as the initiator, would absorb. This limitation can be overcome by monitoring the product radical, in the case that it has a distinct UV spectrum, or by using EPR spectroscopy to monitor the time evolution of the peroxy and/or the phenoxyl radical.

The reaction of α -TOH with cumylperoxy radicals was investigated in several solvents using a conventional flash photolysis apparatus as shown in Figure 3b, where photolysis was accomplished at 300–400 nm using the filtered flash from a Hg discharge tube. The lower efficiency of photolysis (compared to a laser) was compensated by the longer optical path for transient detection of 10 cm (as opposed to 0.7–1.0 in LFP instruments).

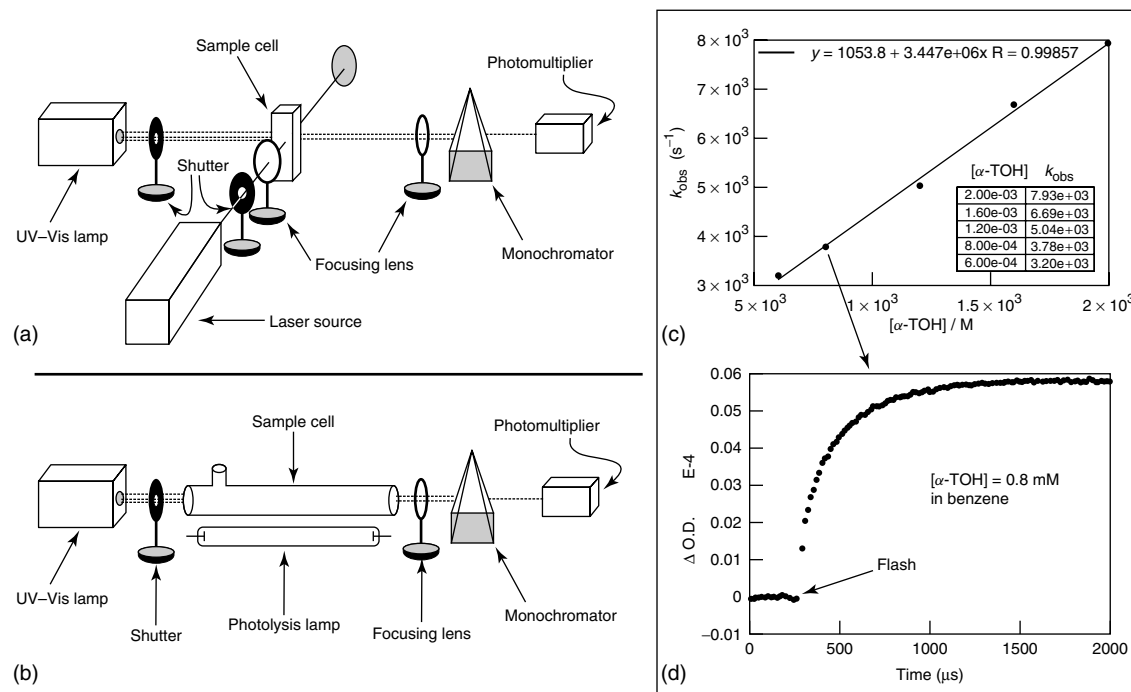
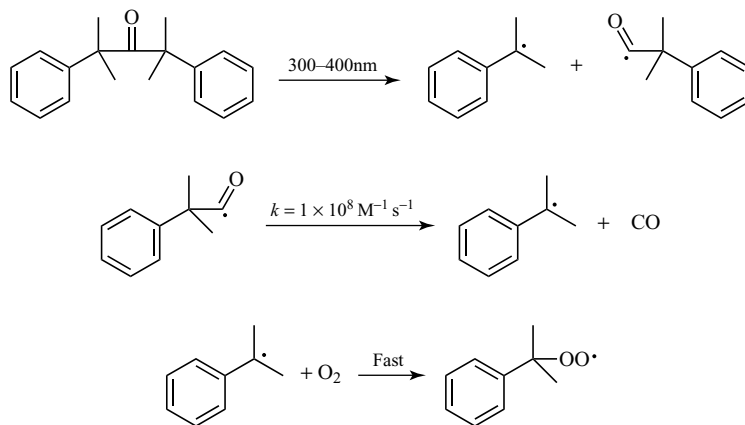


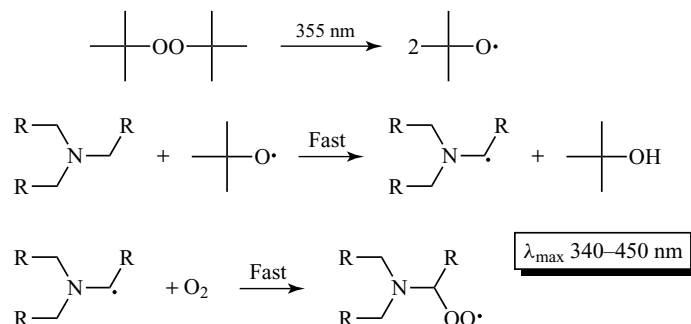
Figure 3 (a) Laser flash photolysis apparatus with UV detection of transient species; (b) conventional flash photolysis apparatus with UV detection of transient species; (c) second-order plot of k_{obs} obtained from pseudo-first-order fitting of the signal growth at 420 nm due to $\alpha\text{-TO}^\bullet$ radical (d), generated by reaction with cumylperoxyl radical in benzene at 298 K.



Scheme 11 Instantaneous and “clean” generation of cumylperoxyl radical by conventional flash photolysis at 300–400 nm of dicumylketone in benzene at 298 K.

The overall reaction (Scheme 11) was monitored by following the growth of α -tocopheroxyl radical at 420 nm (instead of the decay of the cumylperoxyl radicals) under pseudo-first-order conditions (excess of antioxidant), to obtain k_{obs} (Figure 3c) for each concentration of $\alpha\text{-TOH}$; these values, in turn,

yielded the second-order rate constant k_{inh} , according to (37), as $2.7 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ in chlorobenzene and $3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ in toluene at 298 K,⁸⁸ in excellent agreement with the value of $k_{\text{inh}} = 3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ measured in styrene/chlorobenzene (50 : 50) from autoxidation studies at 303 K.



Scheme 12 Generation of α -aminoalkylperoxyl radicals by LFP at 355 nm.

$$k_{\text{inh}} = k_{\text{obs}}[\text{ArOH}] + \text{intercept} \quad (37)$$

In (37), the intercept represents the reaction of peroxyl radical with the solvent and/or the initiator.

Lal     *et al.* have shown that α -aminoalkylperoxyl radicals, conveniently generated from the corresponding tertiary amine by LFP at 355 nm in the presence of di-*tert*-butyl peroxide (Scheme 12), have strong absorbance in the near-UV, from 350 to 450 nm. They were also able to show that these peroxyl radicals have reactivity similar to that of common alkylperoxyl radicals, and could therefore represent a convenient approach for LFP studies with phenols and other antioxidants.⁸⁹ For instance, the reaction of Et₂NCH(OO·)Me with α -TOH, BHT, and 4-methoxyphenol, monitored by following the decay of the peroxyl radicals at 380 nm, resulted in k_{inh} values at 296 K of 1.1×10^6 , 1.0×10^4 , and $6.1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, which can be compared with the corresponding values obtained at 303 K with the inhibited autoxidation of styrene of 3.2×10^6 , 1.1×10^4 , and $1.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, respectively. Similarly, the α -aminoalkylperoxyl radical derived from tri(*iso*-butyl)amine, monitored at 390 nm, gave k_{inh} values with same phenols, which differed by less than a factor of two from the reference values (above), obtained in styrene autoxidations (at 303 K).

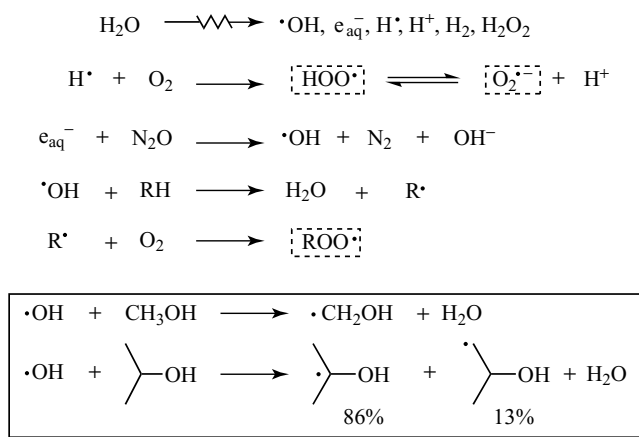
Pulsed radiolysis is a variation of LFP in which a pulse of electrons is used as the ionizing/initiating energy source. Peroxyl radicals (ROO·) and hydroperoxyl/superoxide (HOO·/O₂^{·-}) can be efficiently and instantaneously generated by pulse radiolysis in aqueous media, and monitored via their UV spectrum, to study the kinetics of their reactions with water-soluble antioxidants directly.

This powerful approach provides complementary information to LFP and autoxidation studies, which are mostly confined to organic solvents.

The primary limitation to this approach is that the radiolytic generation of peroxyl or superoxide radicals is never a clean process, and a number of both highly oxidizing and reducing species are formed simultaneously on essentially at the same timescale as the interesting peroxyl radicals. Therefore, kinetic studies often need to be corrected for the parallel (competing) reactions of these additional species, as exemplified in Scheme 13. Alkylperoxyl radicals are generated by subsequent reactions of unselective hydroxyl radicals with organic substrates in the aqueous solution and, depending on the selection of the organic substrate, this can result in a mixture of different alkyl radicals, and corresponding peroxyl radicals following their reaction with oxygen.

Despite these limitations, pulsed radiolysis has had broad applications in the study of antioxidants in water or aqueous mixtures, owing largely to the careful manipulation of reaction conditions in an attempt to control the yield of different species in solution.⁹⁰

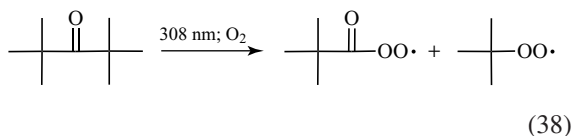
For instance, the rate constant for the reaction of ascorbate in water containing 5% alcohol and/or of other organic solutes was determined as k_{inh} of $1.7 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ with CH₃OO·; $2.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ with C₆H₅CH₂OO·; $4.7 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for HOCH₂OO·; and slightly higher with hydroperoxyl HOO·, the conjugate acid of superoxide, as $1.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, at 37 °C. The reactivity of a number of peroxyl radical species normally not accessible in autoxidation studies have also been investigated in water or water/cosolvent using



Scheme 13 Reactive species generated by γ -radiolysis of water saturated with O_2 , N_2O , and suitable organic solutes as the source of organic peroxy radicals.

pulsed radiolysis, such as $\text{Cl}_3\text{COO}^\bullet$ (and other halogenated alkylperoxy radicals), phenylperoxy radicals, pyridylperoxy radicals, and so on, demonstrating that these can be significantly more reactive than common alkylperoxy radicals.⁹¹

Time-resolved EPR detection of photolytically generated peroxy radicals overcomes the limitation due to their poor absorbance and high-energy UV transitions. Peroxy radicals normally give a broad singlet centered at $g \sim 2.016$, and are therefore observed at lower field with respect to the region where signals from phenoxyl radicals are found ($g = 2.0036\text{--}48$). Ingold and coworkers, by combining EPR spectroscopy and laser flash photolysis of di-*tert*-butylketone in the presence of oxygen and excess of phenolic antioxidant, have been able to measure directly their k_{inh} with *tert*-butylperoxy radicals, generated according to (38). Although results have probably been “contaminated” by the presence of some acylperoxy radicals, which are expected to be more reactive than alkylperoxy, the results of LFP–EPR measurements were in excellent agreement with k_{inh} values obtained using styrene autoxidation.⁴⁴



At lower temperature, the bimolecular decay of tertiary peroxy radicals becomes sufficiently slow

(e.g., $2k_t = 57 \pm 5 \text{ M}^{-1} \text{ s}^{-1}$ at 193 K for cumylperoxy radicals in propionitrile/cumene/*t*-BuOO*t*-Bu, 1:1:1)⁹² to be monitored directly with time-resolved EPR, using a UV lamp and a manual shutter for photolytic generation in the presence of the antioxidant to be investigated. Cumylperoxy radicals can be generated by continuous photolysis of di-*tert*-butyl peroxide in a propionitrile/cumene cosolvent mixture. This method, originally designed by Fukuzumi and coworkers,⁹³ allowed direct measurements of the kinetics of the reaction of cumylperoxy radical with a variety of phenols and other antioxidants in the temperature range 193–243 K (e.g., cf. Figure 4).^{92,93}

2.1.4 The Use of DPPH

The 2,2-diphenyl-1-picrylhydrazyl radical (DPPH $^\bullet$) is electronically related to alkylperoxy radicals (Scheme 14), but is sufficiently persistent to be stored in a bottle. Furthermore, it has a strong visible absorbance at 520 nm ($\epsilon = 1.3 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ in benzene) and a distinctive EPR spectrum ($\text{HSC}_{\text{N}2} = 7.94 \text{ G}$; $\text{HSC}_{\text{N}1} = 9.77 \text{ G}$; $g = 2.0036_4$ in benzene),⁹⁴ making it easy to monitor its reactions by visible absorption or EPR spectroscopy. For these reasons, it has largely been employed as a model radical species to study the formal H-atom transfer reactions of phenols and other antioxidants, assuming that its behavior reflects that of peroxy radicals.

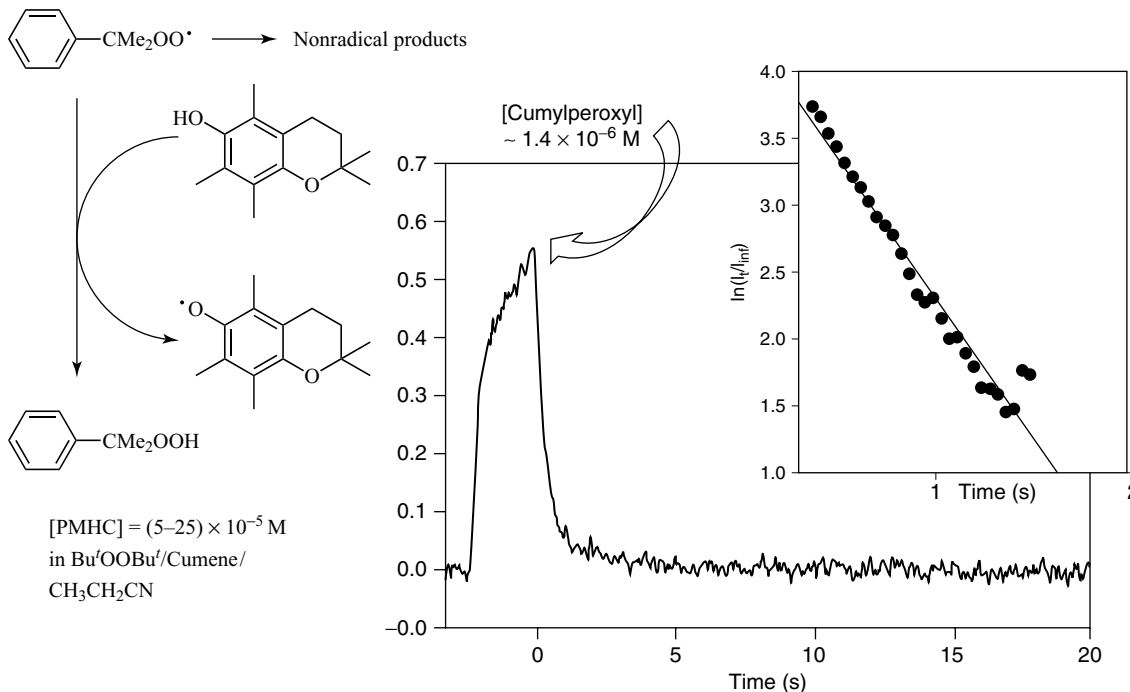
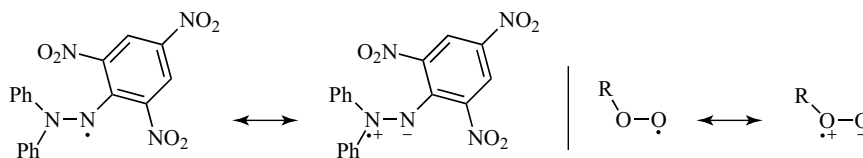


Figure 4 Kinetic EPR measurement of the reactivity of 2,2,5,7,8-pentamethyl-6-chromanol (PMHC) with cumylperoxyl radicals at 193 K.⁹²



Scheme 14 DPPH radical, its polarized resonance form, and their similarity to alkylperoxyl radicals.

In fact, although the reactions of $\text{DPPH}^\bullet$ with phenols are several orders of magnitude slower, their kinetics in nonprotic solvents are found to reflect those of peroxy radicals.^{88,95} As such, for a series of phenols, the relative rate constants for quenching $\text{DPPH}^\bullet$ are expected to parallel those for quenching $\text{ROO}^\bullet$, allowing one to *estimate* the relative antioxidant activity. However, as we have noted above, only a full kinetic study in nonalcoholic solvents would provide meaningful indications, while single spectrophotometric determinations after a fixed time, or the so-called IC_{50} values (often determined in methanol or ethanol!), are of no value with regard to the antioxidant activity of test compounds.

2.2 Thermodynamic Methods

Since k_{inh} is the most important parameter in quantifying the antioxidant activity of phenols, major efforts have been devoted to understanding the factors that govern its magnitude. As the overall reaction of a phenol with a peroxy radical can be described as a formal H-atom transfer from the phenolic OH group to the peroxy radical, the thermodynamics of the reaction is reflected by the difference in the O–H bond dissociation enthalpy (BDE) of the phenolic O–H bond that is broken and the hydroperoxide O–H bond that is formed. Common alkyl hydroperoxides have similar O–H BDEs and, to clear up the field from

the large experimental errors associated with their measurement, Benson and Cohen recommend the general value of 88.6 ± 0.5 kcal mol⁻¹ for the ROO-H BDE, regardless of the nature of the alkyl substituent.⁹⁶ In order to be good antioxidants, it seems reasonable to expect that phenols should have significantly lower O-H BDEs than this value.

When $\log k_{\text{inh}}$ for a number of substituted phenols is plotted against their respective O-H BDEs in an Evans–Polanyi plot, a relationship as depicted in Figure 5 is obtained. The data points distribute linearly, but on three nearly parallel correlations representing from top to bottom, phenols without substituents ortho to the -OH group, phenols having methyl groups in the ortho positions, and phenols having *tert*-butyl substitution in the ortho positions, respectively. It is therefore clear that, to a first approximation, k_{inh} depends on two main factors: (i) the O-H BDE of the phenol and (ii) the steric hindrance around the reactive -OH group.

The empirical linear free-energy relationships in Figure 5 are: $\log(k_{\text{inh}}/\text{M}^{-1}\text{s}^{-1}) = X - (0.333 \pm 0.008)$ (BDE_{OH}/kcal mol⁻¹), where $X = 33.398$ for 2,6-H phenols; $X = 32.016$ for 2,6-Me₂ phenols; and $X = 30.080$ for 2,6-(*t*-Bu)₂ phenols.

Regarding steric hindrance, it should be noted that 2-*tert*-butyl-4-methoxyphenol, having only one ortho position occupied by the bulky *tert*-butyl (while the other is unhindered), is positioned in

the upper correlation (black square), that is, the same as where ortho unsubstituted phenols are found, indicating that both positions adjacent to the phenolic hydroxyl group need to be simultaneously hindered to affect the reactivity. Steric hindrance has a relevant role since, for instance, phenols having the same O-H BDEs, for example, 80 kcal mol⁻¹, would be ~100-fold or 2000-fold more reactive if they have methyls or no substituent in both ortho positions, respectively, in place of the bulky *tert*-butyls.

Despite the importance of steric hindrance, the O-H BDE remains the most important parameter in determining the reactivity of phenolic antioxidants and, as will be discussed later, largely depends on the electronic and stereoelectronic contribution of the ring substituents.

Among the many methods that might be used to determine the O-H BDEs of phenols, only a few have proven to be sufficiently accurate and reliable to provide useful insights. Indeed, it should be pointed out that an error as small as 4% in the determination of a phenolic O-H BDE corresponds to ~3 kcal mol⁻¹, which could lead to a predicted k_{inh} in error by over an order of magnitude at room temperature: that is, the difference between a good and a modest antioxidant! As a consequence, we will detail only a focused selection of such methods in the subsequent sections.

2.2.1 Radical Equilibration EPR

Radical equilibration EPR (REqEPR) is arguably the most accurate method for determining phenolic O-H BDEs, in particular for the determination of relative BDEs (i.e., BDE differences). The technique is based on the measurement of the equilibrium between two phenols and their corresponding phenoxyl radicals inside the cavity of an EPR spectrometer. One phenol serves as the reference compound whose O-H BDE has been determined to a high accuracy. The reference compound with respect to which all other BDEs have been determined is 2,4,6-tri-*tert*-butylphenol, whose O-H BDE was originally determined by Mahoney *et al.* using conventional calorimetry as 81.2 kcal mol⁻¹ at 298 K in benzene.⁹⁷ The BDEs of other phenols can then be determined by equilibration with this phenol, for example, galvinoxyl radical and 2,4,6-tri-*tert*-butylphenol (39):

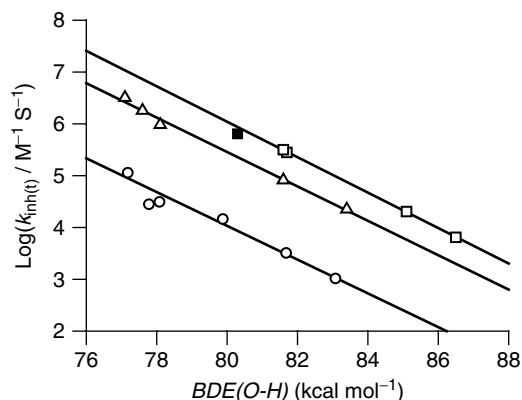
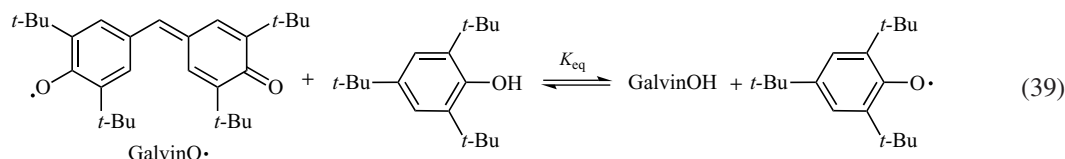
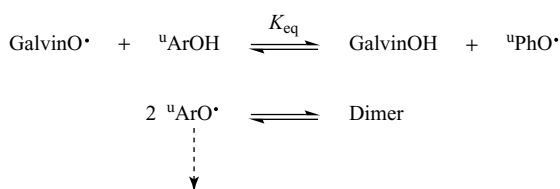


Figure 5 Evan–Polanyi correlation between $\log k_{\text{inh}}$ (in chlorobenzene at 303 K) and BDE_{OH} (in benzene at 298 K) for common phenolic antioxidants having in the ortho positions no substituents ($\square$), two methyl groups (Δ), two *tert*-butyl groups ($\circ$), or one *tert*-butyl and no substituent in the other ortho position ($\blacksquare$).



In the case of persistent aryloxy radical species, such as the 2,4,6-*tert*-butylphenoxyl and galvinoxyl radicals, the equilibrium concentration of the two radical species can be easily obtained from the EPR spectrum of the two equilibrating radicals, while those of the corresponding diamagnetic species can be determined by difference, since the initial concentrations of the reactants are known.⁹⁸ However, experiments in the presence of rapidly decaying phenoxyl radicals require a more complex treatment, since the time evolution of each paramagnetic species needs to be quantitatively monitored, as illustrated in Scheme 15.⁹⁸

The approach was enormously simplified following the discovery that phenoxyl radicals react very rapidly with phenols,⁹⁹ such that the equilibrium between two phenols and their corresponding radicals is established before their spontaneous decay. Under “radical-buffer conditions”, that is,



Scheme 15 EPR equilibration of persistent with non-persistent radicals.

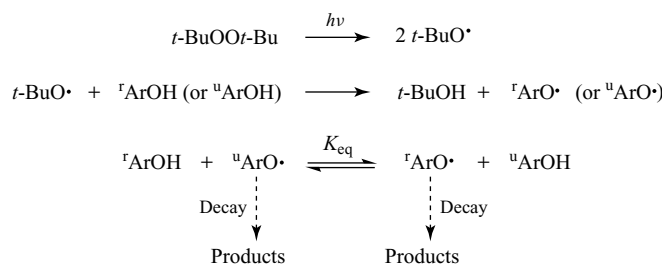
under continuous photolysis of the reaction mixture in the presence of a suitable initiator such as di-*tert*-butyl peroxide, by adjusting the intensity of irradiation and/or the amount of initiator, a steady concentration of equilibrating radicals is reached. The approach is depicted in Scheme 16.

The equilibrium constant is expressed by (40), where $[{}^r\text{ArOH}]_0$ and $[{}^u\text{ArOH}]_0$ represent, respectively, the initial concentrations of the reference and the unknown phenol, which is valid when the consumption of initial phenols during the experiment is negligible.

$$K_{\text{eq}} = \frac{[{}^u\text{ArOH}]_0 [{}^r\text{ArO}\cdot]}{[{}^r\text{ArOH}]_0 [{}^u\text{ArO}\cdot]} \quad (40)$$

The equilibrium concentrations of the radicals can be obtained directly from the EPR spectrum, which will be the sum of the individual spectra of the equilibrating radicals. When possible, the relative concentration of the two species is obtained by double integration for each species of a spectral region that is unblocked by the other. More conveniently and accurately, the experimental spectrum can be iteratively subjected to numerical fittings with computer-simulated spectra, until the correct relative amount of the two species is obtained, as illustrated in Figure 6.¹⁰⁰

From the measured value of K_{eq} , the Gibbs free energy change is obtained according to



Scheme 16 Reactions involved in REqEPR technique under “radical buffer” conditions.

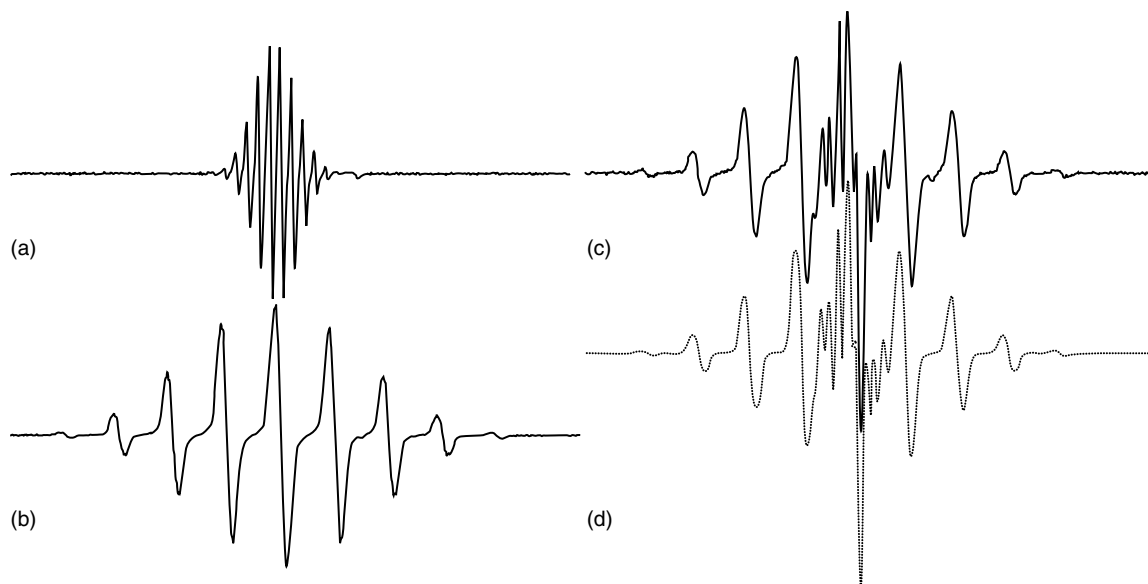


Figure 6 Experimental X-band EPR spectra of $^{\bullet}\text{PhO}$ (a), $^{\bullet}\text{PhO}$ (b), and their mixture (c) obtained by photolyzing a mixture of the corresponding phenols in benzene containing 10% di-*tert*-butyl peroxide, and its computer simulation (D).

(41). Experimentally, the value of ΔS° associated with these equilibria is normally very small ($\pm 1 \text{ cal mol}^{-1} \text{ K}^{-1}$),⁹⁸ and therefore its contribution can be neglected (42) and the O–H BDE of the unknown species can be obtained according to (43).

$$\Delta G^{\circ} = \Delta H^{\circ} - T \Delta S^{\circ} = -RT \ln K_{\text{eq}} \quad (41)$$

$$\Delta H^{\circ} = \Delta \text{BDE}_{\text{OH}} = RT \ln K_{\text{eq}} \quad (42)$$

$$\text{BDE}_{\text{uPhOH}} = \text{BDE}_{\text{rPhOH}} + RT \ln K_{\text{eq}} \quad (43)$$

Because of the logarithmic relationship between the measured K_{eq} and ΔBDE , even rather large experimental errors result in very small errors in BDE_{OH} values, contributing to the accuracy of this approach. One distinctive feature of this approach is that all BDE values are somewhat interdependent, since each newly calibrated phenol can be used as reference for another calibration. In other words, values have all been obtained by consecutive equilibrations between phenols, and they all depend on the original reference value for 2,4,6-tri-*tert*-butylphenol. This implies that they are all internally coherent and, in case BDE value for the original reference is revised, they can all be corrected without any need to remeasure them. This happened in 2005, when the

O–H BDE of 2,4,6-tri-*tert*-butylphenol was revised to $80.1 \text{ kcal mol}^{-1}$.¹⁰¹ Therefore, and O–H BDE measured by REqEPR before 2005 must be revised downward by $1.1 \text{ kcal mol}^{-1}$.¹⁰¹

2.2.2 Photoacoustic Calorimetry

Photoacoustic calorimetry (PAC) is based on the measurement of a sound (acoustic) wave that propagates through a defined volume of solution as the consequence of a rapid enthalpy change associated with a photoinduced reaction.¹⁰² Only the heat released within a defined time interval (essentially instantaneous) can be detected by PAC through a piezoelectric sensor, while the gradual density changes associated with slow heat dissipation cannot be detected. For this reason, PAC has been applied to the measurements of enthalpy changes associated with very fast reactions initiated by a nanosecond laser pulse, and it has proven particularly suitable for the measurement of the O–H BDEs of phenols. The photoacoustic effect is a consequence of the thermal expansion associated with the deactivation (e.g., by internal conversion or chemical reaction) of an excited state produced by absorption of the energy of a photon $E_{h\nu}$. The fraction of absorbed

light f_{th} that is converted into thermal energy E_{th} is related to the absorbance A of the target compound according to (44):

$$E_{\text{th}} = f_{\text{th}} E_{\text{th}} (1 - 10^{-A}) \quad (44)$$

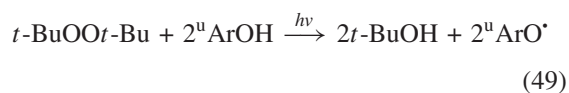
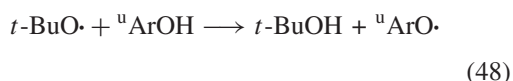
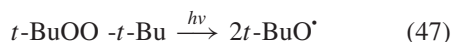
If the thermal expansion is sufficiently fast to be adiabatic, the thermal shock will translate quantitatively into an acoustic shock. Since the volume change is normally related to a number of factors, such as the heat capacity of the solution, the isobaric expansion coefficient, and the volume difference between products and reactants, PAC measurements need require extensive calibration before a reaction enthalpy can be obtained. Indeed f_{th} cannot be measured directly, and the photoacoustic response S_{obs} (the peak-to-peak amplitude of the first and main oscillation, expressed in millivolts) is used to determine the apparent fraction of light converted into heat f_{obs} by (45) (where c is an empirical response factor and χ_e is the adiabatic expansion coefficient of the medium), which in turn is needed to obtain the reaction enthalpy according to (46).

$$S_{\text{obs}} = cf_{\text{obs}} E_{\text{hv}} \chi_e (1 - 10^{-A}) \quad (45)$$

$$\Delta_r H^{\text{sol}} = \frac{\Delta_r V}{\chi_e} + \frac{(1 - f_{\text{obs}}) E_{\text{hv}}}{\Phi} \quad (46)$$

In this expression, $\Delta_r V$ is the change in volume associated with the reaction, while Φ is the quantum yield of the photoreaction; both need to be determined independently to obtain the heat of reaction.

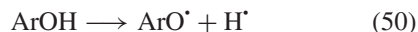
The reaction commonly investigated to obtain BDE_{ArOH} values is described by (47), which is the sum of (48 and 49).



2.2.3 Computational Methods

Quantum chemical calculations represent an advantageous means to estimate the O–H BDEs of phenols and other antioxidants; in particular those that are sparingly soluble in organic solvents or that do not afford persistent radicals. Methods based on density functional theory (DFT) are arguably the most popular, because they provide good estimates of phenolic O–H BDEs at a relatively low computational cost.^{103–105} The accuracy achieved by these calculations is usually within $\pm 2 \text{ kcal mol}^{-1}$ with respect to experimental data. While these data may not be good enough to replace the best experimental measurements, it is certainly sufficient to give valuable insight into the behavior of most natural and synthetic antioxidants. Most importantly, they can predict the thermodynamic properties of molecules prior to their experimental study, representing an invaluable aid for their rational design. For instance, DFT methods have been successfully used to predict the O–H BDEs of new classes of antioxidants, such as pyrimidinols¹⁰⁶ and pyridinols,¹⁰⁷ and to rationalize the role of remote H bonding on the para-substituted phenols.¹⁰⁸

The absolute O–H BDEs of phenols in the gas phase can be obtained by calculating the enthalpy change for the reaction (50). However, to reduce inherent deficiencies in the computational methods at lower levels of theory, the isodesmic reaction (51) can be used to determine relative BDEs, which reveal the effect of substituents on the phenolic O–H BDE (ΔBDE). These can be combined with the “best” experimental O–H BDE of phenol to obtain a reasonable estimate of the absolute O–H BDE of the substituted phenol has recently been reported to be $86.7 \pm 0.7 \text{ kcal mol}^{-1}$ as the consensus value among carefully revised results from REqEPR, PAC, electrochemistry, and high-level computations.¹⁰¹ The isodesmic approach often yields calculated O–H BDEs that differ by less than 1 kcal mol^{-1} with respect to the best experimental results.



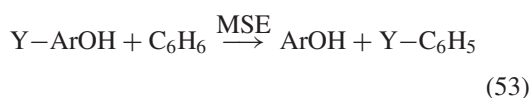
It should be pointed out that DFT methods do have some drawbacks. The contribution of strongly electron-donating (ED) and electron-withdrawing

(EW) substituents on the phenolic O–H BDE, calculated by using the popular B3LYP functional, have been found larger by about 1–2 kcal mol^{−1} than the experimental ones.¹⁰⁶ For instance, the Δ BDE of phenol substituted with *para*-OMe and –NO₂ groups have been calculated as –5.5 and +4.4 kcal mol^{−1}, respectively,¹⁰⁹ whereas the experimental values in benzene are –4.5 and +2.5 kcal mol^{−1}, respectively.¹⁰⁰ Furthermore, B3LYP has difficulties in reproducing results obtained with –CMe₃ substituents, so these are normally replaced by –Me for the purpose of calculations (considering that alkyl substituents bring very similar ED contribution into the phenolic ring). This approach, however, does not reproduce the effect of two *ortho*-CMe₃'s (i.e., disubstitution in 2,6) since the outcome depends on actual steric hindrance of the two substituents, as well as on their electronic contribution.

If the size of the investigated molecule is small, or if supercomputing facilities are available, more rigorous approaches are possible, such as the complete basis-set methods. Among them, the CBS-QB3 method has been shown to perform better than others in reproducing the absolute O–H BDE values (i.e., for (50)) and to describe the intramolecular H-bond effects on the O–H BDEs of phenols.¹¹⁰ The CBS-QB3 method has also been successfully employed to predict the O–H BDEs of nonphenolic antioxidants, such as sulfenic acids¹¹¹ and hydroxylamines.¹¹²

Unlike experimental measurements, computational methods allow the resolution of the effect of ring substituents on the strength of the phenolic O–H bond into the effect on the energies of the phenol and the phenoxyl radical derived therefrom, bringing a deeper comprehension of substituents' contribution to the properties and chemistry of phenolic antioxidants. The two effects are commonly termed *molecule stabilization enthalpy* (MSE) and *radical stabilization enthalpy* (RSE), whose difference yields the *total stabilization enthalpy* (TSE), corresponding to the Δ BDE with respect to phenol or a reference structure lacking the substituent under investigation, that is,¹¹³

$$\Delta\text{BDE} = \text{TSE} = \text{MSE} - \text{RSE} \quad (52)$$



2.2.4 Correlating Thermodynamic and Kinetic Data

The differences in reactivity among phenols with different substitution have been attributed to two main factors: steric hindrance and the phenolic O–H BDE. Both depend entirely on the identity and position of substituents on the aromatic ring. While the role of substituents on steric hindrance might be quite obvious, their contribution to the O–H BDE requires some discussion. In general, ED substituents lower the O–H BDE and increase the antioxidant activity, while the converse is observed for EW substituents; they decrease the reactivity toward peroxy radicals because they increase the O–H BDE. Figure 7 shows the dependence of O–H BDE^{114,115} (and k_{inh}) on Brown and Okamoto's para-substituent parameter σ^+_p for a series of 4-X-2,6-di-*tert*-butylphenols.¹¹⁶ The correlation is amazing, considering that σ^+_p have been defined by the kinetics of the solvolyses of substituted cumyl chlorides in aqueous acetone, while both the O–H BDE and k_{inh} determinations correspond to homolytic reactions in benzene (or chlorobenzene).

The effect of ring substituents also depends on their position: it is maximum for *ortho* and *para* positions relative to the –OH group, while it is modest in the *meta* position. The effect of ring substituents on the BDE_{OH} is approximately additive, and it is possible to use substituent Δ BDE values to calculate the BDE_{OH} of polysubstituted phenols for which experimental data are lacking (as an alternative to computational methods).¹¹⁷ However, additivity is adhered to only until the ring becomes “too electron rich” or “too electron poor”, that is, only in the case it contains, at most, one strong ED or EW group, while polysubstitution with alkyls is tolerated.

As mentioned, quantum chemical calculations allow the separation of the effect of substituents into two contributions: stabilization/destabilization of the phenoxyl radical and stabilization/destabilization of the parent phenol. The sum of the two contributions will result in their overall influence on the BDE_{OH}. Normally, ED substituents stabilize the phenoxyl radical and destabilize (or have little

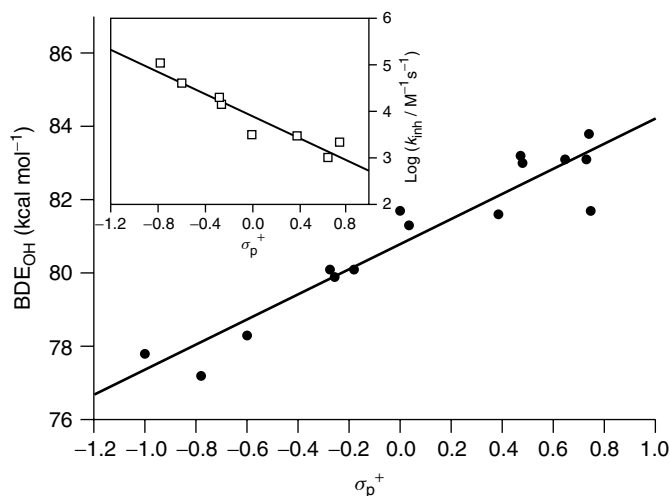


Figure 7 Correlation between para substituent constant σ_p^+ (in water/acetone) and the BDE_{OH} (measured by REqEPR in benzene) for a series of 4-X-2,6-di-*tert*-butylphenols. Inset: Correlation between σ_p^+ and available $\log k_{inh}$ at 303 K in chlorobenzene.

influence on) the parent phenol (hence they decrease the BDE_{OH}); on the other hand, EW substituents normally stabilize the phenol, but have little influence on the phenoxyl radical (hence they increase the BDE_{OH}).

Some specific substituents require deeper discussion to understand their contribution; namely those having the general structure $-XR$, with X being an electronegative heteroatom with at least one lone pair or being a chalcogen atom (S, Se, Te).

When $-OR$ (or $-NR_2$) is in the para position, its contribution on BDE_{OH} and k_{inh} strongly depends on its stereoelectronics, that is, on its electronic properties associated with its conformation: the dihedral angle between the orbital carrying the lone pair and the ring π system. Comparison of compounds **19**, **45** (or **55**), and **56** (from Table 1) illustrates the concept. While they have the same pattern of substitution around the ring (any alkyl group has about the same ED character), 2,3,5,6-tetramethyl-4-methoxyphenol has a higher BDE_{OH} and much lower antioxidant activity than α -TOH or its analog 2,2,5,7,8-pentamethyl-6-chromanol (PMC). This is due to the geometrical constraint of the bicyclic system in tocopherols that forces the ring-O-C dihedral angle so as to have close-to-optimal overlap between the oxygen 2p-type lone pair and the ring π system. Both X-ray crystallographic studies of the phenol and EPR hyperfine splitting constants (hfs) measured for the phenoxyl radical in

solution, indicate an angle 17° between the oxygen lone pair and the axis of the ring π system in PMC. On the other hand, both X-ray and EPR find that the methoxy group in compound **19** is nearly perpendicular to the ring, as a result of the hindered rotation caused by the methyl groups in the 3- and 5-positions, with an angle of 89° between the oxygen lone pair and the axis of the ring π system, thereby preventing overlap (conjugation) between the *para*-oxygen and the ring. Indeed, compound **56**, where the aromatic ring is fused with a five-member ring containing oxygen, forces an ever better overlap of the oxygen lone pair with the ring π system (with an angle of 6°) accounting for its high reactivity (Scheme 17).⁴⁴

Since chalcogens tend to maintain a bonding angle much closer to the 90° of the atomic *p*-orbitals' geometry (as opposed to sp^3 hybridization of oxygen and carbon), as illustrated, introduction of -S- in place of $-CH_2-$ in the fused six-member ring in the analog **49** forces the geometry away from maximum overlap of the oxygen lone pair with the ring π system (the X-ray-measured and DFT-calculated angle is 30°), increasing the BDE_{OH} and decreasing the reactivity. Similarly, replacing the *para*-oxygen with sulfur or selenium in thiatocopherol (**53**) or selenotocopherol (**54**) has resulted in less effective antioxidants (as compared to α -TOH) because of the poorer conjugation of the chalcogen lone pair with the ring.

Table 2 BDE_{OH} values from REqEPR measurements in benzene at 298 K and k_{inh} values from inhibited autoxidation of styrene (or cumene) in chlorobenzene at 303 K for selected monophenolic antioxidants (n represents the stoichiometric factor; when not determined it was assumed as 2).

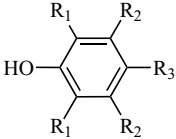
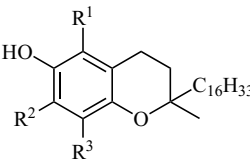
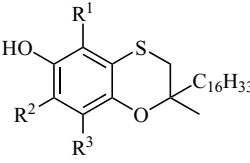
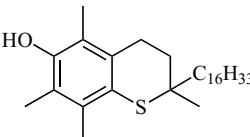
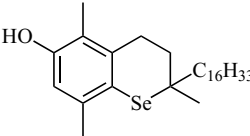
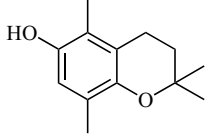
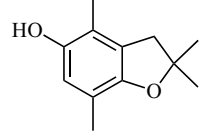
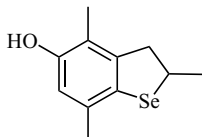
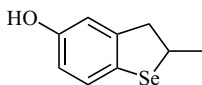
<i>N</i>	Compound			BDE _{OH} ^a (kcal mol ⁻¹)	k_{inh} ^b (10 ⁴ M ⁻¹ s ⁻¹)	<i>n</i> ^b
						
	R ¹ (ortho)	R ² (meta)	R ³ (para)			
4	H	H	H	87.2 (86.7)	0.6 ^d	—
5	H	H	Me	85.1	—	—
6	H	H	CMe ₃	84.2	—	—
7	H	H	OMe	81.7	27 ^d	2
8	Me	H	H	83.4	2.5 ^d	2
9	CMe ₃	H	H	81.7	0.31	2
10	H	CMe ₃	H	85.5	—	—
11	H	OMe	H	85.6	—	—
12	Me	H	Me	81.6	8.5	2
13	Me	Me	Me	—	36	2
14	CMe ₃	H	CMe ₃	80.1	—	—
15	CMe ₃	H	Me	79.9	1.4	2
16	CMe ₃	H	OMe	77.2	11	2
17	Me	H	OMe	78.9	94	2
18	Me	H, Me	OMe	78.1	130	2
19	Me	Me	OMe	80.8	39	2
20	CMe ₃	H	Ph	80.1 ^c	—	—
21	CMe ₃	H	Styryl	77.8 ^c	—	—
22	CMe ₃	H	NO ₂	83.8 ^c	—	—
23	CMe ₃	H	Cl	81.3 ^c	—	—
24	CMe ₃	H	C(O)OMe	83.0 ^c	—	—
25	CMe ₃	H	C(O)OH	83.2 ^c	—	—
26	CMe ₃	H	CN	83.1 ^c	0.099 ^d	—
27	CMe ₃	H	C(O)H	83.1 ^c	—	—
28	CMe ₃	H	SMe	78.3 ^e	3.0 ^e	2
29	CMe ₃	H	S(O)Me	81.6 ^e	0.29 ^e	—
30	CMe ₃	H	S(O ₂)Me	81.7 ^e	0.22 ^e	—
31	CMe ₃ , H	H	OMe	80.3 ^f	64 ^g	1.8
32	H	Me	H	85.5 ^h	—	—
33	H	H	NH ₂	77.2 ^h	—	—
34	OMe, H	H	H	84.7 ^d	0.47 ^d	2.1
35	OMe, H	H	Me	82.8 ^d	1.2 ^d	2.1
36	OMe, H	H	OMe	81.1 ^d	4.8 ^d	2.1
37	OMe, H	OMe	H	—	0.18 ^d	—
38	OMe	H	H	82.1 ^d	1.8 ^d	2.1
39	OMe	H	OMe	78.9	—	—
40	CMe ₃ , SMe	H	CMe ₃	82.2 ^f	0.39 ^g	1.6
41	CMe ₃ , SOctyl	H	OMe	80.6 ^f	0.82 ^g	1.9
42	CMe ₃ , SeOctyl	H	OMe	79.8 ^f	1.7 ^g	2.1
43	CMe ₃ , TeOctyl	H	OMe	78.9 ^f	100 ^g	0.4
44	CMe ₃	H	Te(CH ₂) ₃ OPh	78.6 ^f	0.9 ^g	0.7

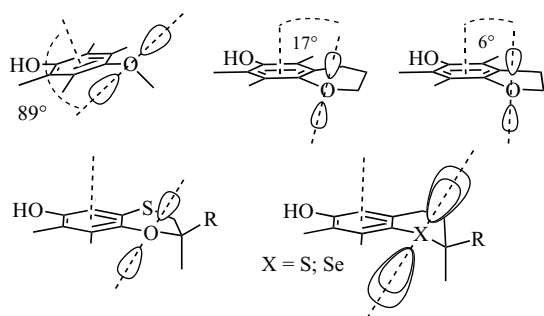
Table 2 (continued)

<i>N</i>	Compound			BDE _{OH} ^{<i>a</i>} (kcal mol ^{−1})	<i>k</i> _{inh} ^{<i>b</i>} (10 ⁴ M ^{−1} s ^{−1})	<i>n</i> ^{<i>b</i>}
						
	R ¹	R ²	R ³			
45 , α-T	Me	Me	Me	77.1	320	2
46 , β-T	Me	H	Me	—	130	2
47 , γ-T	H	Me	Me	—	140	2
48 , δ-T	H	H	Me	—	44	2
						
	R ¹	R ²	R ³			
49	Me	Me	Me	78.8 ^{<i>i</i>}	130 ^{<i>i</i>}	1.9
50	Me	H	Me	80.6 ^{<i>i</i>}	76 ^{<i>i</i>}	1.9
51	H	Me	Me	80.7 ^{<i>i</i>}	58 ^{<i>i</i>}	1.9
52	H	H	Me	81.8 ^{<i>i</i>}	30 ^{<i>i</i>}	1.9
				—	144 ^{<i>j</i>}	1.8 ^{<i>j</i>}
				78.1 ^{<i>k</i>}	120 ^{<i>k</i>}	1.9
				—	380	2
				—	570	2

(continued overleaf)

Table 2 (continued)

<i>N</i>	Compound	BDE _{OH} ^a (kcal mol ⁻¹)	<i>k</i> _{inh} ^b (10 ⁴ M ⁻¹ s ⁻¹)	<i>n</i> ^b
57		77.6 ^l	150 ^l	1.7
58		81.6 ^l	38 ^l	2

^aUnless otherwise stated, data are from Ref. 100.^bUnless otherwise stated, data are from Ref. 44.^cFrom Ref. 115.^dFrom Ref. 118.^eFrom Ref. 114.^fFrom Ref. 119.^gFrom Ref. 79.^hFrom Ref. 117.ⁱFrom Ref. 120.^jFrom Ref. 121.^kFrom Ref. 122.^lFrom Ref. 123.**Scheme 17** Stereoelectronic effect of para X–R substituents in simple and bicyclic phenols.

When –XR substituents with X = O, S, Se, or Te, are ortho to the –OH function, the effect due to the ED behavior is complicated by the occurrence of intermolecular H bonding with the “reactive” –OH, which increases the BDE_{OH} and decreases the antioxidant activity. Since such intramolecular H bonds have a strength on the order of ~3 kcal mol⁻¹, they significantly influence the reactivity of these compounds in apolar solvents.¹¹⁸ Organochalcogen substituents, besides participating intramolecular H bonding when they are ortho to the –OH,

have generally quite complex stereoelectronic properties, as they behave as EW groups in the phenol and as ED groups in the phenoxyl radical, upon rotation with respect to the ring skeleton. A detailed discussion on their stereoelectronic properties and effect on BDE_{OH} and reactivity has been provided.⁷⁹

Ortho disubstitution with very bulky groups such as *tert*-butyls produces a decrease in BDE_{OH} higher than that expected from their individual ED contribution. This may arise since they force the –C–O–H dihedral angle away from planarity, reducing the conjugation of the oxygen lone pairs with the ring and destabilizing the phenol.

2.3 Mechanistic Considerations

For over 60 years, much effort has been directed toward understanding the mechanism by which phenols inhibit hydrocarbon autoxidation.^{124,125} By the early 1960s, there was already consensus among most investigators that the reaction of phenols and chain-carrying peroxy radicals involved a straightforward abstraction of the phenolic H atom by a substrate-derived peroxy radical to give rise

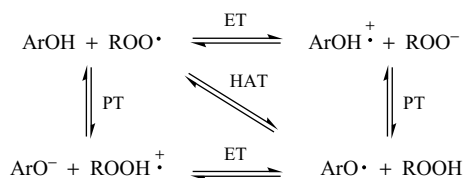


Figure 8 Thermodynamic cycle representing the mechanistic possibilities for the formal H-atom transfer between a phenol and a peroxy radical.

to a hydroperoxide and corresponding unreactive phenoxyl radical.¹²⁶ While this reaction can be written as a formal H-atom transfer, two other possibilities can be envisioned: one wherein the proton and electron are transferred in distinct chemical steps, with the electron moving first and then the proton; or vice versa. These possibilities are demonstrated as a closed thermodynamic cycle in Figure 8.

2.3.1 H-Atom Transfer

Studies of the kinetics of the reactions of substituted phenols with peroxy radicals yield a clear linear free-energy relationship with Brown and Okamoto's σ^+ substituent constant that provide a negative reaction constant ρ^+ (Figure 7 and Refs 127 and 128), suggesting that partial positive charge is being formed in the reaction. This argues against rate-limiting proton transfer, and indicates that either H-atom transfer or rate-limiting electron transfer is the mechanism. Since both the aryloxy radical and the phenolic radical cation are electron-deficient, further delineation is difficult from this data alone.

Early work by Hammond and coworkers¹²⁹ revealed a very small or negligible deuterium kinetic isotope effect (DKIE) on the reaction, which led them to suggest that the mechanism was a rate-determining electron transfer followed by a rapid proton transfer. Shortly thereafter, Ingold and Howard¹³⁰ demonstrated that Hammond's experimental approach had been flawed (protium from product hydroperoxides in inhibited autoxidations could rapidly exchange with the deuterium in the deuterated phenol, precluding the observation of the DKIE), and demonstrated that there was indeed a sizeable DKIE in these reactions. For example, for

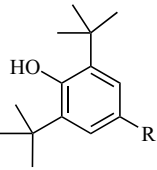
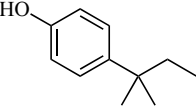
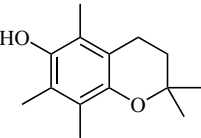
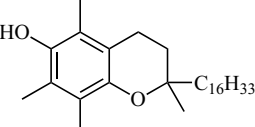
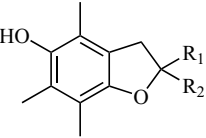
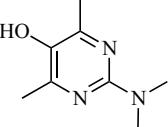
the reaction of BHT with cumylperoxy radical at 65 °C, the initial rate of oxidation was 4.2-fold lower in the presence of 1% D₂O than in the presence of 1% H₂O. The addition of an excess of D₂O to the oxidation mixture served to maintain BHT in its fully deuterated state well into the experiment. Representative DKIEs obtained for different phenols in the intervening years using the same approach is given in Table 3.

Since proton transfers are generally very fast processes, the consensus remains that this reaction goes by a H-atom transfer mechanism. This consensus is further supported by the fact that the kinetics are no faster in protic media, which would better support a proton-transfer/electron-transfer mechanism. Reaction medium can have a profound effect on both the kinetics and mechanism of the reactions of phenols with radicals—and in such a way that further supports the H-atom transfer mechanism. As discussed more thoroughly elsewhere in this encyclopedia, radical reactions in general and atom transfer reactions (see **Halogen and Chalcogen Transfer Chemistry**) in particular are generally not subject to significant differences in rate with changes in their environment. However, this observation is often made with respect to the polarity of the medium, rather than specific solvent–solute interactions. In fact, such specific interactions are key to the understanding of the kinetics of H-atom abstractions from phenols: H-bonding between the phenol and H-bond accepting solvents slow the kinetics down since they render the phenolic H atom unavailable for transfer to the radical—providing further support for a H-atom transfer mechanism. These kinetic solvent effects can be accounted for quantitatively via the expression in (55), which describes the predissociation model shown in Scheme 18.^{134,135}

$$k_{\text{H}}^{\text{S}} = \frac{k_{\text{H}}^{\text{O}}}{1 + K^{\text{S}}} \quad (55)$$

The equilibrium constant for an H-bonding interaction can be expressed as a function of the H-bond donating ability of the acidic partner and the H-bond accepting ability of the basic partner, given as Abraham's α_2^{H} and β_2^{H} constants, respectively. Using these in place of the equilibrium constant in (55) gives (56), which Ingold and coworkers have found quantitatively reflects the kinetics of most H-atom abstractions from phenols

Table 3 Representative deuterium kinetic isotope effects for the reactions of phenols and peroxy radicals.

Phenol	k_H/k_D	T (solvent)	Peroxy	References
	4.2 (R = Me)	65 (cumene)	Cumylperoxyl	130
	6.8 (R = Me) ^a	30 (isopentane)	<i>t</i> -Butylperoxyl	131
	10.6 (R = Me)	65 (styrene)	Styrylperoxyl	132
	10.5 (R = H)	65 (styrene)	Styrylperoxyl	128
	10.5	65 (styrene)	Styrylperoxyl	127
	5.1 ± 0.5	30 (styrene)	Styrylperoxyl	133
	6.4 ± 1.3	30 (acetonitrile)	Styrylperoxyl	92
	4.0 ± 0.5	30 (styrene)	Styrylperoxyl	133
	5.4 ± 0.4	30 (styrene)	Styrylperoxyl	44
	4.6 ± 0.6	30 (styrene)	Styrylperoxyl	44
	R ₁ = Me, R ₂ = H			
	4.4 ± 0.4	30 (styrene)	Styrylperoxyl	44
	R ₁ = R ₂ = Me			
	3.1	50 (benzene)	Styrylperoxyl	106

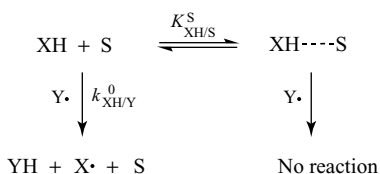
^aEstimated from direct measurement by low-temperature kinetic EPR which gave $k_H/k_D = 11$ at -34°C and 24 at -97°C .

by *tert*-butoxyl and diphenylpicrylhydrazyl radicals.¹³⁶ More recently, Pratt and Jha have shown that this also applies to the more relevant reaction of phenols with peroxy radicals.⁸⁶

$$\log k_H^S = \log k_H^0 - 8.3\alpha_2^H\beta_2^H \quad (56)$$

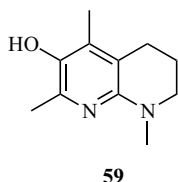
It is of interest to consider the foregoing in the context of the Arrhenius parameters that have been determined for these reactions. Although the data

are quite limited, Howard and coworkers determined the temperature dependence of the rate constants for the reactions of hindered (i.e., 2,6-di-*tert*-butylated) and nonhindered phenols with *tert*-butylperoxyl radicals in the early 1970s. They found that phenol reacted with $\log A = 7.2 \pm 0.5 \text{ M}^{-1} \text{ s}^{-1}$ and $E_a = 5.2 \pm 0.5 \text{ kcal mol}^{-1}$,¹³⁷ while hindered phenols have much lower $\log A$ values (e.g., for BHT, $\log A = 4.6 \pm 0.2 \text{ M}^{-1} \text{ s}^{-1}$ and $E_a \sim 0.8 \pm 0.2 \text{ kcal mol}^{-1}$).¹³¹ Reliable $\log A$ values are not



Scheme 18 Kinetic solvent effects on H-atom transfer from phenols.

available for 2,6-dimethylated phenols, the most commonly studied class, but they must be similar to phenol since reliable rate constants for similar compounds (e.g., **59**) have been measured up to $8.8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (albeit with secondary peroxy radicals),¹⁰⁷ which would imply $\log A = 7.9$ when $E_a = 0$.



Let us consider the E_a values first. The difference between phenol and BHT can be accounted for simply by the difference in the strength of the O–H bonds that are broken in the reaction. While the O–H BDE of phenol is $\sim 87 \text{ kcal mol}^{-1}$, that in BHT is $\sim 81 \text{ kcal mol}^{-1}$ (see below). The BDE for **59** is even lower at $\sim 77 \text{ kcal mol}^{-1}$, suggesting an even smaller (negligible) barrier as suggested by the observed rate constant. Interestingly, the E_a determined for phenol is significantly lower than that determined for toluene under similar conditions ($E_a \sim 11 \text{ kcal mol}^{-1}$),¹²⁹ despite the fact that toluene and phenol have C–H and O–H BDEs that differ only by $\sim 2 \text{ kcal mol}^{-1}$ at most.¹¹³ This is an important point, as it underlies why the inhibition reaction of chain-carrying peroxy radicals with phenols can be so much faster than the chain-carrying reaction of peroxy radicals with hydrocarbons.

It has long been documented that H-atom transfer between two heteroatoms is much faster than H-atom transfer between carbon atoms, or carbon and heteroatoms.¹³⁸ This can be understood by the elegantly simple concept of triplet repulsion, advanced by Zavitsas,^{139,140} wherein the transition state for the formal H-atom transfer reaction can be envisioned as a H atom being exchanged between

two radicals of the same spin, represented by the configuration $X\uparrow H\downarrow Y\uparrow$ (see **Thermochemistry and Hydrogen Transfer Kinetics**). Since the spins on the X and Y fragments are the same, there is a repulsive energetic component associated with bringing them together. Since oxygen is more electronegative than carbon, the spin is more localized on oxygen than on carbon, which lowers the extent of triplet repulsion in H-atom transfer between phenols and peroxy radicals as compared to toluene and peroxy radicals. Zavitsas' view has been reinforced by theoretical calculations, which have attempted to separate out the contributions of the different electronic effects to the barriers of several degenerate H-atom transfers.¹⁴¹

Typical pre-exponential factors for H-atom transfer reactions are $\log A \sim 8 \pm 1 \text{ M}^{-1} \text{ s}^{-1}$,¹⁴² putting the reactions of phenols and peroxy radicals on the low end of things. Furthermore, there would appear to be a massive difference between the hindered and unhindered phenols. Previously, the low A-factors had been rationalized on the basis of the requisite formation of a H-bonded prereaction complex. However, it is unclear why the *t*-butylated phenol would then have a lower A-factor since the equilibrium constant for its formation of a H bond with a peroxy radical will undoubtedly be less than that for a nonhindered phenol. Furthermore, the $\log A$ value for the reaction of peroxy radicals with toluene is essentially the same as that for phenol,¹²⁹ while toluene is totally incapable of making a H bond. Needless to say, this still remains a bit of a mystery.

2.3.2 Computational Insights

The calculated transition state structures for the reactions of phenols and peroxy radicals suggest that they are more appropriately described as proton-coupled electron transfer (PCET) reactions.^{143–145} Formal H-atom transfer reactions can be characterized as taking place via a PCET mechanism when the proton and electron that make up the H atom are transferred between two different pairs of orbitals on the reacting partners.¹⁴⁶ This can be identified in the calculated transition state structures upon consideration of the relevant molecular orbitals (MOs), shown in Figure 9 for the reaction of phenol with a *tert*-butylperoxy

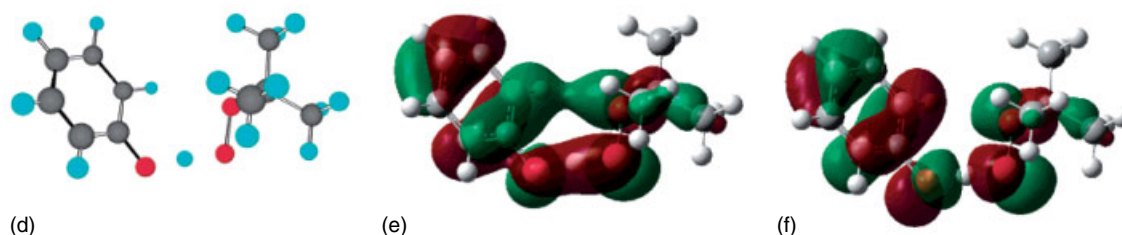


Figure 9 Lowest energy transition state structure calculated for the reaction of phenol with *tert*-butylperoxyl radical. [Reproduced from Ref. 145. © 2007, American Chemical Society.]

radical. The highest occupied molecular orbital (HOMO) (Figure 9e) shows that there is a bonding π interaction between one of the oxygen atom's 2p orbitals that contributes to the phenol's HOMO and one of the terminal oxygen atom's 2p orbitals that contribute to the peroxy's singly occupied molecular orbital (SOMO). In the SOMO (Figure 9f), this is an antibonding π interaction, but since there are two electrons in the bonding orbital and only one in the antibonding one, the π interaction is a net bonding. This O–O π interaction facilitates the electron transfer; in fact, the interaction implies that the unpaired electron is already delocalized across the π systems of the reacting partners in the transition state. At the same time, the proton is exchanged between the nominally nonbonding doubly occupied σ orbitals (i.e., lone pairs) on the same oxygen atoms. The syn orientation of the groups to which the oxygen atoms are bonded (i.e., Ph and *Ot*-Bu) is preferred over one that minimizes steric repulsion between them because of the positive orbital overlap between the two π systems (seen in the HOMO in Figure 9e), a secondary orbital interaction.

It is important to point out that the stationary point preceding the transition state structure on the reaction coordinate is one wherein the phenol is H-bonded to the peroxy radical. This preorients the reactants ideally for a PCET mechanism, while it makes attaining a transition state structure for a H-atom transfer (HAT) mechanism difficult, as it requires breaking the H bond in order to reorient the O–H group such that it is perpendicular to the plane of the aromatic ring and directed toward the peroxy radical such that the H atom is transferred between the two 2p orbitals of the oxygen atoms on the phenoxyl and peroxy radicals.

The intervention of a PCET mechanism is not inconsistent with the structure–activity relationships

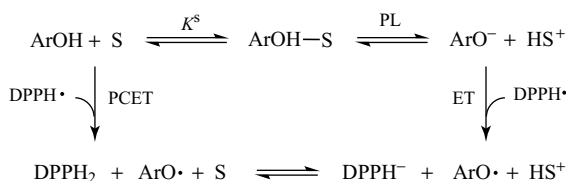
described above. The introduction of ED ring substituents on the phenol raises the energy of its (π) HOMO, thereby enhancing the overlap with the (π^*) SOMO of the peroxy radical, facilitating the “ET” part of PCET.

2.3.3 Solvent Effects

In addition to slowing down the rate of reactions with chain-carrying radicals via sequestration of the phenolic H atom via interaction with H-bond accepting solvents, the reaction medium can also have a substantial effect on the mechanism of the formal HAT from a phenol to a peroxy radical. Two particular reaction conditions are most important to consider: the presence of added acid or added base.

The use of DPPH $\cdot$ as a model for peroxy radical reactions with phenols has lead to the conceptualization of the so-called sequential proton loss electron transfer (SPLET) mechanism, depicted in Scheme 19, which allowed rationalization of the unusually fast reactions of phenols observed in alcoholic solvents.^{95,147}

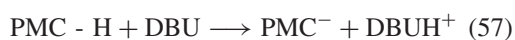
SPLET is essentially a proton transfer–electron transfer (PT–ET) mechanism with the difference being that the initial proton transfer (or proton loss (PL)) is from the phenol to the solvent (or a base),



Scheme 19 The so-called sequential proton loss electron transfer (SPLET) mechanism.

while the ET is from the electron-rich phenoxide anion to the electron-deficient DPPH[•], followed by fast proton exchange with the solvent (or the conjugated acid of the base). This mechanism, which affords very relevant accelerations in the formal H-atom transfer kinetics (by orders of magnitude in some cases), is suppressed by the addition of acids and can be seen as a form of base catalysis. Although it has been reasoned that SPLET would occur also with peroxy radicals,¹³⁶ this has yet to be demonstrated.¹⁴⁸

In recent work, one of us examined the inhibition kinetics of the α -TOH mimic PMC (compound **55** in Table 2) in the inhibited autoxidation of styrene in acetonitrile in the presence/absence of bases.¹⁴⁹ While the addition of 1 equiv of pyridine (PyrH⁺ has $pK_a = 12.3$ in MeCN) did not change the apparent value of k_{inh} measured for PMC ($pK_a \sim 25$ – 30 in MeCN), the addition of 1 equiv of 1,8-diazabicyclo[5,4]undec-7-ene (DBU), a much stronger base (DBUH⁺ has $pK_a = 24.3$ in MeCN), resulted in a significant drop in the antioxidant activity. In the presence of DBU, k_{inh} dropped by about one order of magnitude, and the apparent stoichiometric factor dropped from 2 to ~ 1 . Such an observation was attributed to the competing reaction of the phenoxide with molecular oxygen to yield superoxide (57 and 58), which can initiate a new oxidation chain or consume the antioxidant.



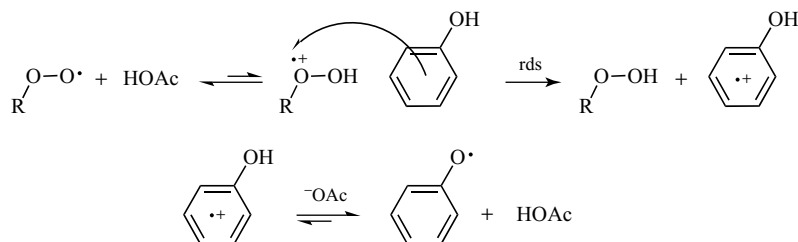
DPPH[•] has a positive standard reduction potential of about $E^\circ = +0.3$ V versus the standard calomel electrode (SCE) in organic solvents,¹⁵⁰ while the corresponding potentials for alkylperoxy radicals (lacking EW substituents) have been reported to range from $+0.3$ to $+0.7$ V versus SCE¹⁵¹ (e.g., for cumylperoxy $E^\circ = +0.65$ V versus SCE in MeCN⁹³). Therefore, both DPPH[•] and chain-carrying ROO[•] are strong one-electron oxidants, while phenoxide anions are normally good reductants with negative E° values¹⁵⁰ (e.g., $E_{red} = -0.52$ V vs SCE for α -TO[•]/ α -TO⁻ in MeCN¹⁵²), suggesting that ET from the phenoxide to both DPPH[•] or ROO[•] should be characterized by a $\Delta E^\circ \sim +1$ V and, therefore, be quite exergonic.

While studies assessing SPLET with DPPH[•] have all been conducted in carefully deoxygenated solutions, the presence of oxygen is unavoidable during autoxidations, as well as the conditions under which aerobic organisms subsist. Triplet oxygen is a weak one-electron oxidant, whose available E° value of ~ 0.5 V¹⁵⁰ suggests that the reaction in (58) should be essentially thermoneutral. Since the concentration of oxygen in nonaqueous media is $\sim 10^{-3}$ M, that is, about 1 million times higher than the steady-state concentration of peroxy radicals during an inhibited autoxidation (or even in greater excess in a cell membrane), the reaction of O₂ with the antioxidant-derived phenoxide anion is likely to outcompete the chain-carrying peroxy radicals. This suggests that, while the SPLET mechanism is possible with peroxy radicals, it appears to have no relevance under most model or biomimetic settings with monophenolic antioxidants.

Acids have recently been demonstrated to dramatically enhance the reactivity of phenols to peroxy radicals in organic solvents.⁹² The phenomenon was shown to be general for half a dozen common phenolic antioxidants and both organic and mineral acids. The rate acceleration increases with the concentration of acid, but not the acid strength; it is largest for carboxylic acids, and requires a relatively polar solvent such as acetonitrile to be effective. Acetic acid has been studied most thoroughly as a catalyst for this reaction and, as an example, has been found to increase the inhibition rate constant of pentamethylchromanol (determined by inhibited autoxidations of styrene) from 6.8×10^5 to 1.1×10^7 M⁻¹ s⁻¹ in acetonitrile containing 88 mM acetic acid. The acid-catalyzed reactions are characterized by an inverse deuterium kinetic isotope effect (e.g., 0.9 ± 0.3 for PMC) in place of the normal isotope effect that is observed in the absence of acid (e.g., 6.4 ± 1.3 for PMC). This key result, taken along with other mechanistic observations, suggests the mechanism in Scheme 20.

2.3.4 Fate of the Aryloxy Radical

Until now, we have not considered the fate of the aryloxy radical that is formed upon H-atom abstraction from the phenol. In fact, under most conditions, the phenoxyl radical goes on to rapidly react with another peroxy radical ($k = 10^8$ – 10^9 M⁻¹ s⁻¹).¹⁵³



Scheme 20 Proposed mechanism of the acid-catalyzed reaction of peroxy radicals with phenols.

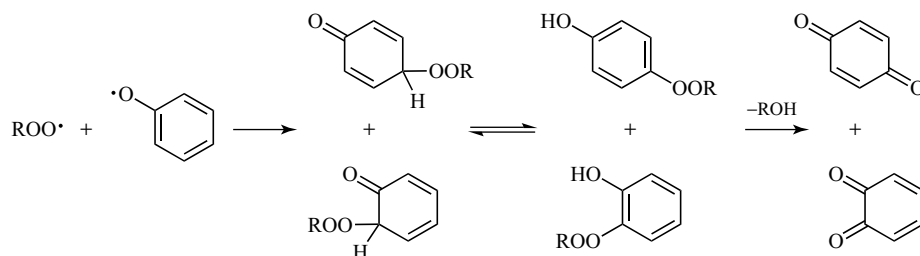
This can sometimes lead to a complex mixture of products and, as such, this second chain-breaking reaction is often described to result simply in “non-radical products.” This is generally an appropriate description, as it underscores the observed stoichiometry of the inhibition of hydrocarbon autoxidation by phenolic compounds under ambient conditions; two chain-carrying peroxy radicals are consumed for each molecule of phenol (see below). The reaction of two peroxy radicals is comparatively slow (e.g., *t*-BuOO• dimerization occurs with $k \sim 10^3 \text{ M}^{-1} \text{ s}^{-1}$).¹⁵⁴

The combination of peroxy and phenoxyl radicals takes place to yield a dienone peroxide, the structure and fate of which depend on the substitution of the phenol. Taking an unsubstituted phenol as an example, the peroxy radical can add to any of the ring carbons of the phenoxyl that possess unpaired electron spin density (*ortho* or *para*). Following tautomerization to restore aromaticity, the weak O–O bond of the peroxide can then fragment and the resultant radical pair can undergo disproportionation to yield the corresponding quinone and alcohol (Scheme 21).¹⁵³

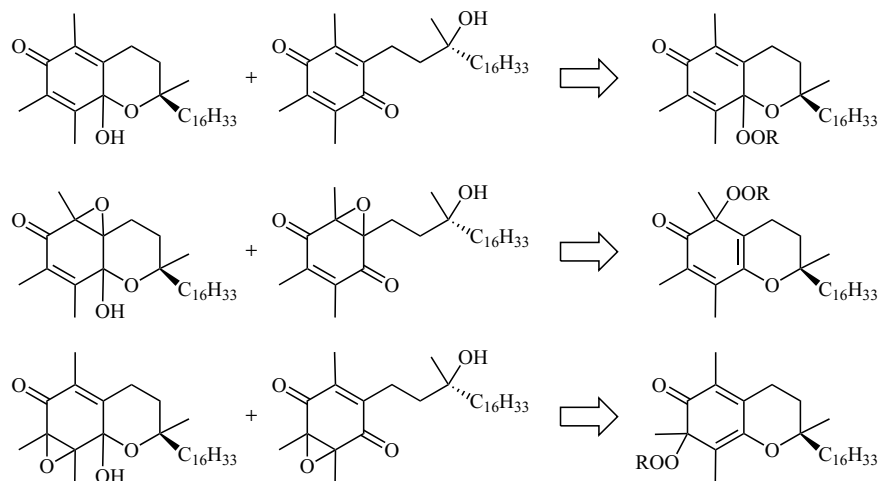
Phenoxyl radicals with substitution at both the *ortho* and *para* carbons still react with peroxy radicals very rapidly, but the lack of a geminate H atom precludes tautomerization, which means

that resultant peroxides decompose to generate more radicals in lieu of nonradical products. This is the reason why phenolic compounds generally have lower stoichiometric factors at higher temperatures. For example, while α -tocopheroxyl likely reacts with peroxy radicals to yield three primary peroxides as a result of coupling of the radicals at the *ortho* and *para* positions, at higher temperatures or over extended periods these peroxides give rise to six major products (Scheme 22),^{155–157} each of which requires the formation of intermediate alkoxy radicals that can go on to initiate chain reactions or consume additional antioxidant.

Therefore, at first glance it would appear that the lesser substituted phenols possess an advantage in their radical-trapping abilities—despite their lower reactivity—since they should more cleanly yield nonradical products. However, it is important to point out that, in competition with peroxy radical trapping by the phenoxyl, dimerization of phenoxyls can occur. For nonhindered phenoxyls, this reaction can be very fast (cf. Table 4) and can compete with capture of the peroxy radicals; for hindered phenoxyls, this reaction is insignificant with respect to reactions with peroxy radicals. The products of these reactions, namely (bis)dienones, may tautomerize to yield (bis)phenols if possible, which can undergo further reactions, some of which



Scheme 21 Representative peroxy radical trapping reaction for simple phenoxyls.



Scheme 22 Products derived from the second peroxy radical-trapping reaction of α -tocopherol, and their immediate precursor.

may not be as fast as those of the original compounds.¹⁵⁸

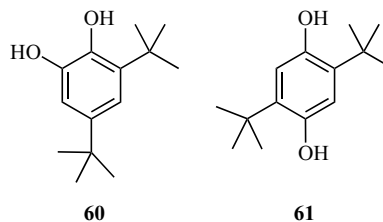
3 CHEMISTRY OF RELATED CHAIN-BREAKING ANTIOXIDANTS

3.1 Other Phenols

3.1.1 Catechols, Resorcinols, and Hydroquinones

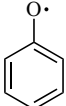
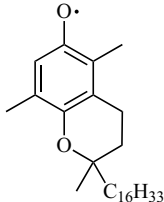
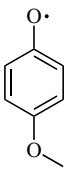
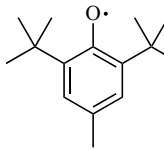
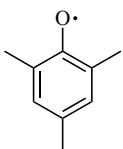
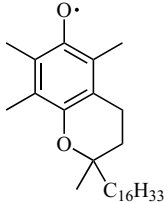
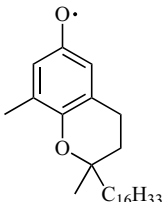
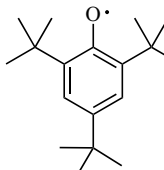
The inclusion of a second hydroxyl group on the aromatic ring can dramatically alter the reactivity of phenols. The effect depends largely on the position where it is included; in general, catechols are slightly more reactive than hydroquinones, and both are much more reactive than resorcinols. The reason for the higher reactivities of catechols and hydroquinones versus resorcinols is based largely on thermodynamics. The O–H BDE in phenol is decreased by a significant margin upon introduction of the second –OH group in the *ortho* or *para* positions (e.g., comparing **60** ($79.3 \pm 0.3 \text{ kcal mol}^{-1}$) and **61** ($80.8 \pm 0.2 \text{ kcal mol}^{-1}$)),¹⁵⁹ but not when in the *meta* position; the O–H BDE of the analogous 3-methoxyphenol has been determined to be $86.7 \text{ kcal mol}^{-1}$.¹⁶⁰ The lower O–H BDE in catechols as compared to hydroquinones is the result of a strengthening in the intramolecular H bond as one of the H atoms is removed and the

semiquinone radical is formed. Consequently, catechols and hydroquinones have very large inhibition rate constants, for example, $2.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for **60** and $1.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for **61** in chlorobenzene at 30°C .⁵⁸ Resorcinols, on the other hand, are not documented to be very effective antioxidants.



The stoichiometry of the chain-breaking reactions is an important consideration in the antioxidant activity of catechols and hydroquinones. Catechols generally have $n = 2$, corresponding to the consequent abstraction of each of the labile phenolic H atoms by peroxy radicals and the corresponding formation of *o*-quinone as a product. In contrast, hydroquinones have stoichiometric factors that vary depending on the medium, ranging anywhere from 0.1 to 2. This is the result of the competing reaction of the intermediate *p*-semiquinone radical with O_2 .⁵⁸ This reaction, which has been shown to proceed with a rate constant of $2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 298 K in chlorobenzene for the semiquinone radical derived from **61**, is believed

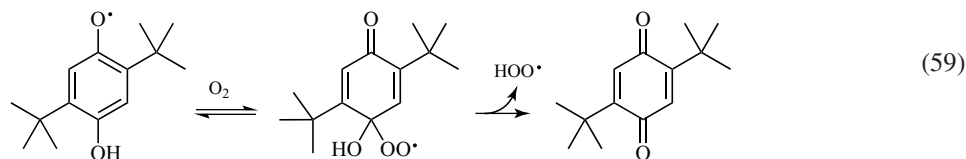
Table 4 Representative self-reaction rate constants for selected phenoxyl radicals. Data from Ref. 44.

ArO•	$2k$ (s^{-1})	ArO•	$2k$ (s^{-1})
	2.6×10^9		5.0×10^4
	1.0×10^9		8.6×10^3
	4.5×10^7		3.0×10^3
	2.0×10^5		0.1

to occur by a two-step addition/elimination mechanism, as is shown in (59). The hydroperoxyl radical can then carry on the autoxidation chain, negating the initial chain-breaking reaction of the parent hydroquinone with a peroxy radical. Depending on the partitioning of the *p*-semiquinone radicals between reactions with peroxy radicals and O_2 , stoichiometric factors between 0 (all reaction with O_2) and 2 (all reaction with $ROO\cdot$) can

be obtained. This is dependent on the O_2 concentration and steady-state $ROO\cdot$ concentration. The reaction is less important for catechols since the intramolecular H bond makes it more difficult to remove the H atom from the *o*-semiquinone radical.

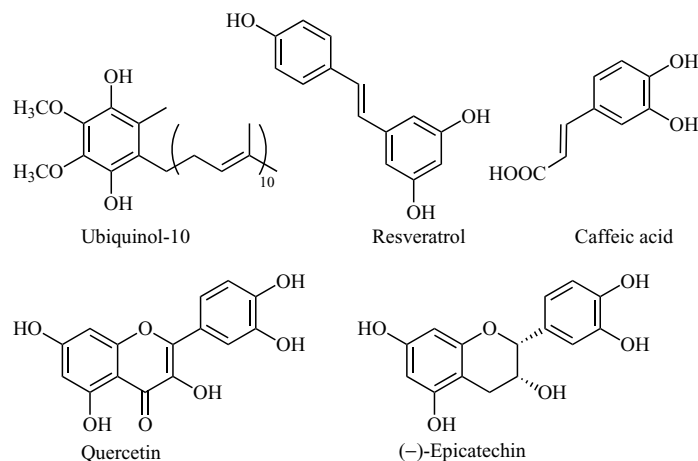
There are many examples of biological catechols, resorcinols, and hydroquinones—in fact, many times these functionalities are found in the



same molecule! Perhaps the most famous hydroquinone is ubiquinol-10, also known as reduced coenzyme Q₁₀. It is an indispensable part of aerobic respiration, as it serves as a two-electron shuttle in complexes I and III of the mitochondrial electron transport chain. It is also an important antioxidant, possessing a (gas phase) O–H BDE of 78.5 kcal mol⁻¹¹⁶⁰ and reacting with peroxy radicals with a rate constant of $3.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ in chlorobenzene.¹⁶¹ Despite having a similar O–H BDE, reduced coenzyme Q₁₀ is roughly one order of magnitude less reactive than α -TOH (see below), since the intramolecular H bonds between the reactive phenolic O–H bonds and the adjacent *o*-methoxy substitution in coenzyme Q₁₀ attenuate its reactivity. This was examined in particular detail for reactions of hydroquinones with alkoxyl radicals, where it was further demonstrated that, as a result of the intramolecular H-bonding interaction, the reduced coenzyme Q is not very susceptible to kinetic solvent effects, as are simpler phenols.¹⁶² These intramolecular H-bonding interactions also figure prominently in the thermodynamics of the reaction of coenzyme Q with radicals. Despite the fact that methoxy is a very good ED group (compare the O–H BDE of 86.2 kcal mol⁻¹ in phenol with the O–H BDE of 81.3 kcal mol⁻¹ in 4-methoxyphenol, determined by PAC¹⁶⁰), its presence in the *ortho* position does not yield a decrease in the O–H BDE because it is offset by the H-bonding interaction, which stabilizes the phenol with respect to the phenoxyl radical (O–H BDE of 86.6 kcal mol⁻¹ in 2-methoxyphenol by PAC¹⁶⁰).

The catechol moiety is found in countless plant-derived compounds, in particular, the phenolic acids (e.g., caffeic acid), or flavonoids such as flavonols and flavan-3-ols, examples of which are quercetin and epicatechin, respectively. While they display good antioxidant activities *in vitro* (e.g., quercetin and epicatechin have $k_{\text{inh}} = 4.3 \times 10^5$ and $4.2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, respectively, in chlorobenzene at 50 °C,¹⁶³ it is unclear whether this is of any significance *in vivo*. In fact, only a fraction (1–5%) of the amount contained in a fruit-rich meal is found in human plasma following ingestion and reaches only submicromolar levels.¹⁶⁴ The majority is metabolized by intestinal bacteria to yield the simpler phenolic acids (which do, however, retain the catechol moiety).

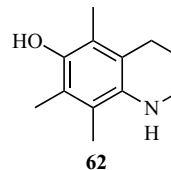
The most famous resorcinol could be resveratrol, found in relatively high levels in red wine. While it is a resorcinol, it is also a “simple” phenol on the other phenyl ring of the *trans*-stilbene. Since the vinyl substituent in the para position of the monosubstituted phenol can serve to delocalize the unpaired electron spin in the incipient phenoxyl radical, it is this moiety that actually reacts with peroxy radicals (its O–H BDE has been estimated to be 83.7 kcal mol⁻¹), and with a fairly good rate constant of $k = 2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at 30 °C in chlorobenzene.⁵⁹ The resorcinol moiety is less reactive since the –OH groups are oriented meta to both the vinyl substituent and themselves, precluding delocalization.



3.1.2 Pyridinols and Pyrimidinols

For decades now, academic and industrial researchers alike have worked to improve the radical-trapping antioxidant activity of phenols. Most efforts to date have met with little success. This is simply because attempts to weaken the O–H bond further than that found in the most reactive phenols (i.e., $\sim 77 \text{ kcal mol}^{-1}$ in α -TOH) via introduction of more strongly ED substituent groups on the phenolic ring has lead to compounds that react directly with O_2 (e.g., **62**),⁴⁴ rendering them pro-oxidants rather than antioxidants. This is a consequence of the fact that both the undesired electron transfer chemistry and the desired H-atom transfer chemistry are functions of the energy of the HOMO, which goes up with increasing numbers and/or strengths of ED groups on the phenolic ring. Furthermore, the ED groups stabilize the radical cation derived from the one-electron transfer chemistry more so than the radical derived from

the H-atom transfer chemistry, making the electron transfer chemistry relatively more favorable upon ring substitution.



In the early 2000s, we presented a strategy to partially circumvent this problem, through the incorporation of nitrogen atoms in the phenolic ring.¹⁰⁶ The resulting compounds, 3-pyridinols and 5-pyrimidinols, containing one and two nitrogens, respectively, can be substituted with more ED groups since they start off more electron-poor than phenol itself.^{64,106,107,165} The nitrogen atoms are placed in the 3 and/or 5 positions since they are unable to yield the pyridone and pyrimidone tautomers that predominate when nitrogen is

Table 5 Examples of highly reactive pyrimidinol and pyridinol radical-trapping antioxidants, their O–H BDEs, and inhibition rate constants.

	O–H BDE (kcal mol^{-1}) ^a	k_{inh} ($\text{M}^{-1} \text{s}^{-1}$) ^b
63	78.2	8.6×10^6
64	77.0	1.6×10^7
65	76.3	8.8×10^7
66	75.4	2.8×10^8

^aFrom REqEPR studies; see Refs 64, 106, 107, 165.

^bIn chlorobenzene by inhibited autoxidation of styrene at 30 °C, except the first example, which was at 50 °C; see Refs 64, 106, 107, 165.

incorporated in the 2 and/or 4 positions. While 3-pyridinols and 5-pyrimidinols have O–H BDEs that are ~ 1 and $2.5 \text{ kcal mol}^{-1}$ higher than in phenol, respectively, they can be weakened predictably upon ring substitution—as is the case for phenols. In doing so, air-stable 3-pyridinols and 5-pyrimidinols bearing strongly ED amino groups are readily synthesized, isolated, and purified, and are found to react with peroxy radicals up to two orders of magnitude faster than phenols (see Table 5 for some examples). The equivalently substituted phenols are essentially impossible to handle outside an inert atmosphere. Mechanistic studies support a H-atom transfer mechanism as for phenols ($k_{\text{H}}/k_{\text{D}} \sim 3$),^{64,106} a negative reaction constant for Hammett-type correlation with σ^+ ,^{107,165} HBA solvents slow kinetics,^{64,106,166} and theoretical calculations yield transition states consistent with a role for PCET in this process.⁹²

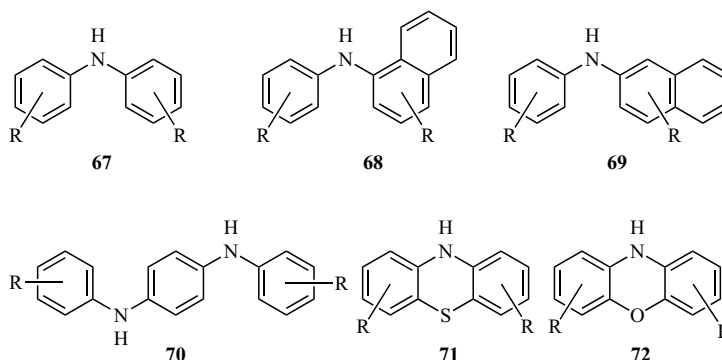
This development has prompted the study of lipid-soluble analogs of pyridinol **65** (which has the best balance of reactivity to peroxy radicals and stability in air, and most closely resembles α -TOH) under more physiologically relevant conditions, for

inhibit these processes in biological contexts is of great interest.

3.2 Aromatic Amines and Other Nitrogen-Containing Compounds

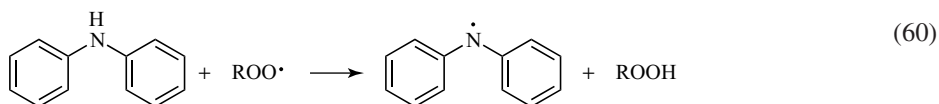
3.2.1 Aromatic Amines

Secondary aromatic amines have long been known to be effective inhibitors of hydrocarbon autoxidation, especially at high temperatures. The most commonly encountered amines are substituted diphenylamines (**67**), so we will consider their reactivity in detail here. However, it should be noted that many other diarylamines are, or have been, used industrially including *N*-phenyl- α -naphthylamines (**68**) and *N*-phenyl- β -naphthylamines (**69**) as well as *N,N'*-diphenyl phenylenediamines (**70**), and still other aromatic amines have been suggested as antioxidants (such as phenothiazines **71** and phenoxazines **72**), but are unlikely to find widespread use because of their instability in air.



example, in human LDL,^{167,168} and unilamellar vesicles (liposomes) comprised of polyunsaturated lipids.⁸⁰ Since the peroxidation of membrane lipids has been implicated in virtually all degenerative diseases, the potential for these compounds to

The initial step of radical-trapping chain-breaking activity is little different from that of phenols. The key step is a formal H-atom transfer from the diphenylamine to a peroxy radical, which yields a diphenylaminyl radical (**60**).

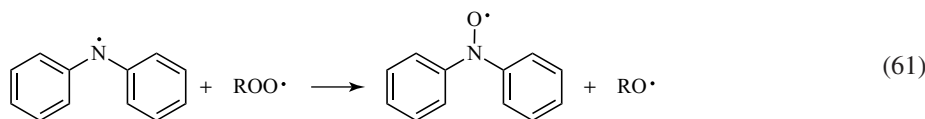


This reaction is facilitated by diphenylamine's relatively weak N–H bond, which has been determined to be $84.7 \pm 0.7 \text{ kcal mol}^{-1}$ (revised according to Ref. 101),¹⁶⁹ which is $2.5 \text{ kcal mol}^{-1}$ weaker than the O–H bond in phenol determined under the same conditions by the same method—REqEPR spectroscopy. The rate constant for this reaction has been determined by the inhibited autoxidation of styrene method to be 4.4×10^4 at 65°C ,¹⁷⁰ and more recently, $1.5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 50°C ,¹⁶⁹ which is a factor of 4 or so greater than for the reaction of phenol with peroxy radicals, owing primarily to the weaker bond. Reliable Arrhenius data for the reactions of diphenylamine and peroxy radicals are not available. However, it should be mentioned that aniline has $\log A = 6.3 \text{ M}^{-1} \text{ s}^{-1}$ and $E_a = 5.0 \text{ kcal mol}^{-1}$,¹³⁷ which is quite similar to that of phenol (see below). Aniline's lower reactivity ($k_{\text{inh}} = 1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ at 30°C)¹³⁷ is due to its stronger N–H bond of $\sim 90 \text{ kcal mol}^{-1}$.¹⁷¹

The role of a formal H-atom transfer mechanism in this reaction is supported by deuterium kinetic isotope effect studies, which yield $k_{\text{H}}/k_{\text{D}} = 3.0 \pm 0.5$ at 65°C .¹⁷⁰ Furthermore, a linear free-energy relationship is clear from the correlation of the logarithm of the inhibition rate constants of a series of ring-substituted diphenylamines with the

be much less susceptible to H-bonding effects than phenols, presumably due to a combination of both less H-bond acidity ($\alpha_{\text{H}}^2 = 0.324$ vs $0.4\text{--}0.6$ for most phenols) and sterics.¹⁷³ Recent theoretical calculations suggest a transition-state structure similar to those calculated for the reactions of phenols with peroxy radicals, whose geometry implies that the mechanism of the formal H-atom transfer could be described as a proton-coupled electron transfer.¹⁷⁴ As for phenols, the structure has significant orbital overlap between the π HOMO of one of the aryl rings and the π^* SOMO of the peroxy radical, suggesting that the electron is already partially delocalized from the diarylamine to the peroxy in the transition state. Presumably, the mechanistic interpretations for the diarylamines extend to the other classes of secondary aromatic amines widely used as antioxidants.

The subsequent chemistry of the diphenylaminyl radical makes aromatic amines arguably more interesting, and probably more useful, than phenols as radical-trapping antioxidants. In contrast with the reaction of phenoxyl radicals with peroxy radicals to yield nonradical products, the reaction of diphenylaminyl radicals with peroxy radicals leads to two radical products: the diphenylnitroxide and an alkoxy radical (61).^{175–177}

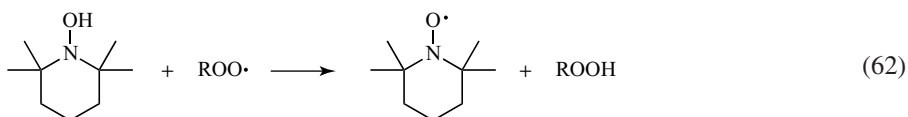


corresponding σ^+ substituent constants. The correlation affords a reaction constant $\rho^+ = -0.89$, which was initially interpreted as meaning that there was a highly polarized transition state for the formal H-atom transfer reaction,¹⁷² but it is also consistent simply with the trend in N–H bond dissociation enthalpies in this series of compounds, which yields $\rho^+ = -1.35$ by experiment and -2.5 by theoretical calculations.¹⁷¹ Kinetic solvent effect studies carried out using the peroxy clock methodology found an inverse linear relationship between the logarithm of the inhibition rate constant and the H-bond accepting ability of the solvent (quantified by Abraham's β_{H}^2 parameter), implying that the amine hydrogen must be free to be transferred in the rate-determining step of the reaction.⁸⁶ Diphenylamine was found to

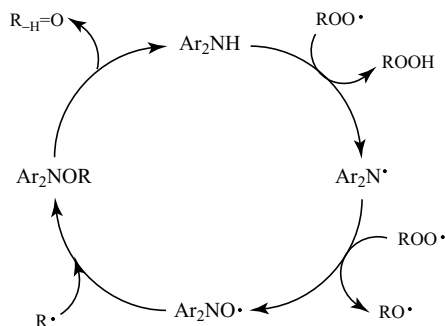
This is formally an O-atom transfer reaction, but likely proceeds first by radical–radical combination followed by fragmentation of the weak O–O bond. Since alkoxy radicals are good initiators of autoxidation, this reaction does not result in a net chain-breaking reaction. However, since the product nitroxide will react with peroxy radicals eventually to give nonradical products (see the following section), the overall observed stoichiometric factor for diphenylamines is generally 2, as for phenols.

It must be qualified that the foregoing is true only at ambient temperatures. In fact, at high temperatures, such as those encountered in the operation of a combustion engine, diarylamines are characterized by much higher stoichiometric factors ($n > 40$). The prevailing hypothesis accounting

for this observation was advanced by Korcek and coworkers of the Ford Motor Company following the results of autoxidations of hexadecane (a model for motor oil) at 160 °C.¹⁷⁸ They found that when a diphenylnitroxide was used as an oxidation inhibitor, the corresponding diphenylamine was formed *in situ*. Furthermore, while the nitroxide was consumed rather rapidly in the oxidation, the amine built up to a substantial concentration before being consumed more slowly, suggesting that it may be the least reactive inhibitor in the system, and the rate of its regeneration is high. They went on to show that alkoxyamines derived from the diphenylnitroxide and chain-carrying hexadecyl radicals decomposed at temperatures above 120 °C to give the diphenylamine in very good yield. Hence, they proposed a catalytic cycle wherein the nitroxide that is generated by the reaction of the diphenylaminyl radicals with peroxy radicals traps an alkyl radical to yield an alkoxyamine, which decomposes to regenerate the original diphenylamine and produce a corresponding carbonyl compound. This catalytic inhibitory activity is summarized in Scheme 23.



The proposed catalytic cycle requires that the nitroxide trap an alkyl radical in competition with O_2 . Since both reactions are diffusion-controlled, this requires a substantial concentration of nitroxide.



Scheme 23 Korcek and coworkers' mechanism for the catalytic inhibition of oxidation by diarylamines.

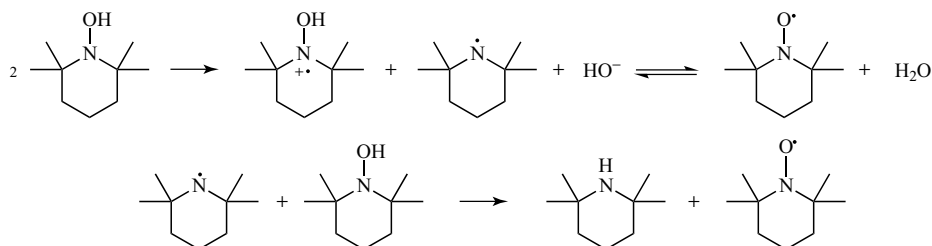
Indeed, in their experiments, Korcek and coworkers used an amount of amine/nitroxide that is on the same order as $[\text{O}_2]$ (i.e., $\sim 1 \text{ mM}$), making this competition possible. It should be pointed out that, in motor oils, it is not unusual for the amine concentration to be at least this high.

3.2.2 Hydroxylamines

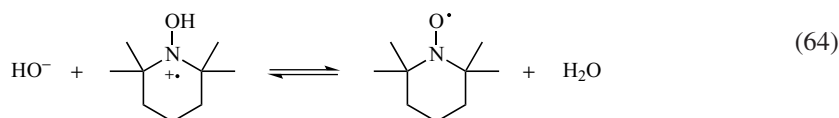
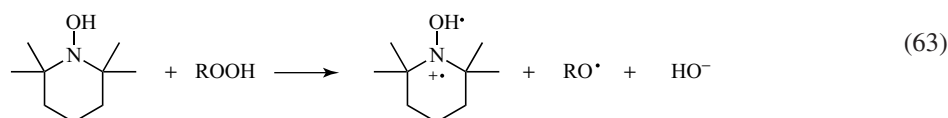
Hydroxylamines are known to have very weak O–H bonds and hence may be expected to be effective antioxidants. For example, TEMPO-H, the hydroxylamine of TEMPO, has an O–H BDE of $69.7 \text{ kcal mol}^{-1}$ —perhaps the weakest O–H bond to be accurately measured (REqEPR).^{179,180} Indeed, its rate constant for reaction with peroxy radicals (62) is $3.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 30 °C in chlorobenzene, making it as reactive as α -TOH. The structurally similar 4-oxo-TEMPO-H was also reported to react quickly with peroxy radicals ($k_{\text{inh}} = 5.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ in *o*-dichlorobenzene),¹⁸¹ albeit a bit slower because of a slightly stronger O–H bond.¹⁸²

The reaction has a DKIE of $k_{\text{H}}/k_{\text{D}} = 3.0$ and is slowed slightly in H-bond accepting solvents (a factor of 1.3 on going from chlorobenzene to CH_3CN). The stoichiometric factor is 1. The reaction likely takes place by a PCET mechanism as for phenols and amines.¹¹²

While the thermodynamics and kinetics of their peroxy radical trapping activity indicate that this class of compounds should function effectively as inhibitors of oxidation, in practice their usefulness as antioxidants is limited by their facile oxidation to nitroxides by product hydroperoxides (63 and 64); as such, under some conditions they may operate as initiators. It should also be pointed out that the hydroxylamines themselves are not very stable, either in the presence or absence of oxygen. The two major products are the corresponding nitroxide and amine, formed in a 2 : 1 ratio, perhaps by the following reactions (Scheme 24):



Scheme 24 Anaerobic decomposition of hydroxylamines to the corresponding nitroxide (2 equiv) and amine (1 equiv).

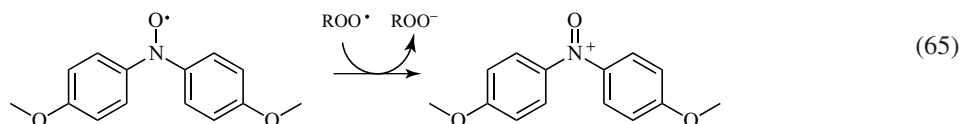


Nonetheless, hydroxylamines can be stabilized by conversion to their corresponding hydrochloride salts, which are not active as antioxidants; in some cases, these water-soluble forms can release the “active” hydroxylamine in biological environments, and have been shown to possess antioxidant behavior both *ex vivo* and *in vivo* in human or other animal tissues.^{183–185}

3.2.3 Nitroxides

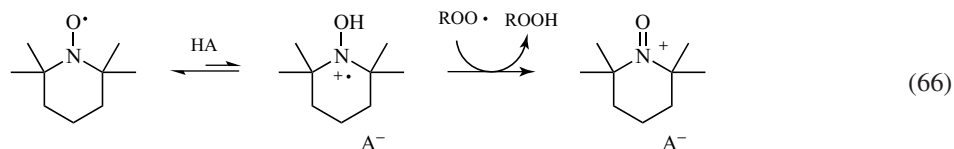
As discussed elsewhere in this encyclopedia, nitroxides have a rich chemistry revolving largely around their ability to trap alkyl radicals (see **Nitroxides in Synthetic Radical Chemistry** and **Nitroxide-Mediated Polymerization and its Applications**). The dogma of the

radical chemistry of nitroxides is that they are unreactive to O₂ or oxygen-centered radicals.³³ As such, for all but a handful of cases, they exhibit antioxidant activity simply by competing with O₂ for the chain-carrying alkyl radicals. The exception would appear to be electron-rich diarylamine-derived nitroxides, which give measurable rate constants for their reactions with peroxy radicals (e.g., 4,4'-dimethoxydiphenyl nitroxide, $k_{\text{inh}} \sim 5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$).¹⁸¹ While the mechanism has not been studied in detail, this may simply reflect the ease with which the peroxy can be reduced by electron transfer from the nitroxide, prompted by the formation of a stable corresponding oxoammonium ion (65). Alternatively, one could envision a Russell-type mechanism similar to that responsible for chain termination in uninhibited autoxidation. Diphenylnitroxides generally have stoichiometric factors of 1.



Recently, we revisited the reactivity of nitroxides with peroxy radicals.¹¹² In fact, we found that nitroxides could be *very* effective antioxidants, but only in the presence of a protic acid. For example, upon inclusion of 10 mM *p*-TsOH in the autoxidation mixture, the reaction went from proceeding with no visible inhibition period to one from which an inhibition rate constant of $1.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ could be derived. Extension of the investigation to a series of organic acids of different strengths showed that the rate constants were clearly dependent on the $\text{p}K_{\text{a}}$ of the acid.

Further mechanistic studies revealed similarities with the previous examples. On changing the solvent from the relatively polar hydrogen-bond accepting (HBA) solvent CH_3CN to the relatively nonpolar non-HBA solvent chlorobenzene, the inhibition rate constants became larger. Furthermore, normal DKIEs were measured ($k_{\text{H}}/k_{\text{D}} = 2.2\text{--}2.4$), similar to those for hydroxylamines and aromatic amines. All in all, the acid dependence, kinetic solvent effects, and kinetic isotope effects point to a mechanism involving an unfavorable equilibrium ($\text{p}K_{\text{a}}$ of $\text{TEMPOH}^{+\bullet}$ is -5.8 in water) preceding a presumably facile H-atom transfer (66):



In an effort to help understand the goings on, we employed theoretical calculations, which indicated that protonated nitroxides are expected to have very weak O–H bonds, $\sim 10 \text{ kcal mol}^{-1}$ weaker than the corresponding hydroxylamines. Moreover, transition-state structures for reactions with peroxy radicals could be calculated, which had negligible activation energies, consistent with the observed fast kinetics.

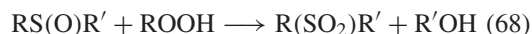
Perhaps, most interestingly, in the presence of the weakest acids (i.e., acetic and benzoic acid), the antioxidant activity of TEMPO became catalytic. That is, the autoxidation remained essentially infinitely inhibited and TEMPO was not consumed in the reaction. This result is curious, as it implies that the oxoammonium ion derived from TEMPO is

reduced back to TEMPO in the reaction. The identity of the reducing agent remains a mystery, but it seems that the most likely candidate is the conjugate base of the acid (i.e., acetate or benzoate). This result presents an alternative, or perhaps complementary, explanation to the large stoichiometric factors observed in diarylamine-inhibited autoxidations at high temperatures since it is well known that carboxylic acids are formed as oxidation products under those conditions.

3.3 Thiols and Other Sulfur-Containing Compounds

Sulfur-containing compounds, particularly those in the S(II) oxidation state, can be effective reductants and most do react with peroxy radicals. For the most part, however, sulfur-containing compounds react in a two-electron fashion with hydroperoxides, and therefore have “preventive” activity as hydroperoxide-decomposing agents rather than chain-breaking activity. For instance, dialkyl disulfides are oxidized first to sulfoxides and

then sulfones upon reaction with hydroperoxides, giving rise to alcohols (67 and 68):



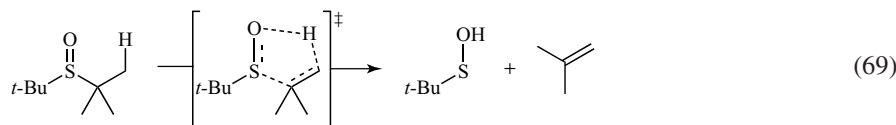
These reactions are acid-catalyzed, and are greatly facilitated by protic solvents.^{186,187}

3.3.1 Thiols

Thiols have a labile H atom and undergo H-atom transfer reactions with many radicals. In the case of peroxy radicals, the rates for these reactions

are modest (i.e., 10^3 – $10^5 \text{ M}^{-1} \text{ s}^{-1}$) and generally compete with the (two-electron) reaction of the thiol with a hydroperoxide under typical autoxidative conditions—nonradical chemistry leading to an alcohol and sulfenic acid as the primary product. The kinetics of the reactions of thiols with peroxy radicals is highly medium dependent; in aqueous

acid from the sulfoxide. Koelewijn and Berger have shown that di-*tert*-butylsulfoxide decomposes at or above 60°C to give rise to 2-methylpropanesulfenic acid and isobutylene (69), the former of which was estimated by them to react with the chain-carrying peroxy radicals in the autoxidation of tetralin with a rate constant of $\sim 1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.¹⁹⁰



solution, the rates are higher, presumably because the thiolate (thiol $\text{p}K_{\text{a}} \sim 8$) reacts by electron transfer. In organic solution, the rates are lower, presumably since a HAT (or PCET) mechanism operates. The S–H BDE of alkylthiols is $\sim 89 \pm 1$.¹⁸⁸

The reaction of thiophenol and tertiary peroxy radicals has been characterized by a very low pre-exponential factor of $\log A = 4.5 \text{ M}^{-1} \text{ s}^{-1}$, which accounts for its modest measured rate constant of only $5.1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ at 30°C , despite its extremely low activation energy of only $1.1 \text{ kcal mol}^{-1}$.¹³⁷ The low activation energy (compared to $5.2 \text{ kcal mol}^{-1}$ for phenol and $5.0 \text{ kcal mol}^{-1}$ for aniline) is likely the result of the weak S–H bond. Experimental S–H BDEs in thiophenol range from 78.7 to $83.9 \text{ kcal mol}^{-1}$,¹⁸⁹ which is lower than in phenol ($\sim 87 \text{ kcal mol}^{-1}$) and aniline ($\sim 89 \text{ kcal mol}^{-1}$). The reasons for the low A -factor are unclear, since it is anticipated that the mechanism of the reaction would be the same as for phenol and aniline: a PCET-type of formal HAT.

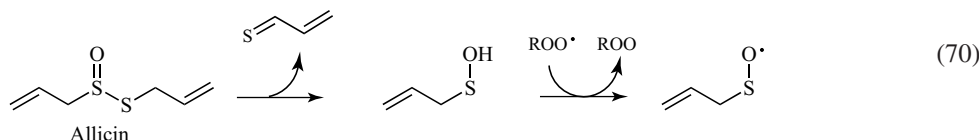
3.3.2 Sulfoxides

Sulfides, once oxidized to sulfoxides as above, can give rise to high radical-trapping activity. The mechanism has not been studied in detail, but is believed to rely on the elimination of a sulfenic

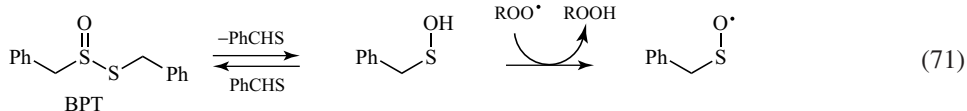
This high reactivity can be explained by the very low O–H BDE of sulfenic acids, an example of which has recently been determined experimentally to be $71.9 \text{ kcal mol}^{-1}$ (for the persistent 9-triptycenesulfenic acid).¹⁹¹ Theoretical calculations further suggest that alkanesulfenic acids react with peroxy radicals by a barrierless PCET mechanism, thereby implying that these reactions are diffusion-controlled.¹¹¹ Hence, the inhibition kinetics of sulfoxides should relate directly to their propensity to undergo elimination, which is particularly facile for hindered sulfoxides such as the di-*tert*-butylsulfoxide studied by Berger and Koelewijn (e.g., $k_{\text{elim}} = 1.8 \times 10^{-3} \text{ s}^{-1}$ for $\text{R} = \text{R}' = t\text{-Bu}$; $4.6 \times 10^{-5} \text{ s}^{-1}$ for $\text{R} = t\text{-Bu}$ and $\text{R}' = i\text{-Pr}$; and $6.3 \times 10^{-8} \text{ s}^{-1}$ for $\text{R} = t\text{-Bu}$ and $\text{R}' = \text{Me}$).¹⁹²

3.3.3 Thiosulfinates

Thiosulfinates, which are abundant in the plants of the *Allium* genus (e.g., garlic, onions, leeks, and shallots), can eliminate sulfenic acids readily owing to the weaker S–S bond in these compounds as compared to the S–C bond in sulfoxides. A particularly reactive thiosulfinate is allicin, the compound responsible for the odor and flavor of garlic. Allicin decomposes readily at room temperature, facilitated by the weak allylic C–H bond that is broken upon elimination of 2-propenesulfenic acid (70).¹¹¹



Most other *Allium* species contain thiosulfonates without equivalently activated C–H bonds, accounting for their lack of comparable antioxidant activity. An exception is the benzylic analog of allicin, *S*-benzyl phenylmethanethiosulfonate (BPT), which has also been demonstrated to be an effective antioxidant. *Peteveria alliacea*, the plant from which BPT was isolated, has been used as a medicine for centuries for essentially the same purposes as garlic. Interestingly, while BPT decomposes to yield phenylmethanesulfenic acid at much the same rate as allicin decomposes to yield 2-propenesulfenic acid, the decomposition of BPT is reversible (71), making it much more useful for applications.¹⁹³



4 SYNERGISTIC BEHAVIOR AND COOPERATIVITY AMONG ANTIOXIDANTS

In the design of commercial antioxidant formulations, whether it be to protect primary petroleum products, polymers, or foodstuffs, it is often convenient to use a combination of antioxidants. Furthermore, it is often that antioxidant additives with different mechanisms of action are chosen to make up the formulation, for example, preventive and chain-breaking, so as to guarantee that failure of one component will be compensated by the presence of the other(s). The same design is evident in the way antioxidant defense systems have evolved in aerobic organisms. Even though we focus our attention on only chain-breaking antioxidants, we note that several of them are found in combination in natural systems where they display an efficacy that is higher than that expected from the sum of the activity of the individual components. Therefore, they have *synergistic* behavior rather than simply *additive*.

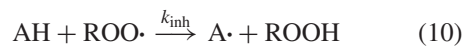
In 1941, Columbic and Matill observed that the antioxidant activity of vitamin E (α -TOH) is enhanced in the presence of vitamin C (ascorbic acid).¹⁹⁴ Since then, several investigations have clearly demonstrated that these two vitamins show

a synergistic behavior. The most exhaustive studies have been reported by Niki *et al.*¹⁹⁵ in homogeneous solutions, and by Ingold and coworkers¹⁹⁶ in multilamellar phospholipid liposomes. Synergism with α -TOH has also been reported for ubiquinol in liposomes^{197,198} or in homogeneous solution,¹⁹⁸ and for several other antioxidants.⁵¹

4.1 Homogeneous Media

The inhibition kinetics of mixtures of antioxidants in homogeneous organic solutions has been

fully rationalized through co-inhibited autoxidation studies.^{59,199} When two antioxidants are added during the autoxidation of a substrate, they will react with chain-carrying peroxy radicals according to their individual inhibition rate constants (k_{inh}). In the case that one of the two compounds (AH) is significantly more reactive toward peroxy radicals than the other (CoAH), that is, $k_{\text{inh}} \gg k'_{\text{inh}}$, it could be expected that it is consumed first (via (10 and 11)), followed by the slower consumption of the antioxidant which reacts more slowly with peroxy radicals (via (72 and 73)).



This would result in an initial efficient inhibition of autoxidation, followed by a less efficient inhibition after consumption of AH, that is, a purely additive contribution of the two antioxidants, as illustrated in trace (d) of Figure 10. However, in some cases, the observed behavior is similar to

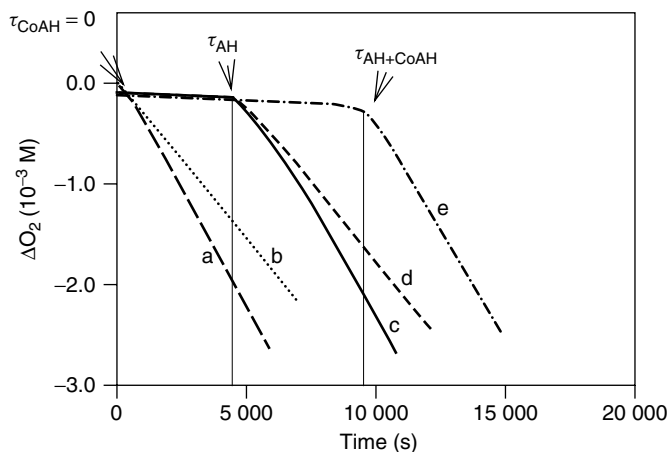


Figure 10 Typical oxygen uptake profile from the AIBN-initiated autoxidation of styrene in the absence of antioxidant (a), in the presence of a modest antioxidant CoAH (b), in the presence of a good antioxidant AH (c), in the presence of a 1 : 1 mixture of AH and CoAH where the kinetics are additive (d), or in the presence of a 1 : 1 mixture of AH and CoAH where CoAH regenerates the more reactive AH as in Scheme 24 (e).

that shown in trace (e) of Figure 10, with a slope of oxygen consumption close to that given by the best inhibitor (AH) and a duration of inhibition identical to that expected from the best inhibitor in case its concentration was equal to the sum $[AH]_0 + [CoAH]_0$, which implies a fully synergistic behavior. Synergism can be explained according to Scheme 25: that is, it is due to regeneration of AH from its radical at the expenses of CoAH.

Depending on the relative rates of regeneration, the inverse reaction (k_r/k_{-r}), and the rate of reaction of $A^\bullet$ with peroxy radicals, the antioxidant system will behave as purely additive ($\tau_{CoAH+AH} = \tau_{CoAH} + \tau_{AH} \approx \tau_{AH}$), purely synergistic ($\tau_{CoAH+AH} = 2\tau_{AH}$), or something in between. The efficiency of regeneration α can be determined from the stoichiometric coefficient measured for

the coantioxidant according to (73 and 74):

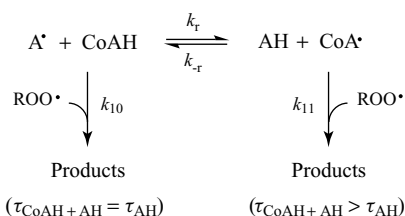
$$n_{CoAH} = R_i(\tau_{AH+CoAH} - \tau_{AH})/[CoAH] \quad (73)$$

$$n_{CoAH} = 2\alpha \text{ with } 0 \leq \alpha \leq 1 \quad (74)$$

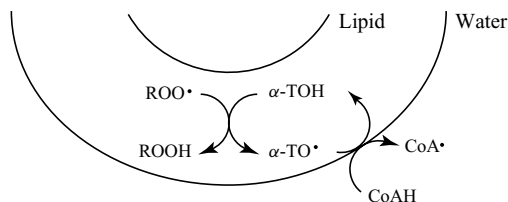
In the case of a coantioxidant such as vitamin C, which normally scavenges only one peroxy radical, (74) becomes $n_{CoAH} = \alpha$. It has been shown that α is close to 1 when the regeneration is essentially irreversible, or when $k_r/k_{-r} \geq 1$: that is, when the coantioxidant has an O–H BDE lower than (or similar to) that of the more reactive antioxidant.

4.2 Heterogeneous Media

In heterogeneous media, the antioxidant and coantioxidant can be confined to two different compartments, that is, the aqueous phase and organic phase of micelles, or some other form of aqueous dispersion. A particularly relevant example is in cells, where the lipid-soluble antioxidants partition to the lipid bilayer (e.g., α -TOH) and the water-soluble antioxidants to the cytosol and/or extracellular matrix (e.g., ascorbate). As such, the interaction of the two antioxidants must take place at the interface, as illustrated in Scheme 26.

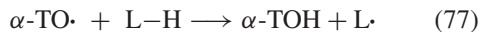
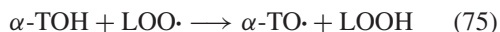


Scheme 25 Cooperativity between antioxidants in homogeneous solution.



Scheme 26 Cooperativity in heterogeneous systems.

When autoxidation occurs in the lipophilic region of such biphasic systems, synergism implies the exportation of the radical outside the “oxidizable compartment,” and into the aqueous environment where the coantioxidant is confined. An important example of this in a biological context involves the interplay between α -TOH and ascorbate in the inhibition of LDL oxidation. In the absence of ascorbate, α -TOH reacts with a chain-carrying lipid peroxyl radical (75); but in competition with the expected second chain-breaking reaction (76), the α -tocopheroxyl radical can react with a lipid in a chain transfer reaction, thereby mediating the chain reaction in lieu of inhibiting it. This has been referred to as *tocopherol-mediated peroxidation* (TMP).²⁰⁰ The reason (76) is slowed in this context relative to (77) is simply due to the vanishingly small steady-state numbers of radicals in the LDL particle. Since they are confined to the particle because of their solubility, they cannot diffuse to other particles in order to undergo either chain termination or (76).



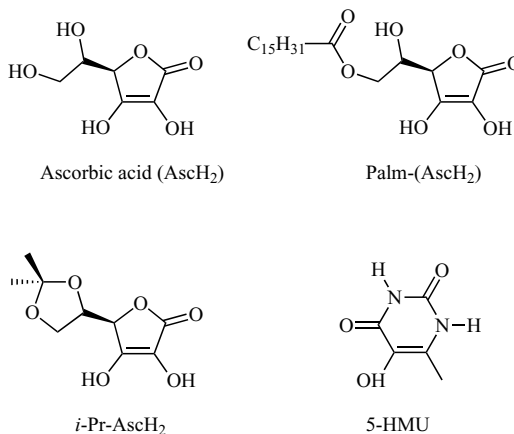
When ascorbate is present in the aqueous phase, it can reduce the α -tocopheroxyl radical back to α -TOH, thereby subverting the TMP reaction (77). Besides the tocopherol/ascorbate couple, recent examples of synergism in heterogeneous media include those in liposomes between α -TOH and water-soluble 3-pyridinols,⁸⁰ or in water/chlorobenzene biphasic system between several organochalcogen-substituted phenols or 3-pyridinols and *N*-acetylcysteine.²⁰¹

5 OTHER RADICAL-TRAPPING ANTIOXIDANTS

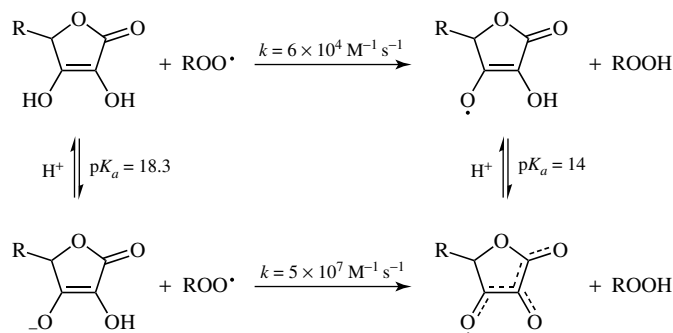
5.1 Ascorbic Acid and Related Compounds

Ascorbic acid (vitamin C) is a potent water-soluble chain-breaking antioxidant whose primary role in biological systems is as a reducing cofactor, comprising the quenching of peroxyl and hydroperoxyl radicals in the aqueous intra- and extracellular environment. It also regenerates α -TOH and ubiquinol from their phenoxyl radicals at the lipid–water interface as illustrated in Section 4.2.²⁰²

Ascorbic acid (AscH_2) has a $\text{p}K_a$ of 4.1 in water, and therefore at physiological pH its antioxidant/reducing activity is to be ascribed to the ascorbate anion (AscH^-). Regardless, the radical-trapping antioxidant activity of both AscH_2 and AscH^- stems from their ability to react with peroxyl (or hydroperoxyl) radicals by formal H-atom transfer from the hydroxyl moiety in the 3- or 2-positions, respectively. The O–H BDEs of AscH_2 and AscH^- have been determined to be 78.0 and 71.8 kcal mol^{−1}, respectively, in water,^{150,203} and their respective rate constants for reaction with $\text{HOO}\cdot$ have been estimated as 1.6×10^4 and $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.²⁰⁴



Owing to the limited air stability of aqueous solutions of ascorbate and the insolubility of ascorbic acid in most lipid environments, ascorbic acid has found only limited industrial application. However, a number of lipid-soluble derivatives such as ascorbyl palmitate (Palm-AscH_2) and the isopropylidene $i\text{-Pr-AscH}_2$ have been employed as antioxidants.



Scheme 27 Antioxidant activity of ascorbic acid derivatives in acetonitrile.

In organic solvents (such as acetonitrile), they still behave as weak acids,²⁰⁵ and have similar antioxidant activity (e.g., in the protection of styrene) as AscH_2 and AscH^- with k_{inh} of 6×10^4 and $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the acid and conjugate base, respectively, as illustrated in Scheme 27.¹⁴⁹

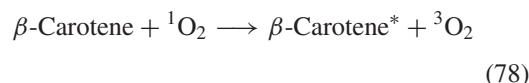
Such a large difference in reactivity (~ 1000 -fold) between the neutral and anionic forms has been found to parallel the very large difference ($\sim 9 \text{ kcal mol}^{-1}$) in their O–H BDEs, which have been determined by REqEPR in *tert*-butanol as 81.0 and $72.2 \text{ kcal mol}^{-1}$ for Palm- AscH_2 and Palm- AscH^- , respectively. Similar values were also obtained from calculations.¹⁴⁹

5-Hydroxy-4-methyluracil (5-HMU), an immunotropic drug, is structurally related to ascorbic acid and has been found to undergo identical behavior with peroxy radicals: its k_{inh} in acetonitrile (at 30°C) was determined to be $1.5 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and was found to be dramatically enhanced in the presence of bases, as a result of partial deprotonation of the ring N–H moiety at the 3-position ($\text{pK}_a = 8.5$ in water).²⁰⁶

5.2 β -Carotene and Related Compounds

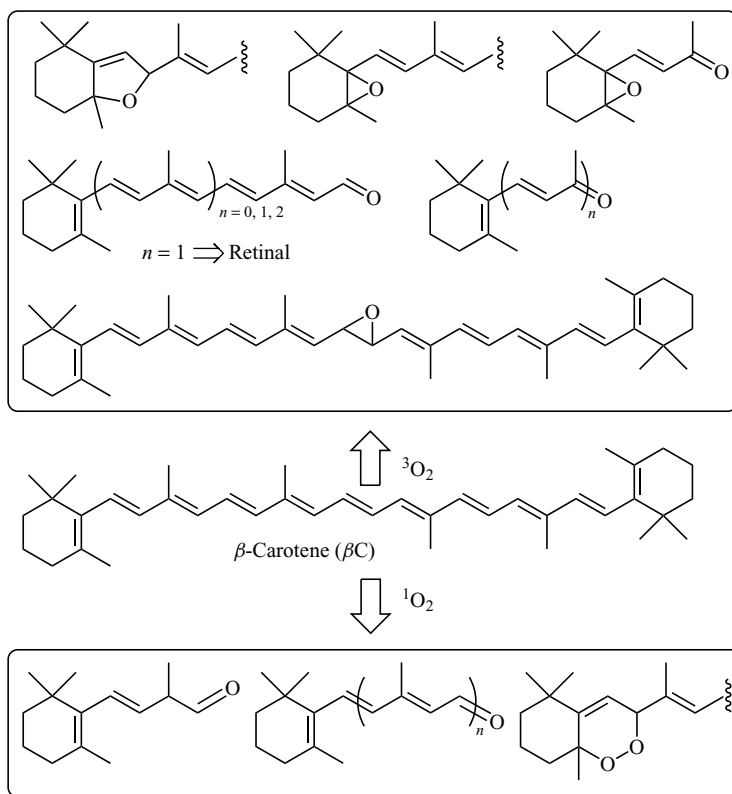
β -Carotene has long been known as one of the most effective natural product quenchers of singlet oxygen ($^1\text{O}_2$), prompting its use as a protectant against skin photodamage. The predominant quenching mechanism is the physical quenching reaction, illustrated in (78), in which the carotenoid converts singlet oxygen into its ground (triplet) state by absorbing excess energy which is then thermally dispersed.²⁰⁷ It has been reported that a single

β -carotene molecule quenches up to 1000 molecules of $^1\text{O}_2$; however, it eventually undergoes oxidation (chemical quenching) to yield endoperoxides (via $4 + 2$ cycloadditions) and carbonyl fragments (from fragmentations of hydroperoxides), as depicted in Scheme 28.⁷⁶

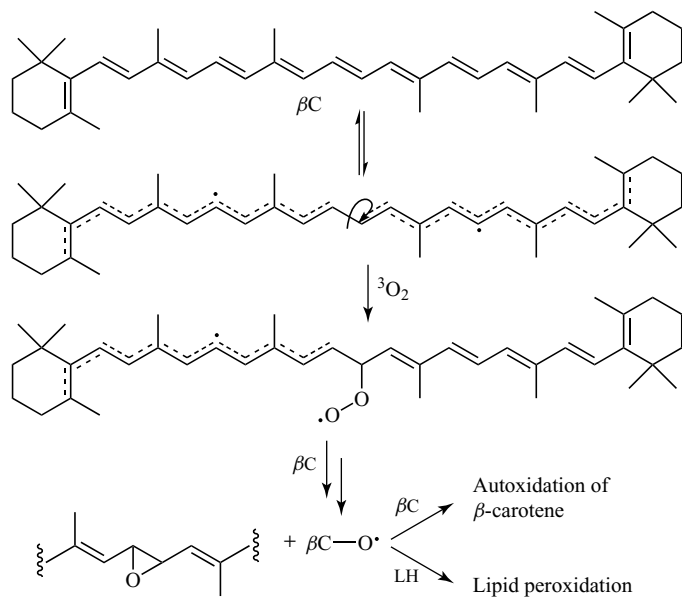


β -Carotene also autoxidizes quite readily. When left in the dark at room temperature, solutions of β -carotene yield a multitude of oxygenated products comprising epoxides, conjugated aldehydes (including retinal, vitamin A), ketones, and dihydrofurans (Scheme 28).²⁰⁹ The initial product distribution undergoes further change in composition with time and yields more oxidized products (including carboxylic acids) with shorter and shorter hydrocarbon chain length. The autoxidation of β -carotene can be inhibited with α -TOH.²¹⁰

The mechanism of autoxidation of β -carotene is believed to be self-initiated, as illustrated in Scheme 29. The unusual mechanism involves the formation of a highly conjugated singlet biradical, which reacts with oxygen to form a triplet peroxy biradical, which can add to another molecule of β -carotene to form a peroxidic triplet biradical that can decompose via several different mechanisms, one of which involves the formation of an epoxide and an alkoxyl radical. In the presence of polyunsaturated lipids (e.g., in biological membranes), either the alkoxyl radical or the peroxy radical initially formed can initiate lipid peroxidation, meaning that β -carotene can act as a pro-oxidant in oxygen-rich lipid environments.



Scheme 28 Typical oxidation products formed by reaction of β -carotene with triplet or singlet oxygen at room temperature.

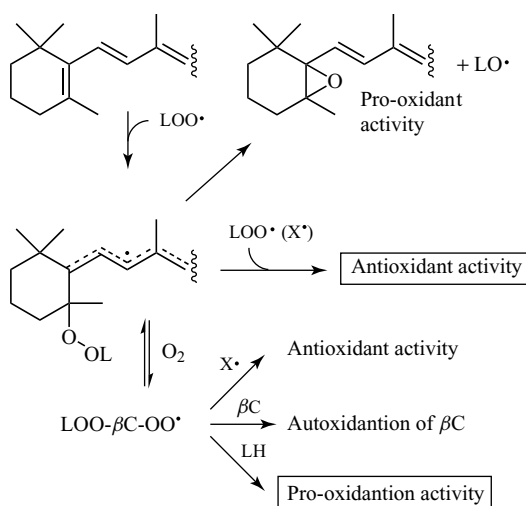


Scheme 29 Self-initiated autoxidation of β -carotene and initiation of lipid peroxidation.

On the other hand, β -carotene blood levels and the dietary intake of carotenoids have long been known to correlate inversely with the incidence of certain human cancers, leading to the suggestion that it plays a beneficial role in preventing lipid peroxidation as an antioxidant.²¹¹

Indeed β -carotene reacts rapidly with peroxy radicals, mainly by addition to the extended π system to yield a highly stabilized alkyl radical; however, the antioxidant behavior of β -carotene depends entirely on the fate of such a LOO- β C $\cdot$ radical, which in turn depends on the experimental and environmental conditions (Scheme 30). It was first shown by Burton and Ingold,²¹² and later confirmed by several other studies,²¹³ that β -carotene can protect oxidizable substrates such as polyunsaturated lipids from autoxidation/peroxidation, but only at low partial pressure of oxygen ($pO_2 > 150$ mmHg), while it loses its chain-breaking behavior or it can turn into a pro-oxidant at higher pO_2 .²¹⁴

This is due to the reversible addition of oxygen to the delocalized LOO- β C $\cdot$ radical to form a variety of peroxy radicals that might propagate the autoxidation chain or bring on rapid carotene autoxidation: this reaction, which is clearly favored by high concentrations of oxygen, competes with the antioxidant behavior that prevails at low pO_2 levels (Scheme 30).



Scheme 30 Antioxidant activity of β -carotene as a function of pO_2 .

Even when antioxidant behavior prevails, it is much less efficient than that of other natural antioxidants such as α -TOH, and only comparable to BHT in homogeneous solution.²¹⁵ Unlike other coantioxidants (e.g., ubiquinol, flavonoids, and ascorbic acid), β -carotene is unable to spare or regenerate α -TOH and, when used in combination, gives no synergism.^{215,216}

Indeed, the antioxidant role for β -carotene in biological systems is highly controversial. For instance, its dietary supplementation was found to be pro-oxidant in rats²¹⁷ and it has been found to afford no protection of LDL oxidation in humans.²¹⁸ Not surprisingly, in controlled clinical trials β -carotene produced an increase in mortality from cancer of the lungs,²¹⁹ a tissue exposed to the highest pO_2 among biological environments.

6 FUTURE PERSPECTIVES

Antioxidant research is a well-established and relatively mature field of application of free radical chemistry, which has benefited from about 60 years of investigation at all levels—from fundamental chemistry to applications in the petroleum and polymer sciences, biology, medicine, and food science. The chemistry of hydrocarbon (and lipid) autoxidation and the basic mechanisms by which they are inhibited by antioxidants are well understood. This is particularly true for phenolic antioxidants, whose chain-breaking antioxidant activity and structure–activity relationships have been characterized within a robust framework based on decades of detailed kinetic and thermodynamic studies. Nevertheless, some specific yet very relevant aspects appear to require further attention. One such aspect is the temperature dependence of their antioxidant behavior; most of the useful data is confined to a narrow temperature range, which is not particularly reflective of the conditions under which the compounds are most often applied (e.g., the protection of polymers during extrusion or motor oils under operative conditions) and has precluded the derivation of the Arrhenius parameters that govern their reaction with peroxy (and other relevant) radicals. These data would allow a deeper comprehension of the mechanism of such reactions, thereby facilitating the prediction of their antioxidant behavior under most conditions. The influence of the medium on phenolic antioxidant activity is another relevant issue that

has received somewhat less attention. Particularly, the occurrence of acid and base catalysis and their role in the antioxidant mechanism and kinetics has only recently been uncovered, and certainly merits further investigation—particularly relating to its implications on the biological role of both phenolic and nonphenolic antioxidants.

Unlike phenolic and phenolic-like antioxidants, comparatively little is known of the antioxidant chemistry of the other relevant compounds introduced above, such as diarylamines and nitroxides (both aliphatic and aromatic). The former have been employed extensively as antioxidants in commercial products and industrial processes; however, their significance has been largely overlooked by the academic scientific community, and a fundamental understanding of their chemistry is still lacking. Nitroxides, on the other hand, are possibly the most investigated radical species and have been used (or proposed to be of use) in an extraordinary variety of scientific and industrial applications. Nevertheless, the mechanism of their antioxidant behavior has long eluded recognition. The very recent discovery of their acid-catalyzed chain-breaking antioxidant activity has been a breakthrough in this area, and most certainly needs to be more thoroughly explored—particularly in light of the recent and rapidly growing awareness of the biological activity and potential pharmaceutical applications of these compounds.

Other important antioxidants that deserve further investigation are sulfur-containing compounds, in particular, sulfenic acids and their precursor thiosulfonates, as well as isothiocyanates and their precursor glucosinolates. Sulfenic acids and sulfinyl radicals are among the least well-characterized functional groups regularly encountered in organic chemistry because of the instability of most derivatives. Nonetheless, they figure prominently in the biochemistry of thiols, the most abundant antioxidants in biological systems, and in the biological activity of (dietary and medicinal) plant-derived disulfides and thiosulfonates. Indeed, further efforts should be made to provide a deeper understanding of their properties and reactivity.

The biological role and medicinal application of antioxidants, as well as their (nutritional) chemopreventive potential, still remains to be clarified, notwithstanding the major efforts devoted to this area of research in recent years. This is due, in part, to the continued uncertainty regarding

the role of oxidative stress and the intervention of free-radical intermediates in degenerative disease—from atherosclerosis to Alzheimer's—as well as cancer and aging. While there is overwhelming evidence that implicates oxidative stress in disease pathogenesis, antioxidant intervention has produced few tangible results that support a causative role. However, it should be pointed out that clinical investigations have so far focused on a relatively limited number of molecules, most notably β -carotene, vitamin E, and vitamin C. β -Carotene has been particularly popular in such experiments, presumably due to its facile monitoring by analytical techniques, leading to the common use of it as a key indicator for antioxidant content and dietary intake in epidemiological investigations correlating fruit/vegetable consumption and occurrence of chronic diseases. This has prompted a focus on β -carotene (and/or retinol, vitamin A) in the majority of clinical trials for dietary antioxidants on primary or secondary prevention of chronic diseases.²²⁰ The disappointing outcomes of the majority of clinical trials carried out to date have somewhat reduced the enthusiasm of the medical community toward the extraordinary potential that antioxidants have in therapy and prevention. However, it must be reiterated that investigations have been largely limited to a very small series of compounds, many of which have not proven to be particularly effective antioxidants in detailed investigations such as those described above (i.e., β -carotene). Indeed, despite their popularity, very few data are available on the bioavailability and metabolic fate of many phenolics, such as the polyphenolic flavonoids and isothiocyanates. Furthermore, to the best of our knowledge, no clinical trial has ever evaluated their activity in humans. The observation of lifespan extension in invertebrates as a consequence of antioxidant treatment,²²¹ among other exciting discoveries, continues to renew enthusiasm in antioxidant research, and clearly indicates that a deeper understanding of the role of oxidative stress and the intervention of chain-breaking antioxidants in disease pathogenesis and aging is one of the most important research topics of our time. The relatively recent recognition that reactive oxygen species contribute much more to cellular signaling in advanced organisms than previously thought²²² complicates things even further, but reinforces that much remains to be done.

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Free Radicals and Metabolic Disorders

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1 INTRODUCTION

Free radicals are often formed and released following tissue injury owing to internal or external pathological processes. In many cases, the triggering role of free radical-generating systems has been associated with distinct pathological interactions. For instance, the ability of ionizing ultraviolet-A radiation to induce skin disorders, ranging from hyperpigmentation to melanoma, results from the generation of chemically reactive radicals in skin cells.^{1–4} Myocardial ischemic-reperfusion injury has been attributed to an enhanced generation of reactive oxygen species (ROS) in ischemic regions.^{5,6} Another example is Paraquat (*N,N'*-dimethyl-4,4'-bipyridinium dichloride)-induced symptoms of Parkinson's disease that result from irreversible nigrostriatal dopaminergic neurotoxicity owing to an impairment of mitochondrial function and production of ROS.^{7,8} In contrast to such well-defined processes, the metabolic syndrome consists of multiple disorders that collectively increase the risk of developing type-2 diabetes (T2D) and cardiovascular disease. A cluster of metabolic risk factors, foremost, hyperglycemia, hyperlipidemia, and obesity, is associated with overproduction of free-radical species, which play significant roles in promoting and exacerbating metabolic abnormalities and related complications.^{9–14} Currently, the prevalence of T2D has reached an epidemic proportions and the number of diabetic individuals in the year of 2030 is estimated to

exceed 300 million worldwide.¹⁵ Thus, attempts to identify new means to treat the disease are intense, and the elimination of free radicals in subjects exhibiting features of the metabolic syndrome is considered a prime target. Therefore, understanding the involvement of free radicals in these metabolic abnormalities is essential. It requires an integrative approach to elucidate the impact of free radicals on cellular and metabolic functions, organ cross-talk, hormonal control mechanisms, and neural regulation. This article focuses on the roles of hyperglycemia, hyperlipidemia, and obesity in free radical-induced metabolic impairments.

2 HYPERGLYCEMIA AND FREE RADICALS

The hallmark of diabetes is hyperglycemia, a condition in which fasting blood glucose levels remain high above the normal range. Several clinical prospective trials (i.e., Diabetes Control and Complications Trial and the UK Prospective Diabetes Study) have established that hyperglycemia promotes severe complications in peripheral organs such as nephropathy, retinopathy, neuropathy, or endothelial cell dysfunction followed by micro- and macrovascular complications.^{16–19} It is generally accepted that intermittent and chronic hyperglycemia mediate long-term modifications of intra- and extracellular macromolecules that in turn alter cells' functions and contribute to the development of peripheral complications.²⁰ Hyperglycemia

results from inadequate insulin secretion owing to pancreatic β -cell failure and/or peripheral insulin resistance. In both cases, high glucose-derived free radicals adversely affect pancreatic β -cells while contributing to the establishment of insulin resistance in the liver and skeletal muscles. The molecular mechanisms that favor free-radical production in living cells are complex and mostly involve nonenzymatic transformations of glucose coupled to an enhanced rate of protein glycation. Consequently, the increased abundance of free-radical species and excessive amounts of glycated proteins severely affect normal cell functions. Cells equipped with efficient antioxidative mechanisms are more protected against the hyperglycemic challenge than cells lacking an efficient radical elimination system. A typical example of the latter is pancreatic β -cells that poorly eliminate free radicals and therefore are exceptionally susceptible to free radical-induced damage.²¹

2.1 Etiology of Hyperglycemia

T2D results from two pathophysiological processes; impaired insulin biosynthesis and glucose-stimulated secretion from pancreatic β -cells and/or peripheral insulin resistance due to alterations in the insulin transduction mechanism of insulin-sensitive tissues.²² Gluco- and lipotoxicity are the two main conditions that adversely affect β -cell function.^{23,24} Numerous *in vitro* and *in vivo* studies have shown that prolonged exposure of β -cells to high glucose and/or lipid levels impair proinsulin synthesis and processing, insulin packaging in granules, and insulin secretion.^{23,25–28} Studies performed on animal models of diabetes and human subjects have shown that insulin resistance results from perturbations in the insulin transduction pathway mainly in the liver and skeletal muscles. Of the main defects found in these two tissues, impaired activation of the adapter protein insulin receptor substrate-1 and -2 (IRS1/IRS2) is the most common. Two main aberrations in IRS function have been identified; the first is an impaired tyrosine phosphorylation following the binding of these proteins to the activated insulin receptor. This reduces the ability of IRS proteins to interact with other transducing proteins in the pathway.^{29–32} The second is the initiation of the phosphorylation of serine moieties in IRS proteins, which directs them to an

enhanced degradation.^{33–40} Since IRS protein interaction with the activated insulin receptor constitutes an obligatory step in insulin transduction in cells, all insulin-mediated cellular functions are downregulated when IRS activation is impaired or its cellular content is reduced.⁴¹ The induction of insulin resistance in the liver compromises the ability of the hormone to suppress endogenous glucose production, to reduce gluconeogenesis, and to augment glycogenesis. Therefore, hepatic insulin resistance results in an uncontrolled and excessive glucose output that worsens hyperglycemia.^{42,43}

Postprandial hyperglycemia normally stimulates insulin secretion from β -cells, which in turn stimulates glucose uptake in skeletal muscles by recruiting the insulin-sensitive glucose transporter-4 to the plasma membrane of myotubes.^{44–46} Prolonged hyperglycemia and hyperlipidemia induce insulin resistance in skeletal muscles by similarly affecting IRS proteins' activity and turnover, thus abrogating the downstream insulin transduction pathway.^{47–49} These postreceptor defects impair insulin-stimulated glucose uptake by skeletal muscles and induce hyperglycemia. Furthermore, when combined with impaired insulin secretion from β -cells, the glucose uptake capacity of the skeletal muscle mass is further impeded and thus exacerbates hyperglycemia.⁵⁰

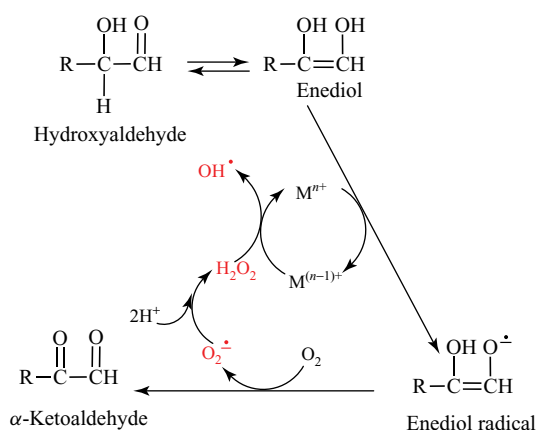
Gluco-lipotoxicity in β -cell refers to various processes that alter the insulin secretory function and survival of the cells when exposed to high glucose and free fatty acids (FFAs) levels. Numerous factors, including glucose, FFA, inflammatory cytokines, and adipokines have been implicated in impairing insulin biosynthesis and secretion and in inducing endoplasmic reticulum (ER) stress and β -cell death in diabetes.^{21,23,24,51,52} Consequently, the decreased insulin secretory capacity and reduction in β -cell mass in islets of Langerhans lead to hypoinsulinemia. When combined with peripheral insulin resistance, this condition further dysregulates peripheral glucose metabolism and aggravates glucose homeostasis.^{53,54}

2.2 Glucose-Derived Free Radicals

Diabetes and oxidative stress have long been connected.^{55,56} Several sources of free radicals, particularly through the mitochondrial respiratory chain and by the action of oxidative enzymes,

such as NADPH oxidase and lipoxygenases, have been identified.²⁰ Glucose autoxidation, protein glycation, and mitochondrial dysfunction are the main processes that overproduce free radicals in diabetes. Nonenzymatic enolization of monosaccharides along with a reduction of molecular oxygen under physiological conditions yields α -ketoaldehydes, hydrogen peroxides, and free-radical intermediates.^{57,58} Thornalley *et al.*⁵⁸ and Wolff and Dean⁵⁹ proposed the mechanism shown in Scheme 1, which describes the enolization of D-glucose and a sequential reduction of a transition metal and molecular oxygen to generate superoxide and ketoaldehyde. Dismutation of the superoxide anion generates hydrogen peroxide, which reoxidizes the transition metal, while reducing a hydroxyl radical. Initially, this model evolved from studies on oxygen consumption and free-radical involvement in glyceraldehyde autoxidation *in vitro*.⁵⁸

Evidence for this mechanism lies in the inhibition of ketoaldehyde formation from glucose in the presence of metal chelators, such as diethylenetriaminepentaacetic acid.^{60,61} This model has prevailed and is often presented in current relevant literature on monosaccharide toxicity. For instance, Okado-Matsumoto and Fridovich⁶² suggest that the tautomerism of open-chain aldoses to the corresponding enediols and their radicals, followed by their rearrangement to the

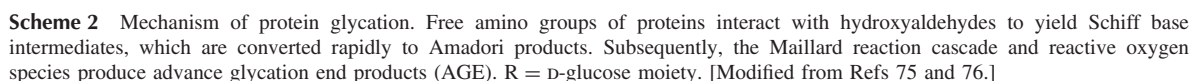


Scheme 1 Glucose autoxidation. D-Glucose enolizes and reduces a transition metal (M) and oxygen to form α -ketoaldehyde. Hydrogen peroxide, which is formed from superoxide anion dismutation, regenerates the metal catalytic oxidation state to produce hydroxyl radicals. R = D-glucose moiety. [Modified from Ref. 59.]

α,β -dicarbonyl derivatives, is the initial and pre-requisite step in the toxicity of short chain sugars. Using Fourier transform infrared (FTIR) spectroscopy, Yaylayan and Ismail⁶³ proposed a dimeric-water catalysis and sugar dimer-self catalysis of enolization. In this process, D-glucose autoxidizes slowly relative to glyceraldehyde; however, the amounts of ketoaldehyde formed in cells over prolonged periods of hyperglycemia may be substantial.⁵⁷ The quarter-of-a-century old debate between Harding and Beswick⁶⁴ and Wolff and Dean⁶¹ on theoretical and technical aspects further clarifies the model. Of a major interest is the association between autoxidation of glucose in the presence of transition metal ions in cells and the incorporation of glucose moieties into proteins.⁶⁵ Nonenzymatic protein glycation is the chemical reaction of reducing carbohydrates with amino moieties. Most D-glucose molecules in water are in the α/β pyranose/furanose ring structures; yet, a small fraction that remains in the open-chain aldehyde form can interact nonenzymatically with available amine residues in proteins.^{66,67}

Scheme 2 shows the interactions of free amino groups of proteins with carbonyl groups that yield Schiff base intermediates. Under physiological conditions, Schiff bases are converted to Amadori products. Subsequently, the Maillard reaction cascade is initiated and leads to the generation of stable carbonylated protein products.^{68,69} These glycation products can be oxidized by free radicals, including hydroxyl radicals, which are formed during glucose autoxidation, to give rise to different advanced glycation end products (AGEs).^{70–73} Apart from monosaccharides, such as D-glucose, AGEs are also produced from glucose metabolites such as glyceraldehyde, glycoaldehyde, methylglyoxal, and glyoxal.^{74,75} It is suggested that in addition to conformational and structural changes induced by carbonylation, protein fragmentation is also increased owing to the augmented generation of ROS through these autoxidative interactions.^{57,73}

Another source for oxidative stress in hyperglycemia is the overproduction of superoxide radicals by mitochondria. Brownlee and colleagues have suggested that overproduction of ROS by the electron-transport system under high glucose conditions underlies various cellular abnormalities typical to diabetes.^{77–79} The flow of electrons from donor molecules to electron acceptors enables the transfer of protons across the mitochondrial membrane,



The increased superoxide production has been associated with the activation of the polyol pathway, increased AGEs formation, activation of protein kinase C (PKC) isoforms, and overactivity of the hexosamine pathway.⁷⁷ The finding that the activity of the key glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is decreased in diabetic animals and patients have been linked to the abnormal activation of these pathways.⁸² The altered GAPDH activity in cells exposed to high glucose levels leads to the accumulation of glyceraldehyde 3-phosphate and upstream glycolytic metabolites. Figure 2 shows the pathways affected by these metabolites^{77,82}: the superoxide-induced activation of poly(ADP-ribose)-polymerase (PARP) adds polymers of ADP-ribose to GAPDH and reduces its enzymatic activity.⁸² Upstream to GAPDH, dihydroxyacetone phosphate generates diacylglycerol, an activator of PKC; triose phosphate is transformed to methylglyoxal, which is a main intracellular AGE precursor. Fructose-6-phosphate is transformed to UDP-*N*-acetylglucosamine, which increases modification of proteins by *O*-linked *N*-acetylglucosamine (GlcNAc). In addition, the increased glucose flux through the polyol pathway consumes NADPH and depletes the reduced glutathione pool in the

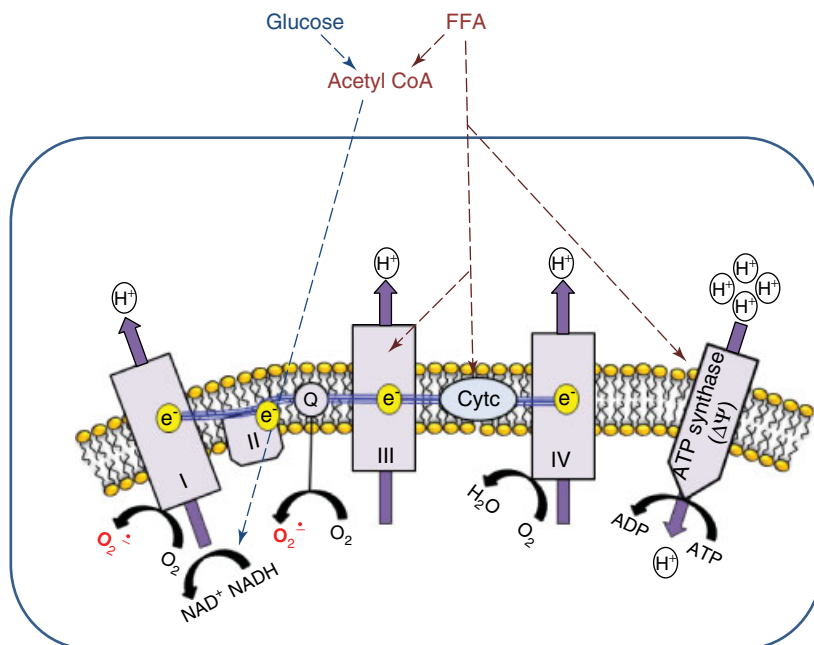


Figure 1 Mitochondrial ROS production. Complexes I and III in the electron-transport chain are the main free-radical generators. High glucose and FFA levels increase NADH/FADH₂ levels. Subsequently, the voltage gradient across the mitochondrial membrane increases up to a level that blocks complex III. Under these conditions, the degree of reduction of complex I increases and excess superoxide is generated by donating electrons to molecular oxygen. In addition, FFA release cytochrome c and has a mild uncoupling effect. [Modified from Ref. 80.]

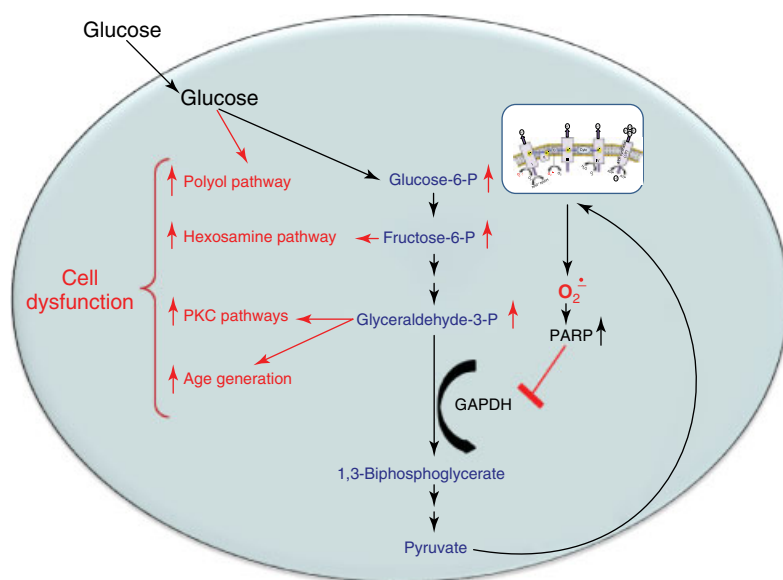


Figure 2 Hyperglycemia and oxidative stress alter normal cell functions. Mitochondrial superoxide radicals activate PARP, which inactivates GAPDH. This results in the accumulation of glyceraldehyde-3-phosphate and of upstream glycolytic intermediates. These intermediates activate various PKC isoforms, increase the polyol- and the hexoseamine pathway fluxes, and augment the generation of AGEs. [Modified from Ref. 80.]

cells. In support of this model is the finding that the scavenging of superoxide radicals rescued GAPDH activity under hyperglycemia condition and corrected the above-mentioned pathways.^{77,83}

2.3 AGE-RAGE-Induced Free-Radical Generation

Intra- and extracellular formation of AGEs underlie the initiation and progression of peripheral diabetic complications. Levels of Amadori and AGE products in mammalian tissues are increased under prolonged hyperglycemia. Glycation and AGEs formation occur extra- and intracellularly. Some AGEs function as activating ligands for receptors for AGEs (RAGE) and operate distinct transduction pathways.^{84,85}

A number of plasma membrane receptors that bind various types of AGEs have been identified and characterized.^{20,86–91} These receptors are ubiquitously expressed and their AGE multiligand specificities have been unraveled.^{20,85,92} Among the AGE-RAGE-dependent cellular effects, the activation of inflammatory signaling is of interest: activated RAGE induces mitochondrial-dependent ROS production and NADPH activation followed the activation of NF- κ B.^{93–97} Several studies have suggested that the activation of NADPH oxidase requires PKC β 2-dependent translocation of subunit p47^{phox} to the plasma membrane and the formation of an active complex with p22^{phox} subunit.^{20,97,98} Other NF- κ B-dependent mechanisms have also been proposed, such as increased expression of inducible nitric oxide synthase (iNOS), cyclooxygenase 2 expression, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and monocyte chemotactic protein (MCP-1).^{99–104} In addition, a role of Toll-like receptor in these interactions has recently emerged.^{105–107} AGE-modified proteins have also been shown to facilitate the degradation of eNOS.¹⁰⁸ Other cellular processes that are altered by AGE-modified proteins in various types of cells include cell proliferation, differentiation, apoptosis, angiogenesis, generation of inflammatory cytokines, and the production and secretion of chemokines.^{20,104,109–114}

The levels of glycated and oxidized lipoproteins are significantly increased in diabetic individuals.^{20,115–118} Lipoprotein glycation is accompanied with oxidation due to the generation

of free radicals during the glycation process.¹¹⁹ Consequently, the metabolic degradation and clearance of VLDL and LDL is impaired and leads to hyperlipidemia, accelerated atherosclerosis, inflammatory signaling, endothelial cell dysfunction, mitogenic effects on vascular smooth muscle cells, foam-cell formation, alteration of platelet function, and pro-coagulant activity.^{20,115,120–126}

The glycation of insulin B-chain at the amino-terminal phenylalanine renders the hormone inactive; yet, although such insulin species were identified in islets of normal and diabetic animal, due to the rapid turnover of the hormone, the impact of this phenomenon on peripheral insulin action is not clear.^{127–130}

The glycation of the N-terminal valine amino group of the β -chain in hemoglobin generates hemoglobin-A1c (HbA1c). This modified protein is used as a biomarker to monitor glycemic control in hyperglycemic individuals. A HbA1c level below 6% is considered normal, while higher levels are indicative of short- to long-term hyperglycemic episodes.¹³¹ Similar to HbA1c, the circulating levels of glycated albumin reflect the glycemic control of hyperglycemic individuals.¹³² Some biological effects of glycated albumin have been linked to proinflammatory signaling, endothelial cell dysfunction, or glomerular nephropathy.^{20,133–136}

These observations indicate that protein glycation, AGEs generation, and the activation of RAGE and RAGE-like receptors are closely involved in the pathophysiology of diabetes and diabetes-related complications. The endothelial cell monolayer in blood vessels is severely affected upon exposure to glycated and AGE-modified LDL. The primary lesions in blood vessels, which promote the formation of atheromatous plaques, have been associated with AGE-induced permeability of the endothelial cell monolayer and with increased chemotactic interactions of monocytes followed by their transcytosis and formation of foam cells.^{119,137} AGE-modified proteins also contribute to the increased incidence of arterial stiffening and restenosis that are common in diabetic patients and appear at younger ages than in the general population.^{20,138–141}

Exposure of the retina to AGE-modified proteins activates microvascular endothelial cells and neoangiogenesis and thrombogenesis^{142–144} along with growth arrest and apoptosis of resident pericytes.¹⁴⁵ Glomerular nephropathy in diabetes

involves thickening of the basement membrane and its interaction with mesangial cells, endothelial cells, and podocytes.^{146,147} These pathological processes are prevented by inhibitors of AGE formation and RAGE blockade.^{142,148–150} AGEs and RAGE also contributed to the development of diabetic neuropathy by causing axonal degradation and demyelination of peripheral nerves. Impaired wound healing in diabetes also involves AGEs and RAGE and alteration in the inflammatory interactions that participate in the healing process.¹⁵¹ The AGE–RAGE–NF- κ B axis has been shown to mediate inflammatory interactions and macrophage invasion associated with these complications.^{152–155}

2.4 Reactive Nitrogen Species

Nitric oxide (NO) and peroxynitrite (ONOO[−]) are the common reactive nitrogen species (RNS). The enzyme nitric oxide synthase (NOS) releases NO radical from L-arginine. Various isotypes of the enzyme are expressed in a cell-specific manner, such as eNOS in vascular endothelial cells and the iNOS in activated macrophages. In the vascular wall, NO mediates vasodilation by relaxing the smooth muscle cells layer, whereas the iNOS-derived NO participates in inflammatory defense mechanisms. The NOS cofactor tetrahydrobiopterin (THB) is particularly susceptible to inactivating interaction, mostly with products of lipid peroxidation, such as 4-hydroxynonenal (4-HNE, see below). Under these circumstances, the lack of THB uncouples NOS that then generates superoxide radicals.¹⁵⁶ Nevertheless, it is not fully clear to what extent RNS play significant roles in obesity and diabetes.¹⁵⁷ While some studies report increased levels of NO metabolites in diabetic individuals,^{158,159} others show significant decrease in NO bioavailability in obesity and diabetes. Several mechanisms have been suggested to explain the latter observations, including reduced NOS expression and function and NOS uncoupling.^{156,160,161}

3 FATTY ACIDS AND FREE RADICALS

Hypertriglyceridemia, low HDL-cholesterol concentration, and high levels of apolipoprotein B-containing lipoproteins are considered

major atherogenic factors in the metabolic syndrome.^{162–165} A significant source for the production of ROS in cells is nonesterified long-chain FFA (and their metabolites).¹⁶⁶ The levels of FFA in plasma and in cells increase under specific physiological conditions, such as restricted nutritional consumption or starvation that mobilize FFA from the triglyceride storage compartment in adipose tissues to peripheral oxidation to meet the organism's energy demands.¹⁶⁷ Hyperlipidemia may also result from genetic abnormalities that alter the structure and function of lipoprotein lipase, LDL receptors, or apolipoproteins.^{168–171} Obesity and diabetes are considered major risk factors in the development of secondary (acquired) hyperlipidemia.^{172–176} Two major metabolic disturbances are associated with the augmented availability of FFA: excessive ROS production and lipid peroxidation. Mitochondrial uncoupling and inhibition of the respiratory chain are the main reasons for FFA-induced ROS production in cells. ROS-induced peroxidation of polyunsaturated fatty acid (PUFA) results in the generation of bioactive aldehyde species, which can act as signaling molecules, on one hand, or cytotoxic agents, on the other.^{156,166,177,178}

3.1 Etiology of Increased Circulating FFA Levels

Clinical studies over the years have demonstrated that elevated plasma FFA levels in T2D patients are common and predictive of the progression of the disease from the pre-diabetic state to overt disease.^{179,180} Normally, the release of FFA from adipose tissues is well-regulated and suits the energy demand of peripheral tissues. This is common when glucose availability to peripheral tissues is limited (e.g., starvation) or when glucose transport and utilization are impaired owing to insulin resistance and downregulation of the glucose transport system in insulin-sensitive- and other tissues.^{181–183} In addition, increased adiposity coupled with insulin resistance in adipose tissues result in an excessive release of FFA, far above the peripheral need.¹⁸⁴ Metabolic overloads, such as overfeeding, hyperglycemia, and/or hyperlipidemia, result in the enlargement of adipocytes, ER stress, hypoxia, and production of ROS, which contribute to the development of insulin resistance in adipocytes.^{185,186} Normally, insulin is a potent

antilipolytic agent in adipocytes through the inhibition of hormone-sensitive lipase that hydrolyzes stored triglyceride to FFA.¹⁸⁷ The loss of this regulatory function in insulin-resistant adipocytes leaves the enzyme free to interact with its positive effectors, catecholamines, and ACTH, resulting in an enhanced TG hydrolysis and increased release of FFA to the circulation.

3.2 Fatty Acids and Mitochondrial Free-Radical Production

FFA can interact with components of the respiratory chain and reduce the rate of the electron transport, which results in an enhanced superoxide anion generation, as suggested in the model proposed by Schönfeld and Wojtczak¹⁶⁶ (Figure 1). FFA inhibit, directly or indirectly, complexes I and III of the electron-transport chain and induce “electron leak” followed by one-electron reduction of molecular oxygen to superoxide anion.^{188–192} It is assumed that increased inner membrane fluidity in the mitochondrion due to FFA incorporation drives this phenomenon.^{193,194} FFA in the outer side of the membrane can interact with cytochrome c and dissociate it from the complex it forms with cardiolipin. The depletion of cytochrome c from the mitochondria interrupts the electron flow from complex III to complex IV.^{195–197} The release of cytochrome c is also associated with the induction of apoptosis in the affected cells.^{198,199} Finally, it is also assumed that increased inner membrane fluidity in the mitochondrion due to FFA incorporation has mild uncoupling effects, which is accompanied with superoxide anion generation.^{193,194} In addition, a role for acyl-CoA thioesters in the generation of ROS in the mitochondrion has been proposed: these compounds, which are the metabolically active forms of FFA, inhibit the adenine nucleotide translocase and di- and tricarboxylate translocases,^{200–202} resulting in the inhibition of ADP/ATP exchange across the inner membrane and subsequently enhance ROS production. Others have shown that these fatty acid thioesters increase the transmembrane potential ($\Delta\psi_m$) and lower the redox state of coenzyme Q, which also results in the generation of mitochondrial superoxide radicals.^{203,204}

Ceramides are amides of sphingosine and long-chain fatty acids, which are abundant in biological membranes. Recently, signaling properties of

ceramides and their derivatives (e.g., ceramide-1-phosphate, glycosyl-ceramide, and sphingosine-1-phosphate) in the regulation of inflammation, apoptosis, proliferation, and differentiation have been described.^{205–208} The biological availability of these mediators depends on the rate of hydrolysis of sphingomyelin through the action of sphingomyelinases.²⁰⁸ It has been found that natural long-chain ceramides exhibit a direct inhibitory effect on complexes I and III activity and release cytochrome c from mitochondria, thus contributing to ROS production.^{208,209} By these interactions, ceramides were associated with mitochondrial ROS generation following hypoxia, glucose depletion or by exposure to tumor necrosis factor- α (TNF- α).^{210,211}

3.3 Fatty Acids and Peroxisomal Generation of Free Radicals

Peroxisomes contain enzymes for α - and β -oxidation of fatty acids.^{21,212,213} Peroxisomal β -oxidation differs from the mitochondrial process in substrate specificity and function.²¹ Members of the ABC transporter family in peroxisomes mediate the transport of thioesters of these long-chain fatty acids (C17–C24)²¹⁴ that are preferably metabolized in there.²¹² Specific peroxisomal acyl-CoA synthetases shorten long-chain fatty acids to shorter acyl-CoAs that can then be transported to mitochondria via the carnitine palmitoyl-transferase (CPT)-1/2 and become fully subjected to oxidation. Unlike the mitochondrial electron-transport chain, in which the FAD is the acceptor, the electrons generated in peroxisomal β -oxidation are transferred to molecular oxygen and generate hydrogen peroxide.^{213,215} In addition, other peroxisomal enzymes, such as α -hydroxyacid oxidase, pipecolic acid oxidase, polyamine oxidase, and ureate oxidase, generate hydrogen peroxide, while the peroxisomal xanthine oxidase generates superoxide anions.²¹³

These peroxisomal reactions generate substantial amounts of hydrogen peroxide.²¹⁶ The latter is normally scavenged by peroxisomal oxidoreductase catalase.²¹ However, in cases when the expression of catalase is reduced or the enzyme is inhibited by posttranslational modifications (e.g., glycation), ROS production markedly increases, as occurs in pancreatic β -cells.^{217,218} The excessive

availability of FFA, which exceeds the mitochondrial oxidative capacity, promotes peroxisomal β -oxidation and increases the generation of toxic radicals.²¹

3.4 Fatty Acids and NADPH Oxidase-Mediated Superoxide Radical Generation

FFA are a known activators of members of the NADPH oxidase (NOX) family. These are transmembrane enzymatic complexes that transfer electrons across the membrane while generating superoxide radicals.²¹⁹ Members of the NOX family are involved in ROS-mediated defense mechanism and inflammation, such as in killing microbial virulence factors, senescence, and cell death.²¹⁹ Recent studies have shown that various NOX complexes are also involved in the etiology of metabolic disorders. For instance, NOX-derived ROS in the adipose tissue participate in the development of insulin resistance and the production and secretion of proinflammatory cytokines.^{220–222} Vascular NOX complexes are a major source of ROS in the vascular system, leading to eNOS inactivation, extracellular matrix modifications, endothelial cell dysfunction, smooth muscle cell proliferation, followed by aortic media hypertrophy, atherosclerosis, hypertension, cardiac hypertrophy and fibrosis, and ultimately diabetic cardiovascular disease.^{223–246} A major source for hepatic NOS-derived ROS is the specialized tissue macrophages, Kupffer cells, which are activated by exogenous factors such as bacterial endotoxins or nutritional factors (e.g., lipids, ethanol). ROS induce hepatic dysfunction including apoptosis, production of collagen in hepatic stellate cells, and in liver ischemia-reperfusion injury.^{229, 247–257}

The model proposed by Schönfeld and Wojtczak¹⁶⁶ (Figure 3) describes how FFA activate the NOX complex to generate superoxide radicals, by inducing conformational changes in the p47^{phox} subunit and facilitating its interaction with the p22^{phox}, which drives forward superoxide generation. In addition, due to their amphiphilic nature, FFA capably interact with and improve the interaction of the Rac GTPase and cytochrome b₅₅₈ and increase the affinity of the complex to oxygen.^{258–262}

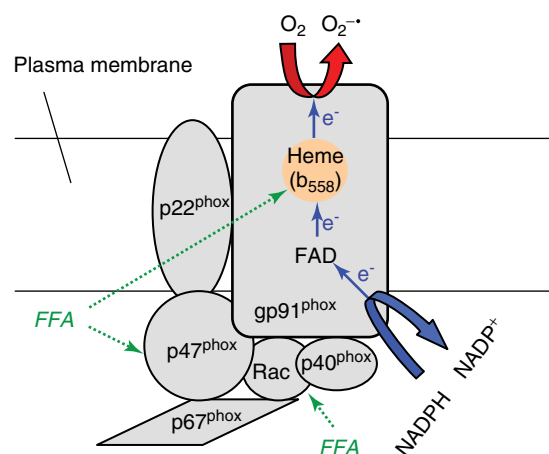


Figure 3 Sites of interaction of FFA with the NADPH oxidase complex. The active NADPH oxidase complex is formed by assembling membrane-associated subunits (p22^{phox} and gp91^{phox}) and cytosolic subunits (p47^{phox}, Rac, p40^{phox}, p67^{phox}). Solid lines and arrows indicate electron (e^-) transfer. FFA interact with p47^{phox} and facilitates its interaction with the p22^{phox}, which drives forward superoxide generation. [Reproduced from Ref. 166, Copyright (2008), with permission from Elsevier.]

3.5 Lipid Peroxidation

The term *lipid peroxidation* describes series of enzymatic and nonenzymatic reactions that generate many products with diverse physiological and pathophysiological functions. The peroxidation of PUFAs generates a group of reactive aldehydes, known as 4-hydroxyalkenals, which can act dose dependently as signaling molecules or as cytotoxic agents. Increased production of ROS in cells intensifies the peroxidation of PUFAs. Several alternative chemical mechanisms for the generation of 4-hydroxyalkenals from *n*-3 and *n*-6 PUFAs have been proposed.^{263–268} Niki has recently summarized and reviewed this topic²⁶⁹ (see also **Lipid Peroxidation**). The initiation step is mediated by hydroxyl radical- and lipid peroxyl radical-mediated abstraction of bisallylic H atom from *n*-3 and *n*-6 unsaturated fatty acids or their lipoxygenase-derived hydroperoxy metabolites to form conjugated diene lipid hydroperoxides. These products further undergo intramolecular rearrangement and chain-breaking reactions to generate various saturated and unsaturated aldehydes, among which unsaturated 4-hydroxyalkenals mediate critical biological and cytotoxic functions.

Figure 4a¹⁷⁸ outlines the nonenzymatic peroxidation pathways that lead to the production of 4-hydroxy-2*E*-hexenal (4-HHE) and 4-hydroxy-2*E*-nonenal (4-HNE). The generation of 4-HNE and 4-hydroxy-2*E*,6*Z*-dodecadienal (4-HDDE), shown in Figure 4b,¹⁷⁸ begins with 12- and 15-lipoxygenases (12-LO and 15-LO)-mediated conversion of *n*-6 PUFAs to their respective hydroperoxy metabolites. While 4-HDDE is exclusively generated from 12-hydroperoxyeicosatetraenoic acid (12-HpETE), the peroxidation product of 15-HpETE (the 15-LO metabolite of arachidonic acid (AA) and other *n*-6 PUFAs) is 4-HNE.²⁷⁰ Free radicals increase the flux of PUFAs and their hydroperoxy metabolites in two ways: first, the H atom abstraction and interaction with oxygen to form lipid peroxyl radicals which promotes the nonenzymatic cascade up to the generation of 4-hydroxyalkenals.^{264,265,267,268,271} The second mechanism is a free radical-mediated inactivation of the enzyme glutathione peroxidase (GPx), which transforms LO-derived hydroperoxy metabolites of AA to their respective biologically active hydroxy metabolites (e.g., 12-hydroeicosatetraenoic acid, 12-HETE).²⁷² ROS-induced inactivation of GPx

increases the flux of hydroperoxy metabolites of lipoxygenases through the peroxidation cascade.²⁷³

Figure 5 summarizes these processes in the transformation of AA to 4-HNE and 4-HDDE: following the hydrolysis of AA from the *sn*-2 position of phospholipids by the action of members of the phospholipase A2 family, the enzymes cyclooxygenase-1 and the inducible cyclooxygenase-2 catalyze the transformation of AA to prostaglandin H2, the precursor substrate of prostaglandin and thromboxane synthases. AA is also transformed to various ETEs and HETE s through the *cytP*₄₅₀- ω -hydrolase- and *cytP*₄₅₀-epoxidase pathways. The metabolism of AA by 12-LO and 15-LO results in its transformation to 12-HpETE and 15-HpETE, respectively. These are further reduced by GPx to the biologically active 12-HETE and 15-HETE. The peroxidation of AA, 12-HpETE, and 5-HpETE begins with the H atom abstraction through the chain of reaction that generates the respective 4-HNE and 4-HDDE. This model suggests that the cell-specific generation of the various 4-hydroxyalkenals depends on the pattern of expression of the various lipoxygenases and the relative abundance of the ω -3- and ω -6 PUFAs in the cells. The other factor that controls the cellular levels of 4-hydroxyalkenals is the cell's capacity to transform them to their carboxylic form by the

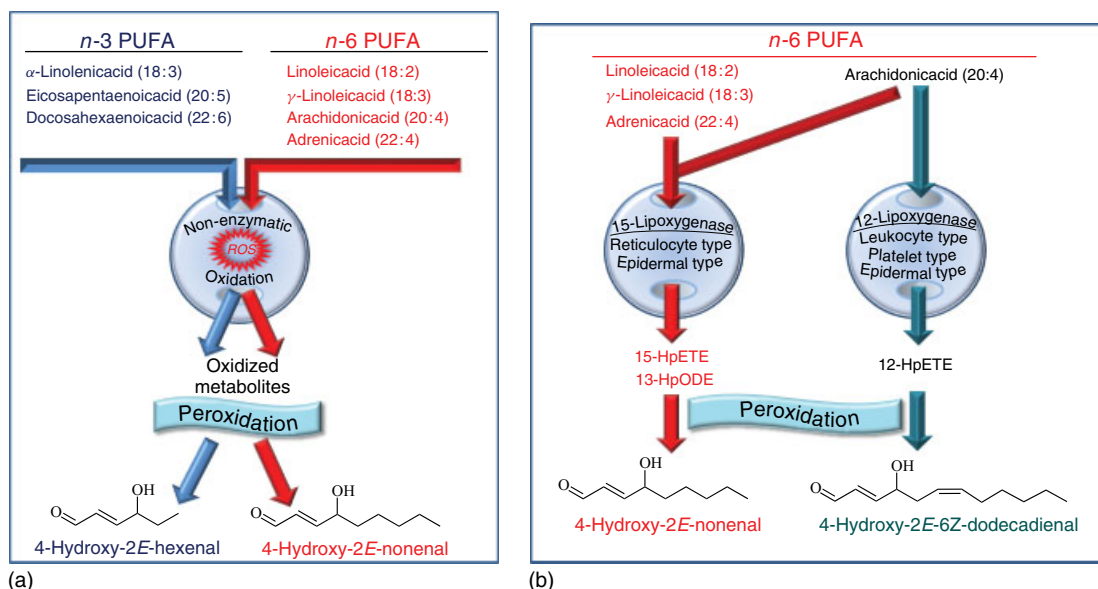


Figure 4 Peroxidation of polyunsaturated fatty acids. (a) Nonenzymatic generation of 4-HHE and 4-HNE from *n*-3 and *n*-6 PUFAs, respectively. (b) Lipoxygenase-initiated peroxidation of *n*-6 PUFAs and the generation of 4-HNE and 4-HDDE. [Reproduced from Riahi *et al. Am J Physiol Endocrinol Metab.*, 2010 [178]. The American Physiological Society, used with permission.]

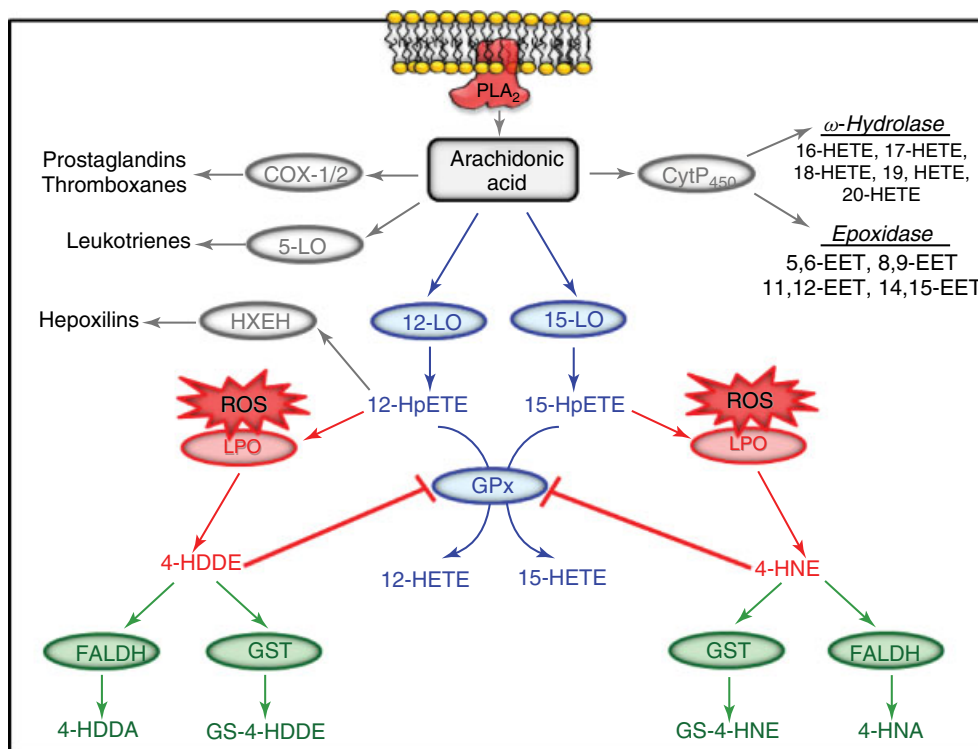


Figure 5 Metabolism and peroxidation of arachidonic acid. Cyclooxygenase (COX)-, 5-lipoxygenase (5-LO)-, CYP450-, and hepxilin epoxide hydrolase (HXEH) mediate the transformation of arachidonic acid to the respective metabolites (gray). The enzymes 12-lipoxygenase (12-LO) and 15-lipoxygenase (15-LO) transform arachidonic acid to 12- and 15-hydroperoxyeicosatetraenoic acid (HpETE); downstream, glutathione peroxidase (GPx) transforms them to the respective 12- and 15-HETE (blue). Reactive oxygen species (ROS)-induced lipid peroxidation (LPO) of 12- and 15-HpETE results in the generation of 4-HNE and 4-HDDE (red). These reactive aldehydes interact with and inactivate GPx, leading to an increased rate of 12-HpETE and 15-HpETE peroxidation. The neutralization reactions of 4-HNE and 4-HDDE to the corresponding 4-hydroxynonenal (4-HNA) and 4-hydroxydodecadienoic acid (4-HDDA) are mediated by fatty aldehyde dehydrogenase (FALDH) and glutathione-S-transferase (GST) (green). [Reproduced from Ref. 177. Copyright Informa Healthcare. Reproduced with permission.]

action of fatty aldehyde dehydrogenase (FALDH) or by their conjugation to glutathione by the action of glutathione-S-transferase (GST). Covalent interactions of 4-hydroxyalkenals with GPx inactivate this enzyme and increase the flux of AA, 12-HpETE, and 5-HpETE through the nonenzymatic peroxidation cascade.

It is believed that *n*-3 PUFAs are a beneficial dietary supplement. Thus, of a particular interest is the *fat-1* mouse model that expresses the *Caenorhabditis elegans* 6-desaturase (*fat-1*) gene, which converts *n*-6-PUFAs to *n*-3 PUFAs.²⁷⁴ These mice exhibit improved cellular and organ functions, such as prevention of neoplasia,²⁷⁵ improved glucose homeostasis,²⁷⁶ and efficient anti-inflammatory interactions.²⁷⁷ Nonetheless, recent studies suggest

that excess of *n*-3 PUFAs and their subsequent transformation to 4-hydroxyhexenal (4-HHE) may be harmful. For instance, intraperitoneal or intravenous administration of high doses of 4-HHE resulted in peritonitis and liver damage, respectively.²⁷⁸ Some studies showed that *fat-1* mice were immunologically compromised and exhibited impaired resistance to tuberculosis.²⁷⁹ A photooxidative retinal damage in these mice was positively correlated to the level of the docosahexaenoic acid and the extent of lipid peroxidation.²⁸⁰

We have recently reported that the generation of 4-HDDE increases significantly in vascular endothelial cells exposed to high glucose levels²⁸¹ and that 4-HDDE is a potent activating ligand of the peroxisome proliferator-activated

receptor δ (PPAR δ). Similarly, Coleman *et al.*²⁸² found that 4-HNE was an intracellular agonist of PPAR δ in 3T3L1 preadipocytes. These findings are particularly important in view of the various metabolic and regulatory functions PPAR δ mediates, such as anti-inflammatory interactions,²⁸³ repression of inflammatory gene expression in macrophages,²⁸⁴ increased oxidative capacity of FFA in mitochondria,^{285,286} augmented cholesterol export, and regulation of glucose metabolism and insulin sensitivity.²⁸⁷

Many studies on beneficial and detrimental effects of 4-HNE have appeared in recent years^{267,269,288–295} and some other signaling targets of 4-HNE have been suggested, such as c-Jun N-terminal kinase (JNK),²⁹⁶ p38 mitogen-activated protein kinases (p38MAPK),²⁹⁷ cell cycle regulators,²⁹⁸ and protein kinase- β and - δ (PKC β and PKC δ).^{299,300} Nonetheless, these studies do not claim that 4-HNE is a classical ligand of these proteins. In fact, these effects may result from the capacity of 4-HNE to form covalent adducts with macromolecules and evoke variable physiological and pathological responses. For instance, Niki and colleagues^{269,301,302} showed that nontoxic levels of 4-HNE improve the antioxidant defense of cells by activating NF-E2-related transcription factor-2 (Nrf2) and increasing the expression of antioxidant enzymes. However, high 4-HNE levels inhibit and/or inactivate various enzymes (oxidoreductases, transferases, hydrolases, lyases, and isomerases), membrane proteins (carriers, receptors, ion channels, transporters), and cytoskeletal proteins.²⁸⁸ Of interest is the capacity of 4-HNE to increase production of ROS by covalently modifying thioredoxin-1 and compromising its antioxidant function.³⁰³ These and similar effects of 4-HNE are also related to the induction of NF- κ B-mediated proinflammatory effects^{304,305} and stress-induced apoptosis.³⁰⁶

High levels of 4-HNE have been linked to mitochondrial dysfunction. Some key proteins in the mitochondrial respiratory chain (e.g., the adenine nucleotide translocator (ANT) or cytochrome c oxidase) and enzymes in the TCA cycle (α -ketoglutarate dehydrogenase and isocitrate dehydrogenase) are particularly susceptible to 4-HNE-induced inactivation.^{307–311} These interactions further modify the electron-transport chain and augment ROS production in the affected mitochondria.

It should be emphasized that 4-hydroxyalkenals also bind covalently to membrane phospholipids and cholesterol.^{272,312,313} These interactions distort the normal lipid bilayer structure of membranes, their integrity, fluidity, and consequently their functions. In addition, the oxidation of LDL is mediated by radical-induced formation of hydroperoxides and 4-HNE.^{314–316} The resulting oxLDL is involved in macrophage activation, foam-cell formation, and atherosclerosis.^{317–319} Oxidized LDL is taken up by macrophages via scavenger receptors (i.e., CD36, SR-A) that induce foam-cell formation in the intima of blood vessels.³²⁰ Therefore, 4-HNE is considered an atherogenic factor that contributes to the pathology of the metabolic syndrome. Oxidative stress in cells that predominantly express 12-LO leads to the generation of 4-HDDE (Figure 4b). Low levels of 4-HDDE may regulate various cell functions by interacting with PPAR δ ^{281,282}; however, an excessive production of 4-HDDE (as well as other 4-hydroxyalkenals) can result in covalent modifications of macromolecules and aberrant cell function, as was found in pancreatic β -cells³²¹ and the juxtaglomerular apparatus in the kidney.³²² Possibly, such effects of 4-HDDE may be found in leukocytes, platelets, and epidermal cells, prostate cancer cells, and selected neural cells, which express the 12-LO isotypes.³²³

The role of 4-hydroxyalkenals in diabetes has recently been reviewed.¹⁵⁶ Hyperglycemia initiates lipid peroxidation in cells owing to the overproduction of glucose-derived free radicals. Moreover, an increased expression of 12- and 15-LO in cells exposed to high glucose levels leads to an increased production of 12- and 15-HpETE, the precursors of 4-HNE and 4-HDDE, respectively. Clinical observations on increased levels of 4-HNE-modified albumin in type-2 diabetic patients support the role of glucose-induced lipid peroxidation in diabetes.³²⁴ Moreover, β -cell dysfunction and the development of macrovascular disease and the accelerated deterioration to atherosclerosis had been also associated with an elevated production of 4-hydroxyalkenals.¹⁵⁶

4 OBESITY AND OXIDATIVE STRESS

White adipose tissue, the predominant fat depot in man, is consisted of mature adipocytes and preadipocytes along with vascular endothelial cells,

macrophages, mast cells, and dendritic cells.³²⁵ Adipose tissue is distributed in multiple depots in the body, mainly subcutaneous, visceral, and ectopic fat (e.g., epicardial, perivascular, gonadal).^{326,327} The fat storage capacity in these depots is remarkably high and is associated with tissue hypertrophy and hyperplasia and is initiated by high calorie food intake and a combination of hormonal and signaling pathways that induce a proportional growth and differentiation of preadipocytes to mature adipocytes upon increased availability of fat.³²⁸ Hypertrophied and fat-laden adipose tissues suffer from local hypoxia, which induce local inflammation and apoptosis.^{329–331} In addition, the increased availability of FFA and glucose affect the electron-transport chain in mitochondria to generate ROS. Indeed, the inflamed phenotype in the adipose tissue is characterized with an increased production of free radicals, generated mainly by activated macrophages.³³² This oxidative stress, combined with the increased production and presence of inflammatory cytokines and elevated FFA, activates stress kinases in the adipose tissue, which further induces insulin resistance, increase expression of proinflammatory genes, and promotes ER stress.^{332–337}

4.1 The Secretome of Adipose Tissues

Metabolic, oxidative, and inflammatory signals regulate the secretory functions of mature adipocytes. The two prime adiposity signals secreted from nonobese and noninflamed adipose tissues are leptin and adiponectin. The expression of these two factors is inversely regulated; increased total body fat augments the expression of leptin and reduces the expression of adiponectin. The former interacts with hypothalamic food intake and energy expenditure centers and the latter contributes to whole-body insulin sensitivity, particularly in skeletal muscle.^{338,339} Obese adipose tissues secrete many other factors, such as IL-6, IL-8, chemerin, MCP-1, plasminogen activator inhibitor-1 (PAI-1), RANTES, resistin, retinol binding protein 4 (RBP4), TNF- α , or visfatin.^{338,340–342} Insulin resistance in skeletal muscles,^{339,343–345} vascular cell dysfunction,³⁴⁶ atherosclerosis,^{347,348} and peripheral inflammatory processes^{340,342,349} are induced by some of these secreted proteins.³²⁵ Chemotactic factors, such as MCP-1, recruit circulating monocytes. The inflamed and apoptotic environment in

the obese adipose tissue activates these recruited and resident macrophages and further intensifies inflammation.³⁵⁰

Monteiro and Azevedo³³² have recently suggested a comprehensive model on the interplay between obesity, inflammation, and the metabolic syndrome (Figure 6). It suggests that the metabolic stress in fat cells leads to increased ROS generation, overproduction of adipokines, and activation of stress kinases, which potentiate the transcription of inflammatory genes and induce insulin resistance. Adipocyte death due to necrosis and apoptosis attracts macrophages, activates them to further reinforce inflammation, ROS production, and secretion of inflammatory cytokines, while reducing the production and secretion of the anti-inflammatory adiponectin. FFA also interact with Toll-like receptors in adipocytes and further enhance the inflammatory response. In addition, FFA accumulate in the liver and alter fat and lipoprotein composition and function. Furthermore, FFAs also induce insulin resistance in skeletal muscles. This model also claims that fat affects intestinal permeability and microbiota, which may also be involved in the production of inflammatory cytokines that act peripherally.

4.2 Lipid Peroxidation in Obese Adipose Tissues

Lipid peroxidation in obese adipose tissues is augmented due to an increased availability of PUFAs and ROS. An adipose cell-specific PLA₂ (AdPLA₂), with a preference to *sn*-2-bound AA and linoleic acid in phosphatidylcholine, has recently been discovered in mature adipocytes,^{351,352} and its expression is upregulated following a high fat diet.³⁵³ AdPLA₂ increases the availability of PUFAs, AA in particular, which are transformed by lipoxygenases to the respective hydroperoxy derivatives. The oxidative environment in fat-laden and inflamed adipocytes then favors the generation of 4-hydroxyalkenals by initiating the peroxidation cascade, as described above. A strong support for this mechanism comes from the 12-LO-KO (knock-out) mouse, which does not develop low-grade inflammation when fed a high calorie diet. Moreover, despite adipose cell hypertrophy, 12-LO-KO

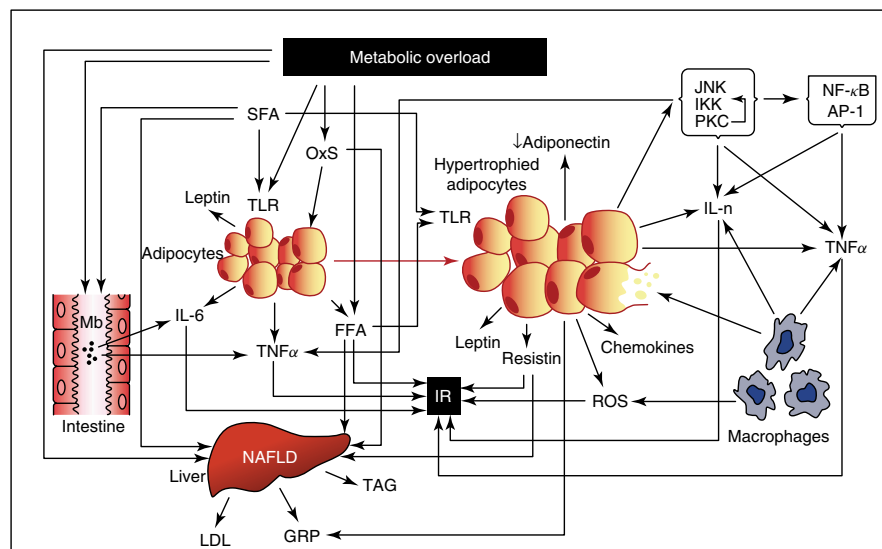


Figure 6 The cross-talk between obesity and inflammation. Overview of the complex interplay between obesity and inflammation in the metabolic syndrome: metabolic overload impact leads to the production of ROS and adipokines, as well as activation of kinases that potentiate the transcription of inflammatory genes and interfere with insulin signaling. Adipose cell hypertrophy induces cell apoptosis and death and chemotactic recruitment of activated macrophages, which further enhance the production of ROS and inflammatory cytokines, whereas the secretion of the anti-inflammatory adiponectin is reduced. Increased levels of SFAs, from the diet and lipolysis in adipose tissues, accumulate in the liver, among other organs. Fatty livers overproduce LDL and proinflammatory cytokines such as IL-6 of CRP. SFA also activate Toll-like receptors in adipocytes and further enhance the inflammatory response. In addition, increased FFA levels induce insulin resistance in adipose tissues, the liver, and skeletal muscles. Dietary fat also affects intestinal permeability and interacts with microbiota to generate inflammatory factors that act systemically. AP-1, activator protein-1; CRP, C-reactive protein; FFA, free fatty acids; IL-n, interleukins; IKK, inhibitor of NF- κ B kinase; Int, intestine; IR, insulin resistance; JNK, c-Jun N-terminal kinase; LDL, low density lipoprotein; M, microbiota; NAFLD, nonalcoholic fatty liver disease; NF- κ B, nuclear factor κ B; Oxs, oxidative stress; PKC, protein kinase C; SFAs, saturated fatty acids; TAG, triacylglycerols; TLR, Toll-like receptors; TNF α , tumor necrosis factor- α . [Reproduced with permission from [332].]

mice exhibit significantly lower macrophage infiltration and activation in the visceral adipose tissue, in comparison with the high calorie diet-fed wild-type mice.³⁵⁴ A role for 4-HNE in altering adipocyte functions has been established: adiponectin secretion was reduced and insulin resistance was induced in 4-HNE treated 3T3-L1 adipocytes.^{297,355,356} A deletion of the *mGsta4* gene created a mouse model with an impeded capacity to neutralize 4-HNE.^{297,355} High calorie diet induced adipose tissue hypertrophy and increased macrophages infiltration and activation to the adipose tissue in these GST-KO mice. Therefore, it is concluded that in addition to the role of an oxidative environment and ROS production, PUFAs peroxidation and the generation of 4-hydroxyalkenals also contribute to the development of the proinflammatory phenotype of adipose tissues.

5 FREE RADICALS AND DIABETIC COMPLICATIONS

Many studies have implicated increased oxidative stress, augmented lipid peroxidation, and altered antioxidant capacity of cells and organs in the development of obesity- and diabetes-related complications.¹⁵⁷ The major complications attributed to free radicals and lipid peroxidation products are peripheral insulin resistance that affects the liver, adipose tissues and skeletal muscles, β -cell dysfunction, protein modifications, membrane alterations, and extracellular matrix modifications which cause end-organ malfunctions, such as nephropathy, retinopathy, neuropathy, and impaired wound healing. Although free radicals and lipid peroxidation products share similar chemical interactions in various cell types, the outcome of these interactions

vary in a cell-specific manner leading to various complications.

5.1 Roles of ROS in Inducing Diabetic Complications

A major effect of ROS is the induction of insulin resistance by interfering with the insulin receptor-mediated signal transduction. The binding of insulin to the insulin receptor triggers the autophosphorylation of distinct tyrosine moieties in the intracellular domains of the receptor's β -subunits. Once phosphorylated, these subunits bind IRS proteins and the tyrosine-kinase catalytic domain of the receptor phosphorylates tyrosine moieties in the docked IRS molecules. The resulting complex recruits other proteins and the various pathways of insulin signaling are then activated, leading to cell-specific effects, such as translocation of glucose transporters to the plasma membrane of skeletal muscles or the inhibition of the hormone-sensitive lipase in adipocytes.^{357,358} The termination of the insulin receptor-mediated effects is achieved by dissociating IRS from the insulin receptor complex.

ROS play a key role in downregulating IRS interaction with insulin receptor by inducing serine phosphorylation in IRS proteins and their subsequent proteolytic degradation. It was shown³⁵⁹ that IRS1 content in adipocytes was markedly reduced following the induction of oxidative stress. Serine residue phosphorylation in IRS proteins is mediated by several Ser/Thr kinases, including mTOR, S6K1, and PKC γ and PKC ζ .^{157,360} The outcome of the phosphorylation of the serine moieties has been delineated. For instance, Ser³¹⁹ that is phosphorylated by PKC ζ ³⁶¹ disrupts the interaction between the insulin receptor and the phosphotyrosine-binding (PTB) domain of IRS1, thus impeding the insulin receptor signaling pathways. S6K1 (p70 ribosomal protein S6 kinase 1)-mediated serine phosphorylation of IRS1 is also upregulated by various stressors, including obesity, increased levels of FFA, TNF- α , and other ROS-producers.³⁶⁰ Similarly, JNK-induced phosphorylation of Ser³⁰⁸ uncouples IRS1 from the insulin receptor.³⁸

In addition, peripheral insulin resistance is also induced by adipocyte-derived factors.³²⁵ T2D is associated with reduced secretion of adiponectin, thus limiting its peripheral anti-inflammatory and

insulin-sensitizing effects. It has been suggested that a vicious cycle between insulin and adiponectin operates in T2D patients, in which hyperinsulinemia, which develops due to insulin resistance, suppresses adiponectin secretion, which further deteriorates peripheral insulin sensitivity.³⁶² Other molecular mechanisms linking ROS to the development of peripheral insulin resistance, such as ROS-dependent activation of JNK, p38, and IKK β , have recently been proposed.³⁶³

Endogenous and exogenous ROS induce β -cell dysfunction. Gluco-lipotoxicity in β -cells combines all known deleterious interactions caused by hyperglycemia and increased FFA levels. These interactions include glucose autooxidation, mitochondrial ROS production, activation of NADPH oxidase, nonenzymatic protein glycation, and RAGE-mediated effects or increased metabolite flux in the polyol and hexosamine pathways.^{24,59,364–366} Recently, it has been suggested that the expression and function of thioredoxin and thioredoxin-interacting (TXNIP) proteins is regulated in β -cells by glucose²⁴; specifically, the increased expression of TXNIP leads to oxidative stress resulting in β -cell apoptosis.^{367–373} Oxidative stress also induces ER stress in β -cells, which was associated with an adaptive response of the cells to the stressful conditions. However, prolonged ER stress can deteriorate to death promoting processes and demise of β -cells. The latter response may involve overproduction of ROS.^{374,375} This *double-edge* effect of ER stress and the unfolded protein response in β -cells has recently been described and discussed.^{24,376–378}

5.2 Roles of Lipid Peroxidation in Inducing Diabetic Complications

Protein carbonylation (by glycation or lipid peroxidation-induced adduct formation) causes multiple deleterious effects in cells and tissues. While the role of protein glycation in inducing such complications has been well-investigated and described,^{77,379–381} the role of 4-hydroxyalkenal-induced modifications in diabetes and obesity-induced complications is less recognized.

Various studies have alluded to a key role of 4-hydroxyalkenals in inducing β -cell dysfunction: an increased expression of 12-LO in islets

of diabetic rats was associated with an impaired insulin secretory function.³²¹ Overexpression of 12-LO in cultured INS-1E β -cells significantly reduced their glucose-induced insulin secretory capacity.³⁸² Conversely, 12-LO knockout mice maintained normal β -cell function when fed a diabetogenic high fat diet.³⁵⁴ It has been suggested³⁸³ that such reactive aldehyde species are involved in the destruction of rat pancreatic islet β -cells by cytokines.³⁸⁴ Pharmacological inhibition of 12-LO prevented cytokine-induced β -cell death.³⁸⁵ The marked susceptibility of β -cells to oxidative stress- and ROS-induced damages has been attributed to their inherent poor intrinsic antioxidant defense.^{218, 386–388} This condition, coupled to a progressive 4-hydroxyalkenal-induced inactivation of the 4-hydroxyalkenal neutralizing enzymes FALDH and GST further contribute to β -cell dysfunction.

Hyperglycemia is a major and independent risk factor in the etiology of cardiovascular disease in the metabolic syndrome.^{389,390} The earliest event in this process is endothelial cell dysfunction, which is induced by various stressors, including free radicals and overproduction of 4-hydroxyalkenals. For instance, the expression of adhesion molecules (i.e., ICAM, VCAM) in endothelial cells was altered in the presence of 4-HNE.³⁹¹ Uncoupling of eNOS is induced by 4-HNE-dependent inactivation of THB.³⁹² Moreover, 4-HNE is also involved in the activation of macrophages and foam cells in atherosclerotic blood vessels.³¹⁴ This is attributed to 4-HNE-induced expression of class A scavenger receptors, which transform macrophage to foam cell.³²⁰ Smooth muscle cell proliferation in blood vessels is increased in the presence of 4-HNE.^{393–395} *In vivo* studies show high content of 4-HNE-protein adducts in aortae of streptozotocin (STZ)-diabetic rats.³⁹⁶

6 SUMMARY

Overproduction of free radicals results from an increased availability of glucose and/or FFA to the mitochondria and peroxisomes and following glucose autooxidation, AGE generation, activation of NADPH oxidase, and lipid peroxidation. Detrimental effects of ROS and AGE in the metabolic syndrome include peripheral insulin resistance and impaired β -cell function and viability. In addition,

lipid peroxidation is intensified in the presence of ROS. The peroxidation of PUFAs results in an excessive generation of 4-hydroxyalkenals followed by the formation of covalent adducts with macromolecules, which alter their function. It is important to note that an effective endogenous antioxidant defense and efficient neutralization system of 4-hydroxyalkenal can prevent or delay harmful effects of these agents. Conversely, poor antioxidant defense and ineffective neutralization of ROS and reactive aldehyde species leave cells vulnerable to the combined damaging effects of oxidative stress and peroxidation, as in the case in β -cells in diabetes. Therefore, in addition to the prevention of metabolic disorders by lifestyle and diet changes and pharmacological interventions, an antioxidant therapy is one of the strategies for the treatment of the metabolic syndrome.

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Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications

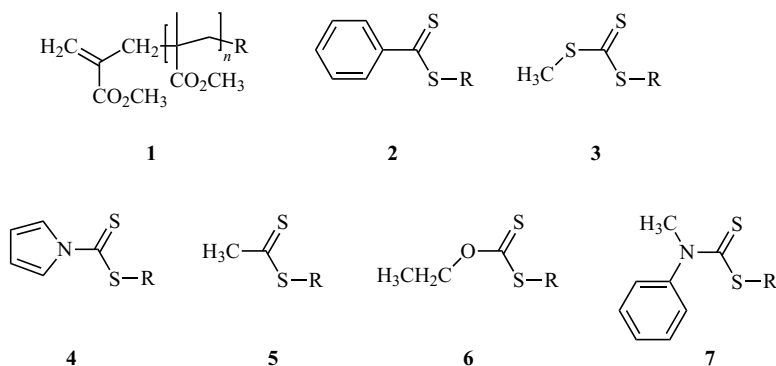
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1 INTRODUCTION

The use of degenerative chain transfer to control the structure of polymers obtained from radical polymerization was revolutionized in the late 1990s when two research groups independently reported a polymerization using thiocarbonyl thio compounds as chain transfer agents that yielded polymers of controlled molecular weights and narrow molecular weight distributions. The simultaneously reported methods of reversible addition fragmentation chain transfer (RAFT) polymerization by the Commonwealth Scientific and Research Organization (CSIRO)¹ and the macromolecular design via interchange of xanthates (MADIX) by Zard and coworkers in collaboration with Rhodia^{2,a} are arguably the most versatile techniques of living radical polymerization and have become two of the most employed controlled polymerization protocols. Since the two techniques are based on the same mechanism, the term “RAFT” will

be used throughout this article to describe both approaches. Rather than providing a comprehensive review on RAFT chemistry, this article aims at giving an overview of RAFT and highlighting the major strengths as well as limitations of this chemistry. There exists a series of excellent reviews on the topic, and readers wishing to obtain detailed information on all aspects of the RAFT process are directed to those.³ The key strengths of the RAFT process for polymer design are its high tolerance of monomer functionality and reaction conditions as well as its (in-principle) non-rate-retarding nature. A RAFT process—provided the RAFT agent is judiciously chosen—does not induce any rate retardation effects, as the radical concentration during the polymerization is identical to that of a conventional free-radical polymerization process. The only—rather minimal—reduction in radical concentration is caused by the chain-length dependence of the bimolecular termination rate coefficient.⁴ The tolerance of the RAFT process to functional groups



Scheme 1 A selection of RAFT agents.

is extremely high, which permits the synthesis of well-defined polymeric architectures exhibiting almost any functionality, in a wide range of solvents.

The article is divided into several sections, which in turn explore the mechanism of polymerization, the range of polymer molecular weights achievable, the range of monomers in which the polymerization is controlled by RAFT, the various polymeric architectures that can be obtained, the type of end-group functionalities available to RAFT-made polymers, and the process of RAFT polymerization, including emulsion systems.

2 THE MECHANISM OF RAFT POLYMERIZATION

2.1 Mechanism of RAFT Polymerization

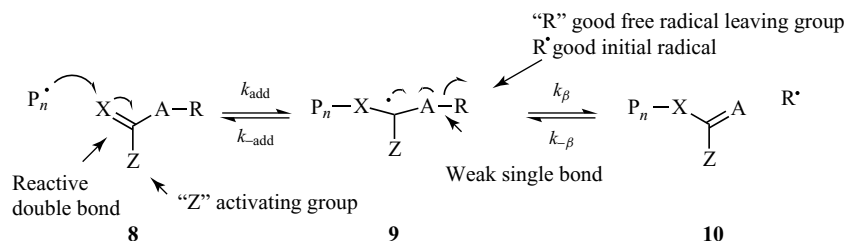
RAFT polymerization finds its roots in synthetic organic chemistry based on radical addition–fragmentation processes developed since the 1970s. Among the best known examples of this technique are the Barton–McCombie deoxygenation process with xanthates and later the degenerative transfer of xanthates and related thiocarbonyl thio derivatives in radical addition reactions (see **Xanthates and Related Derivatives as Radical Precursors**).⁵ In the 1980s, several groups started to consider the use of addition–fragmentation chain transfer agents in radical polymerization as a means to control the molecular weight and end functionalities of polymer chains.⁶ The first generations of chain transfer agents all led to irreversible chain transfer

mechanisms and, as a consequence, the polymerization scheme was similar to that of a telomerization reaction. Methacrylate macromonomer RAFT agents (**1**, Scheme 1) appeared in 1995 as the first reversible addition–fragmentation chain transfer agents capable of promoting free-radical polymerizations with living/controlled characteristics.⁷ Later in 1998, a wide variety of thiocarbonyl thio RAFT agents (**2–7**, Scheme 1) including aromatic **2** and aliphatic **5** dithioesters, trithiocarbonates **3**, xanthates **6**, and dithiocarbamates (**4**, **7**) were first reported as quite reactive and efficient control agents in comparison to the macromonomer **1**.^{1,2}

Commonly, RAFT agents are compounds with the general structure **8** (Scheme 2) where the C=X double bond is reactive (in general, X = CH₂ or S). The proper selection of the Z group is crucial in the sense that it must give the RAFT agent **8** (and **10**) an adequate reactivity of the C=X bond for the incoming radical and stability of the intermediate radical **9**. In order to obtain suitable conditions for a RAFT polymerization, the product of the transfer reaction **10** must itself be a good transfer agent. This criterion is fulfilled when A and X are identical. Therefore, RAFT can be seen as a degenerative chain transfer process similar to the one met in radical addition reactions involving thiocarbonyl thio derivatives.

In Scheme 2, R is a radical leaving group that, ideally, should reinitiate polymerization in a fast and quantitative way.

A RAFT polymerization consists of the simple introduction of tenths to several molar percent of a thiocarbonyl thio transfer agent in a conventional free-radical polymerization system. The key feature of the mechanism of RAFT polymerization is a

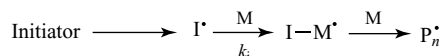


Scheme 2 Reversible addition fragmentation chain transfer (RAFT) mechanism.

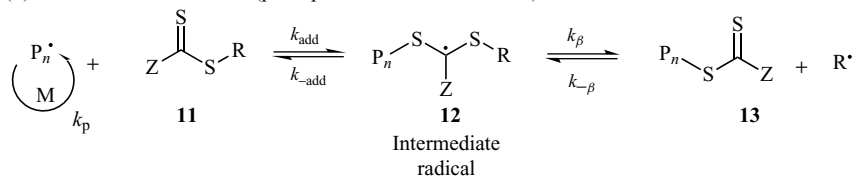
sequence of reversible addition–fragmentation reactions as described in Schemes 2 and 3. The reactions associated with RAFT equilibria shown in Scheme 3 add to those that occur during conventional radical polymerization, namely initiation, propagation, transfer, and termination. At the beginning of the polymerization, polymer chains are initiated (e.g., by an azo initiator) and the addition of a propagating radical ($P_n^\bullet$) to the thiocarbonyl thio compound $RSC(Z)=S$ (**11**) followed by fragmentation of the

intermediate radical **12** generates a polymeric thio-carbonyl thio compound $P_nSC(Z)=S$ **13** and a new radical $R^\bullet$. The formed radical $R^\bullet$ is capable of reacting with the monomer to form a new radical ($P_m^\bullet$). A rapid equilibrium between the active propagating radicals ($P_n^\bullet$ and $P_m^\bullet$) and the dormant thiocarbonyl thio-capped chains **13** provides equal probability for all chains to grow and allows the synthesis of polymers with narrow molecular weight distributions. At the end of the polymerization, the majority of chains

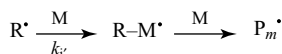
(i) Initiation



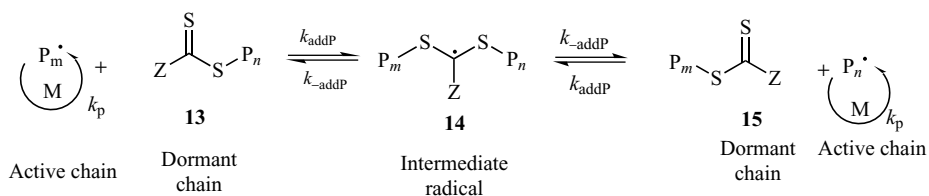
(ii) Reversible chain transfer (pre-equilibrium or initialization)



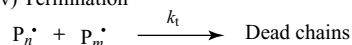
(iii) Reinitiation



(iv) Chain equilibration (main equilibrium)



(v) Termination



Scheme 3 Mechanism of RAFT polymerization showing the initiation, propagation, reversible chain transfer, reinitiation, chain equilibration, and termination steps.

bear the RAFT end group and can be isolated and manipulated as stable products.

As inspection of Scheme 3 indicates, the radical concentration—provided the intermediate RAFT adduct radical is short-lived—is not lower than in a conventional polymerization process. Thus, bimolecular termination events occur and lead to the presence of some nonfunctional material, typically in the range of 5–10%. The control over the molecular weight characteristics is imparted when the targeted molecular weight is significantly lower than that which would be formed under the same conditions but in the absence of the RAFT agent, and is such that the concentration of macromolecules with thiocarbonyl thio-derived ends is much greater than the concentration of chains generated by initiation/termination.

2.2 Kinetics of RAFT Polymerization

Although many RAFT systems show little or no effect of the RAFT agent concentration on the overall rate of polymerization, much past and present debate was reported on the kinetics of the RAFT process, the kinetics of setting of pre- and main equilibria, and what side reactions might add to the complexity of the studied RAFT systems. The RAFT process creates short chains in the early stages of polymerization, which increase in size over the course of the polymerization. As a consequence, the chain-length dependence of the propagation and termination rate coefficients can have a visible impact on the rate of RAFT polymerization compared to a conventional process. Some more marked effects of the addition of a RAFT agent have been reported in the literature, such as

- an inhibition or a period of time during which very little or no polymerization occurs before the polymerization starts;
- rate retardation, that is, a decreased rate of polymerization compared to the same polymerization without a RAFT agent.⁸

Most of the reported cases of inhibition are related to the pre-equilibrium or the so-called initialization step (Scheme 3), where the starting RAFT agent is converted to an oligomeric or polymeric

RAFT agent. For instance, during RAFT polymerization of vinyl acetate and *N*-vinyl pyrrolidone with xanthates, selective initialization occurred in which there was a substantial conversion of the initial RAFT agent into a single unit species before conversion into high molecular weight chains.^{9,10} The effect was attributed to the rate coefficient of the addition of R' to monomer being much slower than that for propagation. Mechanisms for retardation in RAFT polymerization mediated by, in particular, dithiobenzoate RAFT agents have attracted much interest over the last decade. For instance, cumyl dithiobenzoate carries a stabilizing phenyl Z group and a leaving cumyl R group. This RAFT agent has been shown to cause inhibition as well as retardation for a range of monomers. Indeed, in the low-temperature RAFT polymerization of styrene mediated with cumyl dithiobenzoate, the rate of polymerization is initially small—compared to the blank experiment without RAFT agent—and steadily increases.⁹ This could be due to the slow fragmentation of the RAFT adduct radicals formed during the pre-equilibrium, termination of the adduct radicals with themselves or propagating radicals, and slow reinitiation. The mechanism and kinetics of dithiobenzoate-mediated RAFT polymerization were critically evaluated a few years ago.¹¹ Much of the debate surrounding the source of the retardation and inhibition has arisen because of a lack of direct experimental evidence for the lifetime of the RAFT adduct radicals. By necessity, many studies for the determination of individual rate coefficients have taken place within a polymerizing system and require the fitting of data to an assumed kinetic model. This assumption can have a significant influence on the calculated results. Recently, a combination of the spin trapping technique and electron spin resonance (ESR) spectroscopy was employed to obtain the first direct experimental determinations of addition, fragmentation, and self-termination rate coefficients within a model dithiobenzoate system, confirming—at least in this system—a slow fragmentation rate of close 10^{-2} s^{-1} at ambient temperature. These results were found to be in excellent agreement with *ab initio* quantum chemical calculations.¹² Mass spectrometry has also been used to provide evidence for the occurrence of intermediate radical termination during RAFT polymerization of acrylates and styrene with dithiobenzoate RAFT agents. Some studies found traces of three-armed

star polymers¹³ (yet never in sufficient quantities to accord with a high termination rate coefficient), but other studies—both mass spectrometric¹⁴ and via fluorescence marking¹⁵—found none. Perrier and coworkers¹⁶ recently proposed a possible compromise between the slow-fragmentation and intermediate-radical-termination models for retardation in RAFT polymerization with the same RAFT agents. According to the proposed model, intermediate radical termination occurs, but only for initiator-derived or oligomeric species.¹⁷ A complete resolution of all kinetic complexities occurring during the RAFT process is still outstanding.

2.3 Transfer Constants

The rate of consumption of the RAFT agent depends on two transfer coefficients: $C_{tr}(=k_{tr}/k_p)$ and $C_{-tr}(=k_{-tr}/k_i)$, which describe the reactivity of the propagating radical (P_n^*) and the expelled radical (R^*) toward the thiocarbonyl thio moieties, respectively.

The rate coefficient for chain transfer is defined by the product of the rate coefficient for addition to the RAFT agent (k_{add}) and a partition coefficient which represents how the adduct is partitioned between the products and starting materials (1):

$$k_{tr} = k_{add} \frac{k_{\beta}}{k_{\beta} + k_{-add}} \quad (1)$$

In a similar fashion, k_{-tr} is defined for the reverse process (2):

$$k_{-tr} = k_{-\beta} \frac{k_{-add}}{k_{\beta} + k_{-add}} \quad (2)$$

The reverse process cannot be neglected when low- k_p monomers such as styrene or highly reactive RAFT agents (e.g., dithiobenzoates) are used. Moad *et al.* suggested that, when C_{-tr} was ignored and set to zero, the experimental C_{-tr} values should be termed *apparent constants*.¹⁸ They proposed that C_{tr} could be neglected when the independence of C_{tr} on the RAFT agent concentration is established.¹⁸ During polymerization, the propagating radicals P_n^* and P_m^* have similar lengths and reactivities. Therefore, the intermediate radical species **14** is symmetrical and k_{appP} and k_{-addP} are supposed to

be equal. It appears that the rate coefficient for reversible chain transfer (interchain transfer) $k_{tr,PnX}$ is primarily a function of the rate coefficient for addition to the RAFT terminal group (3). The magnitude of interchain transfer depends on the interchain transfer constant $C_{tr,PnX}(=k_{tr,PnX}/k_p)$:

$$k_{tr,PnX} = k_{addP} \frac{k_{-addP}}{k_{-addP} + k_{-addP}} = \frac{k_{addP}}{2} \quad (3)$$

As with any type of living polymerization, the rate of consumption of the RAFT agent and the rate of interchain transfer will dictate the molecular weight profiles and the molecular weight distributions during polymerization.¹⁶

2.4 Molecular Weights and Molecular Weight Distributions

In radical polymerization, the number-average degree of polymerization $\overline{DP}_n$ is defined as the ratio of the monomer concentration consumed at time t and the concentration of chains created at the same time (4). In (4), x is the fractional monomer conversion, $[M]_0$ is the initial monomer concentration, $\Delta[X]_t$ is the concentration of transfer agent consumed at time t , d is the number of chains produced in a radical–radical termination event, and f is the initiator efficiency. As a consequence, the expression of $\overline{M}_n$ is defined by (5) where $M(M)$ is the molar mass of the monomer and $M(RAFT)$ is the molar mass of the RAFT agent.

$$\begin{aligned} \overline{DP}_n &= \frac{[\text{Reacted monomer}]_t}{[\text{Created chains}]_t} \\ &= \frac{x[M]_0}{\Delta[X]_t + df([I_2]_0 - [I_2]_t)} \end{aligned} \quad (4)$$

$$\overline{M}_n = \frac{x[M]_0 M(M)}{\Delta[X]_t + df([I_2]_0 - [I_2]_t)} + M(RAFT) \quad (5)$$

The fraction of living chains (L) (if it is assumed that initiation and termination are the only side reactions) is given by (6).

$$L = \frac{\Delta[X]_t}{\Delta[X]_t + df([I_2]_0 - [I_2]_t)} \quad (6)$$

The reaction conditions are usually selected such that the contribution of initiator-derived chains is negligible (i.e., $L \sim 1$). Under these conditions and in the case of a complete consumption of the RAFT agent early in the reaction (the so-called ideal case), the expressions of $\overline{DP}_n$ and $\overline{M}_n$ are simplified as expressed in (7) and (8), respectively.

$$\overline{DP}_{n,id} = x \frac{[M]_0}{[X]_0} \quad (7)$$

$$\overline{M}_{n,id} = \overline{DP}_{n,id} M(M) + M(RAFT) \quad (8)$$

In nonideal cases, the transfer to the RAFT agent is not fast enough relative to propagation and $\Delta[X]_t$ must replace $[X]_0$ in the mathematical expressions.

A simple integration of the kinetic equation for propagation and transfer reactions gives access to (9) which expresses the effect of C_{tr} of the RAFT agent on the relative evolution of RAFT agent and monomer concentrations during polymerization.

$$\frac{[X]}{[X]_0} = \left(\frac{[M]}{[M]_0} \right)^{C_{tr,X}} \quad (9)$$

From (9), the concentration of chains formed at time t is obtained (10).

$$\begin{aligned} [\text{chains}]_t &= \Delta[X]_t = [X]_0 - [X]_t \\ &= [X]_0 - [X]_0 \left(\frac{[M]}{[M]_0} \right)^{C_{tr,X}} \end{aligned} \quad (10)$$

Equation (10) is simplified as

$$\Delta[X]_t = [X]_0 (1 - (1 - x)^{C_{tr,X}}) \quad (11)$$

Equations (12) and (13) define $\overline{DP}_n$ and $\overline{M}_n$, respectively, for nonideal systems in which the consumption of the RAFT agent is not instantaneous during polymerization:

$$\overline{DP}_{n,non id} = x \frac{[M]_0}{[X]_0} \frac{1}{(1 - (1 - x)^{C_{tr,X}})} \quad (12)$$

$$\overline{M}_{n,non id} = \overline{DP}_{n,non id} M(M) + M(X) \quad (13)$$

Two main cases can be distinguished:

- If $C_{tr} \geq 1$, then $\overline{DP}_n$ equals $[M]_0/[X]_0$ at the end of the polymerization (14). Therefore, the final $\overline{M}_n$ value is controlled under these conditions.

$$\overline{M}_{n,non id} \xrightarrow{x \rightarrow 1} \overline{M}_{n,id} \xrightarrow{x \rightarrow 1} \frac{[M]_0}{[X]_0} M(M) + M(X) \quad (14)$$

- If $C_{tr} < 1$, the experimental $\overline{DP}_n$ values will remain greater than the targeted ones throughout the polymerization, and some unreacted RAFT agent will be present at the end of the polymerization.

The greater the C_{tr} value, the earlier the stage of the polymerization at which the RAFT agent will have fully reacted. A linear growth of $\overline{M}_w$ as a function of monomer conversion is obtained for $C_{tr} > 10$.

In the 1990s, Müller and coworkers predicted the dependence of the degree of polymerization and polydispersity on conversion for polymerizations based on a degenerative transfer mechanism.^{19,20} The theoretical profiles were applied for RAFT polymerizations and were compared with experimental data obtained for methyl methacrylate (MMA) polymerization in the presence of dithiobenzoate esters (Figure 1).^{19,20}

The evolution of polydispersities during polymerization is mainly dictated by the interchain transfer constant $C_{tr,PnX}$. The faster the reversible chain transfer, the narrower the molecular weight distributions, as the chains tend to all have the same probability of growth. Müller *et al.* obtained an expression of $\overline{M}_w$ as a function of C_{tr} (15).

$$\begin{aligned} \overline{M}_{w,non id} &= \frac{[M]_0}{[X]_0} \left(2 + \frac{(2 - x)(1 - C_{tr,X})}{C_{tr,X}} \right) \\ &\times M(M) + M(X) \end{aligned} \quad (15)$$

It was also established that $\overline{M}_w$ and $\overline{M}_w/\overline{M}_n$ values evolve as indicated in (16) and (17) at the end of the polymerization, respectively.

$$\begin{aligned} \overline{M}_{w,non id} &\xrightarrow{x \rightarrow 1} \overline{M}_{w,id} \xrightarrow{x \rightarrow 1} \frac{(C_{tr,X} + 1)}{C_{tr,X}} \\ &\times \frac{[M]_0}{[X]_0} M(M) + M(X) \end{aligned} \quad (16)$$

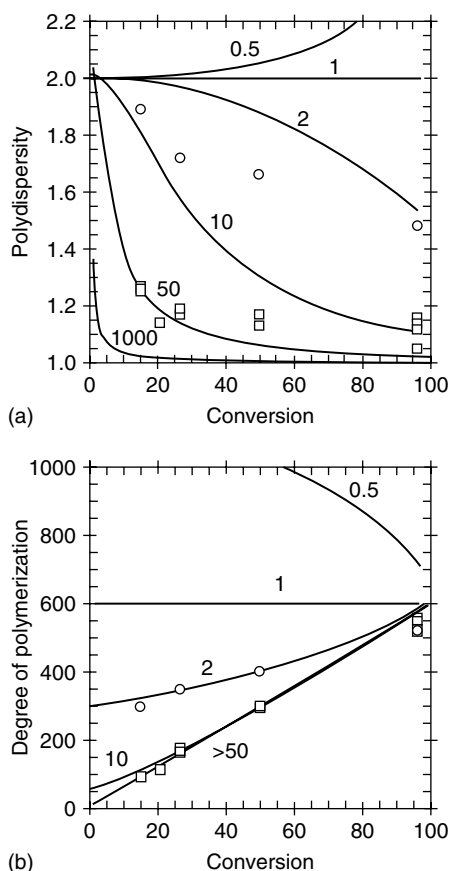


Figure 1 Predicted dependence of (a) polydispersity and (b) degree of polymerization on conversion in polymerizations involving reversible chain transfer as a function of the chain transfer constant. Predictions are based on the equations proposed by Müller *et al.*^{19,20} with $\alpha = 10^{-7}$, β as indicated, and $\gamma = 605$. Experimental data points are for methyl methacrylate polymerization in the presence of dithiobenzoate esters $\text{Ph}(\text{C}=\text{S})\text{SR}$ (0.0116 M) where $\text{R} = -\text{C}(\text{Me})_2\text{CO}_2\text{Et}$ (○) and $\text{R} = -\text{C}(\text{Me})_2\text{Ph}$ (□). [Reproduced from Ref. 18. © American Chemical Society, 2003.]

$$\begin{aligned} \overline{M}_w/\overline{M}_n &= \frac{\overline{M}_{w,\text{non id}}}{\overline{M}_{n,\text{non id}}} \xrightarrow{x \rightarrow 1} \frac{(C_{\text{tr},X} + 1)}{C_{\text{tr},X}} \\ &= 1 + \frac{1}{C_{\text{tr},X}} = 1 + \frac{1}{C_{\text{tr},\text{PnX}}} \quad (17) \end{aligned}$$

Therefore, a good approximation of $C_{\text{tr},\text{PnX}}$ is obtained by determining the polydispersity index (PDI) value at the end of the polymerization.

2.5 Measurement of Transfer Constants

A number of methods have been reported for determining values of the transfer constants to the RAFT agent. Conventional approaches, such as the Mayo method, are only suitable for low transfer constants and are not appropriate for most of the RAFT agents. An alternative strategy for determining C_{tr} is based on the kinetic model developed by Müller *et al.*^{19,20}

By combining (7) and (12) with (18), it is possible to follow the $\overline{DP}_{n,\text{id}}/\overline{DP}_{n,\text{non id}}$ ratio during polymerization in order to determine C_{tr} .

$$\ln \left(1 - \frac{\overline{DP}_{n,\text{id}}}{\overline{DP}_{n,\text{non id}}} \right) = C_{\text{tr},X} \ln(1 - x) \quad (18)$$

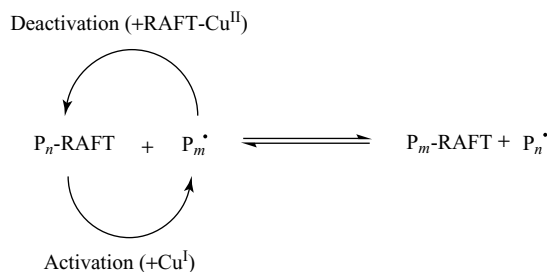
By doing so, C_{tr} is obtained on the basis of one single polymerization experiment. Using this approach, however, the polymerization must be monitored—usually by size-exclusion chromatography (SEC)—at conversions where $\overline{DP}_{n,\text{non id}}$ is still greater than $\overline{DP}_{n,\text{id}}$ (i.e., at conversions where $\overline{M}_{n,\text{exp}} > \overline{M}_{n,\text{th}}$). Therefore, this method is not suitable for high C_{tr} values (>5). The main drawbacks of the two reported techniques are the limitation to relatively low C_{tr} values and the use of experimental $\overline{M}_n$ values usually determined by SEC, which may alter the accuracy of the C_{tr} values. The most used and preferred technique for measuring C_{tr} is based on (9), which is an expression for the evolution of RAFT agent and monomer concentration as a function of C_{tr} . The double-log regression of (9) gives direct access to C_{tr} in one single experiment. This method is known to be more accurate than the others because it is solely based on the accurate measurement of the concentrations of the RAFT agent and monomer over time, for instance by high-performance liquid chromatography.

3 MOLECULAR WEIGHT RANGE

The control over molecular weight, while retaining living chain ends, as well as obtaining a narrow polydispersity, are the key characteristics of living polymerization processes. The most efficient control is typically exerted by anionic polymerization systems, where narrow molecular weight polymers exceeding 10^6 Da are accessible for some

polymer systems (e.g., polystyrene and poly(methyl methacrylate)), as these systems do not suffer from irreversible termination processes. In living radical systems such as RAFT or atom transfer radical polymerization (ATRP) (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**), such high molecular weights are not available with low polydispersities. As seen in the previous section, the reasons for this limitation are the continuous increase of terminated material with increasing monomer-to-polymer conversion as well as a loss in end-group fidelity of the living end groups (e.g., elimination (ATRP) or oxidation and hydrolysis (RAFT) reactions). In addition, the most important factor restricting high molecular weights is the limit to which the concentration of the controlling agent can be lowered in relation to the employed radical initiator concentration. An efficient RAFT process relies on the high rate of reaction between the propagating chains and the thiocarbonyl thio moiety, which exceeds the rate of termination of two macroradicals ideally by a factor larger than 10^4 . A strong reduction in the RAFT agent concentration thus leads to a decrease of the above ratio, and typically molecular weights exceeding 200 kDa are not accessible without a loss of control, that is, a significant broadening of the molecular weight distribution as well as the occurrence of hybrid behavior. Hybrid behavior is a phenomenon that occurs when the addition rate of the propagating radicals with the initial RAFT agent ($R_{\text{add}} = k_{\text{add}} [\text{RAFT}] [P_n]$) is significantly lower than that of propagation ($R_p = k_p [P_n] [M]$). An inspection of the respective rate law expressions indicates that it can be caused by too low an addition rate coefficient, k_{add} , (e.g., when attempting to mediate a styrene polymerization with a xanthate) or too low a concentration of the RAFT agent. Its macroscopic manifestation is an initial sharp increase in the molecular weight at very low conversion, followed by linear macromolecular growth with conversion, which asymptotically approaches the theoretical limit. Inspection of the respective rate equations thus indicates that attempts to generate high molecular weight polymers via the RAFT process with a concomitant suppression of hybrid behavior should be carried out at high monomer concentrations with RAFT agents that enable the rapid addition of macroradicals, such as dithiobenzoates.

To address the problem of preparing high molecular weight polymers (and concomitantly improving the block copolymer formation process) via the RAFT process, Matyjaszewski and colleagues recently introduced a methodology that combines RAFT chemistry with the ATRP process, allowing the generation of well-defined, high molecular weight material.²¹ The process takes advantage of the fact that dithioesters can act as pseudo-halogens under conditions that are normally employed during an ATRP process. The key idea here is that, in both ATRP and RAFT, termination reactions occur (in RAFT even more than in ATRP, due to the nonreduced overall propagating radical concentration), yet there is no steady radical influx into a combined RAFT/ATRP system, preventing a tailing of the molecular weight distribution. The general working principle of concurrent RAFT/ATRP is depicted in Scheme 4. The authors were able to demonstrate that the system functions well for styrene and MMAs, when cumyldithiobenzoate is employed as the RAFT agent. For example, poly(methyl methacrylates) could be prepared with a molecular weight of up to 500 kDa and a polydispersity of approximately 1.3. Thus, the process represents an efficient avenue for the preparation of high molecular weight polymers via an adapted RAFT process. An alternative—and also relatively facile—method has recently been suggested by Gerstel and Barner-Kowollik, who employed a diradical initiating species derived from Bergman cyclization to achieve high molecular weight RAFT generated polymers with relatively narrow polydispersities (up to 400 kDa).²²



Scheme 4 Proposed reaction mechanism for concurrent RAFT/ATRP. Note that no additional thermal initiation source is required. Concurrent RAFT/ATRP allows the generation of high molecular weight polymers ($M_n > 500$ kDa) with relatively low PDI (< 1.3). [Adapted from Ref. 21. © American Chemical Society, 2008.]

While it is often desired to prepare macromolecules with low polydispersity and high molecular weights, it is also sometimes a requirement to generate well-defined polymeric materials in the oligomeric range (e.g., for the provision of modular macromolecular building blocks for the preparation of brush-like structures). The RAFT process is especially suited for generating well-defined, high end-group fidelity, low molecular weight material, as long as the RAFT agent/monomer combination is chosen such that hybrid effects (see above) do not prevent the generation of very low molecular weights (i.e., the pre-equilibrium is passed rapidly). From the kinetic equations governing the RAFT process, it is immediately evident that the (instantaneous) degree of polymerization versus monomer-to-polymer conversion correlation can never pass through the origin and only through degree of polymerization = 1. If the degree of polymerization versus conversion correlation were to pass through the origin, the ratio of the propagation rate coefficient, k_p , and the addition rate coefficient of the macro- and primary radicals to the initial RAFT agent, k_{add} , had to be zero, implying that k_{add} must be infinity or k_p zero—two conditions which cannot be fulfilled.²³ Very low PDI polymers in the oligomer range (number average molecular weight between 500 and 5000 Da) can be obtained when the radical concentration is kept low over the duration of the polymerization and a high k_{add} RAFT agent and relatively low k_p monomer are employed. Although such a scenario sounds somewhat exotic, it is easy to implement, for example, in the systems styrene/cumyldithiobenzoate (CDB) or cyanoisopropylthiobenzoate (CPDB) and—at temperatures not exceeding ambient to reduce k_p as much as possible—in acrylate/CDB or CPDB systems. The degree of low molecular weight control with low polydispersities is an advantage of RAFT over ATRP and other processes, where (due to the persistent radical effect) control tends to increase only with increasing conversion and thus concomitantly increasing molecular weights.

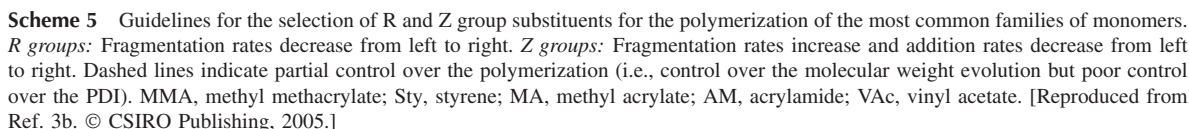
4 MONOMER RANGE

One of the key strengths of the RAFT process is its high tolerance of functional groups. RAFT polymerization has been shown to effectively mediate

the polymerizations of almost all the monomers that can be polymerized via conventional free-radical polymerization, in the bulk, organic, and aqueous solvents. Often, the control over polymerization depends on the careful choice of the RAFT agent. Scheme 5 gives general guidelines for the choice of appropriate substituents of a RAFT agent, depending on the monomer considered.

The polymerization of styrene is very well controlled when mediated by dithioesters, trithiocarbonates, and dithiocarbamates (where the nitrogen lone pair does not strongly conjugate with the thiocarbonyl bond), with typical PDIs ranging from 1.03 to 1.25, while poor control is obtained from xanthates and alkyl dithiocarbamates (with PDIs ranging from 1.5 to 2.0). Preventing the conjugation of the lone pair of the Z group heteroatom with the thiocarbonyl thio group can increase the reactivity toward radical addition of the C=S bond of these RAFT agents. This is achieved by the inclusion of electron-withdrawing groups attached to the alkoxy Z group or, in the case of dithiocarbamates, where the nitrogen lone pair is conjugated into an aromatic ring system. In addition, the intermediate radical is less destabilized by the lone pair, which reduces the rate of fragmentation, thus improving the RAFT agents' ability to mediate the polymerization. Unfortunately, the limited number of functionalized styrene derivatives restricts the access to functional materials.

Acrylates and acrylamides are among the most versatile monomers with respect to the classes of RAFT agents that can control their polymerization. Acryloyl propagating radicals are relatively reactive because they are secondary radicals and therefore have a low steric bulk. Furthermore, acrylates do not possess any strong radical stabilizing groups. The relative instability of acryloyl propagating radicals means that a wide range of R groups can be used since many are more stable and thus better leaving groups than these radicals. Additionally, the adduct radical that is formed by addition of an acryloyl radical is relatively stable, and therefore a Z group that produces a lower stabilizing effect, such as in dithioacetates, trithiocarbonates, and appropriately substituted dithiocarbamates, is necessary to promote fragmentation of the adduct radical. Dithiobenzoate-mediated acrylate polymerizations, on the other hand, often exhibit an induction and rate retardation phenomenon, the origin of which has been discussed extensively in the literature.²⁴



Methacrylates and methacrylamides are among the more challenging families of monomers to polymerize via the RAFT process, because of their bulky tertiary propagating radicals. In order for a methacryloyl propagating radical to efficiently add to the thiocarbonyl bond of the mediating chain transfer agent (CTA), the reactivity of the thiocarbonyl bond toward radical addition must be high. Furthermore, the adduct radical formed by addition of the propagating radical to the RAFT agent must be sufficiently stabilized so that fragmentation does not occur too rapidly. For these reasons, xanthates offer very little control over the polymerization of methacrylates. The thiocarbonyl groups of aliphatic dithioesters, trithiocarbonates, and dithiocarbamates (with aromatic Z groups) are more reactive than those of xanthates. In addition, the Z groups of these

RAFT agents do not cause as much destabilization of the adduct radical as xanthates, and therefore they exhibit reduced rates of fragmentation, resulting in increased control over the polymerization. However, the most appropriate Z groups for the polymerization of methacrylates are phenyl (e.g., dithiobenzoates), as the thiocarbonyl group is relatively reactive and the adduct radical is most stabilized by these RAFT agents. The choice of R group on the CTA is particularly important in methacrylate polymerizations because, as with all successful RAFT polymerizations, the R group must be a better leaving group than the propagating radical. The most successful R groups for methacrylate polymerization are both bulky and capable of stabilizing the radical. Cyanoisopropyl and cumyl R groups tend to be the most effective as they possess steric bulk and functional groups (-CN and -Ph, respectively) that are able to stabilize the R group-derived radical. Interestingly, there are very few RAFT agents with an R substituent generating a secondary radical that gives good control over methacrylic polymers.²⁵ The families of (meth)acrylate and (meth)acrylamide monomers are of great interest to

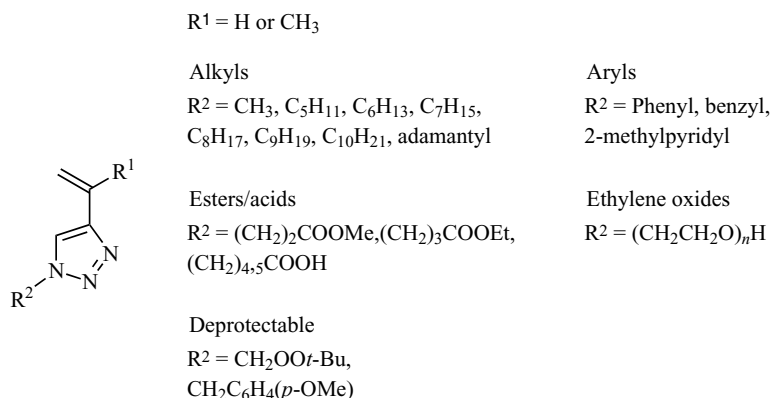


Figure 2 Examples of functional 4-vinyl-1,2,3-triazole monomers. [Reprinted with permission from Ref. 27a. Copyright 2006 American Chemical Society.]

polymer chemists, since they offer a wide range of functionalities. Indeed, in addition to the hundreds of monomers commercially available, one can transform any molecule bearing a hydroxyl or amine functional group into the corresponding monomer, by simple esterification with (meth)acryloyl chloride. Such a modular approach to monomer design enables the introduction of a wide array of functionalities into monomeric building blocks.

Vinyl acetate (VAc) is a relatively low reactive monomer (i.e. generating a highly reactive radical) owing to poor stabilization of the propagating radical and low steric bulk. Since the lack of stability of VAc propagating radicals makes it a poor leaving group in the RAFT adduct intermediate radical, only RAFT agents such as xanthates and *N,N*-dialkyl dithiocarbamates, with a Z group that destabilizes the intermediate radicals, can effectively mediate the RAFT polymerization of VAc. The same is true for other monomers of relatively high reactivity, such as vinyl pyrrolidone. Interestingly, RAFT is, to date, the best technique to control the polymerization of vinyl acetate and its derivatives.

Beyond these common families of monomers, a variety of other monomer classes have been successfully polymerized by RAFT, including, for instance, isoprene, 2- and 4-vinylpyridine, acrylonitrile, and vinyl sulfonate esters. Mori *et al.* showed that xanthates could efficiently control the polymerization of this latter family of monomers to yield sulfonated block copolymers.²⁶

An elegant approach to increase the range of functional monomers was introduced by Hawker

and coworkers, who presented the RAFT polymerization of 4-vinyl-1,2,3-triazole monomers. These triazole derivatives are easily synthesized via copper-catalyzed [1 + 3] dipolar cycloaddition and present an entirely new class of functional monomers (Figure 2).²⁷

There may be occasions when the desired functionality cannot be introduced via the monomer prior to polymerization because of incompatibility with the RAFT agent (see below) or incompatibility with the reaction conditions. In this case, it is common to exploit high-yielding organic addition reactions (“click” chemistry, see section below *Modular Design* and **Radical Thiol–X Click Chemistry**) to add the targeted functionality to the polymer after polymerization, in a modular approach. To this effect, a number of monomers have been designed that allow the addition of functional groups postpolymerization. The most common examples of this convergent synthetic strategy employ activated esters such as *N*-(meth)acryloxysuccinimide²⁸ and pentafluorophenylmethacrylate,²⁹ as well as aldehyde derivatives such as 4-vinylbenzaldehyde,³⁰ methyl vinyl ketone, and phenyl vinyl ketone³¹ (for addition of amines). It is also interesting to note that thiol exchange reactions have been used, by polymerizing monomers such as pyridyldisulfide ethylmethacrylate via RAFT to create a polymeric scaffold, which can be functionalized by the addition of a variety of thiols.³²

The mechanism of RAFT polymerization relies on the activation of the monomer double bond

to enable efficient fragmentation from the intermediate radical, which gives control over the molecular weight of the resulting polymer. It follows that vinyl monomers, for which the double bond is not activated, are still challenging to polymerize efficiently via RAFT. In certain cases, a more reactive RAFT agent, such as one from the families of xanthates and *N,N*-dialkyl dithiocarbamates, is more adapted to such monomers. For instance, the polymerization of diallyldimethyl ammonium chloride (DADMAC) was shown to be controlled by xanthates, to yield polymers of well-controlled molecular weights.³³ Attempts have been made to control the polymerization of 1-alkenes³⁴ and allyl butyl ethers³⁵ yet, to date, only copolymerization with active monomers (acrylates and acrylamides) have led to relatively good control with a low amount of the nonactivated alkene present in the final product. The controlled polymerization of ethylene, one of the most widespread monomers in free-radical polymerization, still remains a challenge.³⁶

A noteworthy drawback of RAFT polymerization in terms of functionality is the reactivity of the thiocarbonyl thio group toward amines. Primary and—under appropriate conditions—secondary amines react with the thiocarbonyl thio group to form carbamates, which leads to the deactivation of the chain transfer agent. Therefore, it is difficult to control the RAFT polymerization of amine-containing monomers. Of course, a simple route to circumvent this problem is to use the modular approach described below, where the amine functionality is added to the polymer backbone postpolymerization.

5 POLYMERIC ARCHITECTURES

With ever-increasing application-based demands on polymeric materials in the fields of biotechnology and nanotechnology, gaining fine control over macromolecular structure to produce precisely engineered materials is currently a key issue for polymer scientists to address. In order to produce polymers for such specific applications, it is necessary to have control over not only the molecular weight and incorporated functionalities but also, and perhaps of more importance, the architectural design—that is the three-dimensional connectivity between the monomer units—of the polymer. When carefully

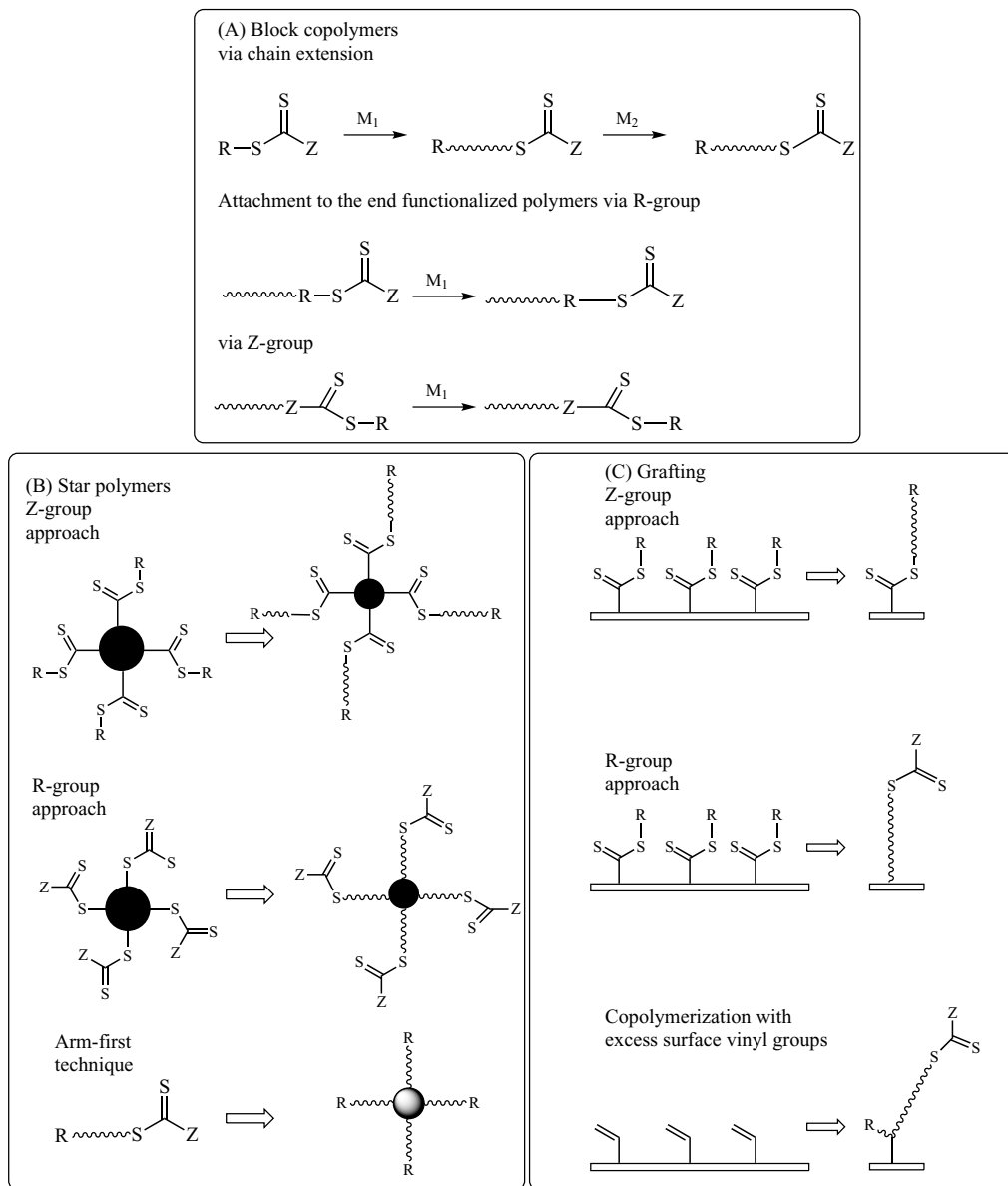
designed, RAFT polymerization opens the door to a wide range of polymer architectures—thus the ability to subtly tune polymer properties—via a number of variable approaches.

Similar to other living radical polymerization techniques, block copolymers, star and comb polymers, as well as graft polymers are all accessible by attaching the controlling RAFT agent to a (multi)functional core linking moiety (as shown in Scheme 6). In addition, more complex multiblock systems based on these architectures can be obtained by chain extension of the RAFT moiety capped block.

Unique to the RAFT process are the possible modes of attaching the RAFT group covalently to the (multi)functional moiety.³⁷ The nature of the controlling agent allows two distinct approaches, the R- and Z-group approaches, to the design of complex architectures, of which only one is easily available in, for example, ATRP (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**)³⁸ and nitroxide mediated polymerization (NMP, see **Nitroxide-Mediated Polymerization and its Applications**).³⁹ While all the aforementioned techniques focus on a starting with multifunctional RAFT agents and divergent syntheses, the presence of the thiocarbonyl thio group postpolymerization also allows for an arm-first (or convergent) synthesis of all these structures, where this end group can be utilized in conjugation reactions.

The critical issue in all these approaches is the ability to maintain the fidelity of the thiocarbonyl thio end group. Undesired bimolecular termination reactions, high initiator concentrations, or chain transfer to monomer or solvent can reduce the amount of RAFT end-capped polymer chains. It is therefore paramount that, before attempting to generate complex architectures, optimization and fine-tuning of polymerization variables (such as those discussed in the previous sections) are carried out on simpler systems.

In the following sections, we will highlight the example of block copolymer synthesis in much greater detail to demonstrate the variety of parameters and synthetic techniques, from both divergent and convergent pathways, available in RAFT systems. We will also discuss some of the limitations of these systems and strategies that can be employed to avoid these situations. It should



Scheme 6 Selection of complex polymer architecture formation pathways prepared via RAFT polymerization. [Adapted from Ref. 37. © Wiley-VCH Verlag GmbH & Co. KGaA, 2008.]

be noted that all the benefits and shortcomings discussed with regard to the block copolymer synthesis are also applicable to the synthesis of some of the more exotic polymer architectures. For additional specific examples of RAFT systems being employed for the formation of higher order architectures, the reader is directed to Refs 3, 37, 40 and 41.

5.1 The Example of Block Copolymers: Divergent Synthesis

Block copolymers are arguably the most important polymer class that can be prepared via living radical polymerization processes, including RAFT chemistry. A wide variety of block copolymers have indeed been accessed via the RAFT

process—including amphiphilic ones—mostly via a sequential polymers design, implying that a first block is prepared, which is subsequently (after isolation) redissolved and chain-extended with a second monomer. In theory, this process can be repeated several times, thus in principle providing access to narrow-polydispersity multiblock copolymer structures. In practice, the generation of block copolymers of high purity requires a careful choice of the RAFT agent as well as a compatible solvent for both blocks. As the RAFT process relies on a radical addition fragmentation equilibrium, not all combinations of monomers may be employed to generate the respective blocks. The more disparate the reactivities of the associated propagating radicals, the more problematic it is for the formation of the respective block structure. For example, it is—with classical RAFT agents—impossible to generate block copolymers of polystyrene and poly(vinyl acetate), as there exists no common RAFT agent. The polymerization of styrene can be mediated by a wide array of RAFT agents (see above), while vinyl acetate may only be mediated by xanthates and dialkyl dithiocarbamates, which cannot induce control over styrene polymerizations. Two principal solutions to this problem exist. The first will be addressed in detail below in the section on *Modular Design*, where the two blocks are independently generated and subsequently ligated via an efficient conjugation strategy. The second approach entails the design of a RAFT agent, which can offer universal control over any monomer, irrespective of the reactivity of the propagating radical center.

Before we turn our attention to universal RAFT agents, the section below will explore some of the limitations as well as strengths of block copolymer generation. Prior to exploring some detailed chemistries, a general word of caution: It has been common practice in the literature to demonstrate the efficiency of chain extension via a plot showing the evolution of the molecular weight distribution as well as the initial block in a diagram where all distributions are normalized with regard to their peak maximum. Such a representation can be misleading in judging the quality of the chain extension, as it overemphasizes the M_p of each distribution. With such a representation, it cannot be adequately judged what quantity of material is not chain-extended (“left behind”). It is thus much more preferable to scale the

extension molecular weight distributions relative to the achieved monomer-to-polymer conversion of the second monomer. A detailed description of the two forms of data presentation can be found in Ref. 42.

Within the literature, a wealth of functional examples with regard to block chain extension by sequential monomer addition can be found. As with homopolymerizations mediated via the RAFT process, block extensions can suffer from loss of control when attempts to reach high molecular weight blocks are made. However, access to moderate molecular weight blocks (~50–70 kDa) with good reaction control is readily achievable. Rizzardo, Moad, and coworkers demonstrated two examples with the synthesis of poly(methyl methacrylate)-*b*-styrene and poly(dimethylaminoethyl methacrylate)-*b*-styrene.⁴³ Both systems had an overall molecular weight of greater than 100 kDa while the polydispersity was kept below 1.3. Because of the excellent functional group tolerance of RAFT polymerizations, access to hydrophobic–hydrophobic (e.g., poly(methyl methacrylate)-*b*-styrene), hydrophilic–hydrophilic (e.g., poly(*N,N*-dimethylacrylamide)-*b*-(*N,N*-dimethylvinylbenzyl-ammonium chloride)⁴⁴) and hydrophobic–hydrophilic (e.g., poly(octadecyl acrylate)-*b*-(*N*-vinyl pyrrolidone)⁴⁵) diblock systems are possible.

The formation of block copolymers by sequential monomer addition is in no way limited to only AB diblocks. There are a number of examples of higher order ABA and ABC triblocks formed using the diblock copolymer as a macro-RAFT agent. Zhao, Perrier, and coworkers have demonstrated this to the greatest extent, producing a series of ABCD tetrablock copolymers, all of which, as shown by the representative example in Figure 3, displayed little to no loss in control of the polymerizations, even after the addition of the fourth block (e.g., polystyrene-*b*-(*N*-acrylomorpholine)-*b*-(*N*-isopropylacrylamide)-*b*-(methyl acrylate), $\overline{M}_n = 23\,200$ Da, PDI = 1.19).⁴⁶ Using similar chain-extension conditions but switching from a mono- to a bis-RAFT agent allows facile access to symmetrical triblock copolymers. Moad and coworkers applied this type of bis-RAFT agent to the synthesis of poly(styrene-*co*-acrylonitrile)-*b*-(butyl acrylate)-*b*-(styrene-*co*-acrylonitrile) copolymers for applications as thermoplastic elastomers.⁴⁷ This again demonstrates that moderately high molecular

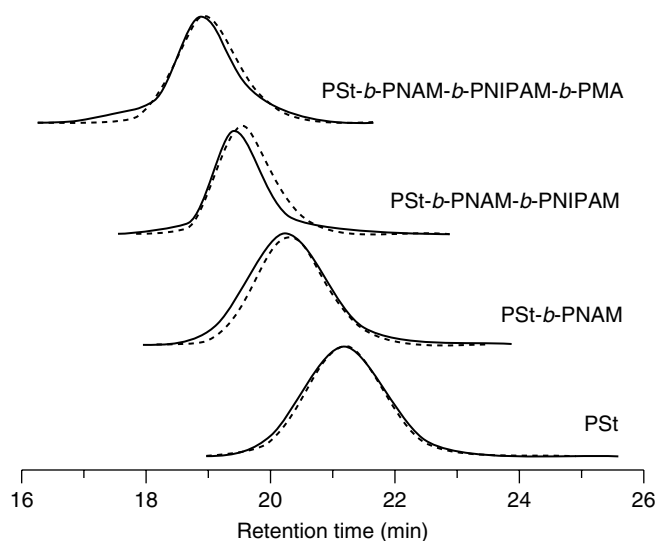


Figure 3 SEC traces of polystyrene, polystyrene-*b*-(*N*-acrylomorpholine) (PSt-*b*-PNAM), polystyrene-*b*-(*N*-acrylomorpholine)-*b*-(*N*-isopropylacrylamide) (PSt-*b*-PNAM-*b*-PNIPAM), and polystyrene-*b*-(*N*-acrylomorpholine)-*b*-(*N*-isopropylacrylamide)-*b*-(methyl acrylate) (PSt-*b*-PNAM-*b*-PNIPAM-*b*-PMA) prepared via subsequent chain extensions via the RAFT process employing *S*-methoxy-carbonylphenylmethyl *S*-trimethoxysilylpropyltrithiocarbonate (MPTT). [Reproduced with permission from Ref. 46. Copyright 2009 American Chemical Society.]

weight initial (poly(butyl acrylate), $\overline{M}_n = 77\,000$ Da) and chain-extension blocks (polystyrene block ~ 50 kDa) can be synthesized using this methodology, without having to sacrifice reaction control (PDI = 1.2).

While not exclusively related to block copolymer synthesis, the formation of many of the more complex architectures available through RAFT polymerization—including those based on a single monomer—share the characteristics and caveats of linear block copolymer formation. One technique to obtain such structures (akin to the triblock synthesis mentioned before) is the use of higher level multifunctional RAFT agents. A synthetic approach with a multifunctional core or a RAFT agent functionalized polymer backbone allows the synthesis of polymer star or graft to polymers, respectively. Whether the RAFT agents are linked via their Z- or R-groups to the core/backbone of the molecule governs whether the thiocarbonyl thio moiety remains at the center or is found at the periphery of the arms' chains. The choice of Z- versus R-group approach has consequences when considering the synthesis of diblock copolymer variations of such molecules, as the choice of starting agent will dictate which block ultimately finishes nearer the core. In addition, the

choice of Z- versus R-group has significant consequences with regard to the uniformity of the generated polymeric materials. In the R-group approach, multifunctional RAFT agents can lead to multimodal molecular weight distributions, owing to the fact that the core is a radical-carrying entity, allowing star-star coupling to occur. Z-group approaches can lead to limited molecular weights, potentially caused by steric crowding around the multifunctional core to which the thiocarbonyl thio moiety is tethered. As it is not the aim of the current article to explore in depth complex macromolecular architecture formation via the RAFT process, the interested reader is referred to the existing reviews and studies on this topic.^{42,48} Alternatively, graft-type polymers can be formed using a grafting-through technique employing the polymerization of macromonomers (or a combination of monomer and macromonomer), which have reactive vinyl end groups, in the presence of a suitable RAFT agent. Access to highly branched systems is further possible by the addition of a controlled amount of multifunctional vinyl compound.⁴⁹

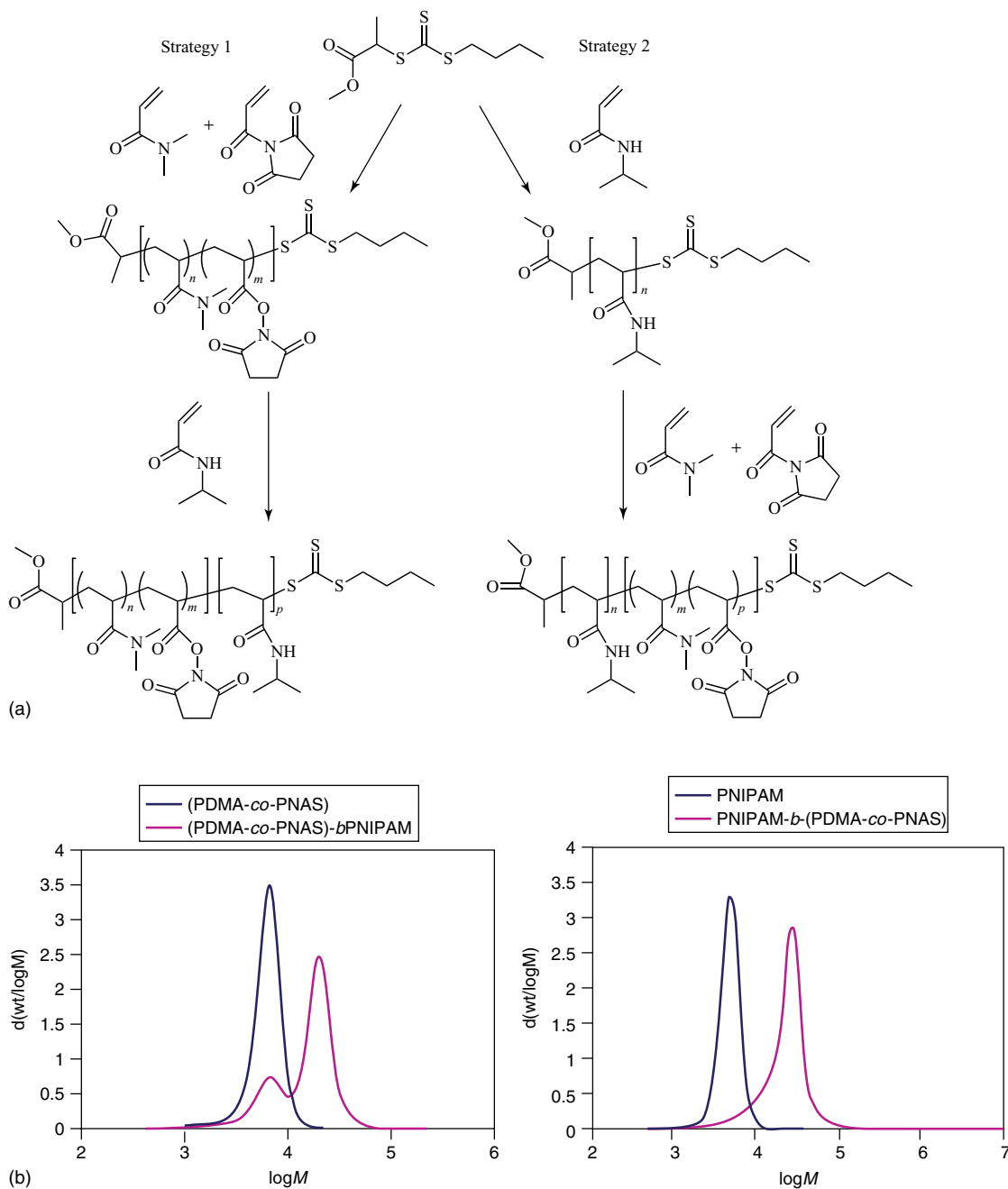
When planning the synthesis of block copolymers, it should be noted that the leaving group of the newly formed macro-RAFT agent is the previously polymerized chain. It is therefore very

important to consider the order in which the blocks are polymerized. If the monomers vary markedly in reactivity (e.g., styrenic/acrylic or methacrylic), this can impact on the preferential fragmentation of transient macro-RAFT radicals in the direction of the most stable radical during the chain transfer step. Such problems are illustrated in the polymerization of MMA and styrene.¹⁸ When MMA is polymerized in the presence of cumyldithiobenzoate ($\bar{M}_n = 14700$ Da, PDI = 1.21) followed by block extension with styrene to approximately double the molecular weight, complete conversion to poly(methyl methacrylate)-*b*-styrene is observed ($\bar{M}_n = 35000$ Da, PDI = 1.24). Taking the same experimental conditions but reversing the block order gives a very different result. Examination of the final mixture shows the presence of unchanged polystyrene macro-RAFT agent ($\bar{M}_n = 20000$ Da, PDI = 1.15) as well as uncontrolled poly(methyl methacrylate) homopolymer ($\bar{M}_n = 290000$ Da, PDI = 2.63), similar to that obtained from a conventional radical polymerization. While this example illustrates the point using two monomers of clearly differing reactivity, in some cases the differences are not as obvious. When examining the example shown in Scheme 7, a low level of blocking efficiency is observed when a poly(*N*-acryloyloxysuccinimide-*co*-*N,N*-dimethylacrylamide) (P(DMA-*co*-NAS)) macro-RAFT agent is used to polymerize *N*-isopropylacrylamide (NIPAM). When the blocks are reversed however, the formation of well-defined copolymers is achieved.⁵⁰ As mentioned previously, sometimes even when taking into account block order, some monomer combinations cannot be polymerized under controlled conditions using classical RAFT agents. While there are dual polymerizations approaches (e.g., RAFT-ATRP) and alternative ligation techniques that allow such copolymers to be synthesized, there is also a substantial focus on the synthesis of new-generation universal RAFT agents to circumvent the difficulties associated with block formation from monomers of disparate reactivity.

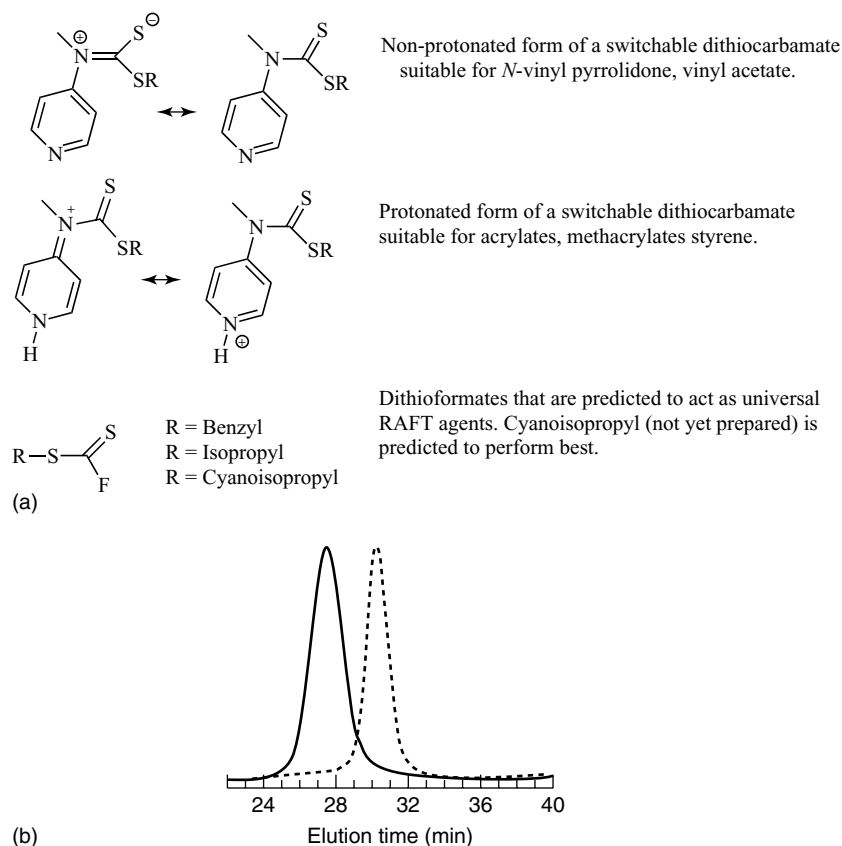
The first design of a universal RAFT agent was suggested by Coote, Barner-Kowollik, and colleagues. These authors noted—via quantum chemical calculations—that when $Z = F$, the fluorine group should increase the reactivity of the C=S double bond toward radical attack, while ensuring that the generated adduct RAFT radicals are

rapidly fragmenting. At first sight, such a situation seems impossible to achieve, as the driving force of the addition reaction of the attacking radical is directly correlated with the stability of the generated adduct. As a consequence, a highly reactive radical will add to thiocarbonyl thio compounds with a stabilizing Z-group (such as phenyl) and the resulting intermediate species will only sluggishly fragment. When fluorine is employed as a Z-group, a homoanomeric effect allows a highly destabilized intermediate radical while maintaining the C=S bond reactivity over a wide attacking radical reactivity range.⁵¹ It goes without saying that the leaving group must suit the nature of the propagating radical. To date, only F-RAFT agents featuring isopropyl and benzyl R-groups have been prepared (see Scheme 8) and employed to mediate styrene, acrylate, and ethylene³⁶ polymerizations. Variants featuring more suitable R-groups (such as cyanoisopropyl) are synthetically difficult to access. Only the provision of such F-RAFT agents may make them suitable to mediate a wide range of disparate reactivity monomers and thus the potential applicability of F-RAFT has yet to be demonstrated.

Synthetically more accessible, and thus more widely employable, is a class of switchable RAFT agents recently introduced by Rizzardo, Moad, Thang, and colleagues.⁵² These authors employ a dithiocarbamate compound that can be reversibly protonated, thus changing the stability of the electronic configuration of the C=S double bond (see Scheme 8). Employed for this purpose are dithiocarbamates carrying a pyridyl ring attached to the carbamate nitrogen. When the pyridyl nitrogen is protonated, the electronic properties of the carbamate nitrogen are changed. In its protonated state, the C=S bond length is decreased, making the RAFT agent suitable to control the polymerization of (meth)acrylate-type monomers as well as styrene. In its unprotonated state, these RAFT agents are suitable for mediating the polymerization of monomers, forming reactive propagating radicals, such as vinyl acetate or *N*-vinyl pyrrolidone. The ability to use such a RAFT agent for the preparation of block copolymers from monomers with disparate reactivities was recently shown. In this example, styrene is polymerized first with the protonated RAFT agent. The obtained macro-RAFT agent is subsequently deprotonated with sodium carbonate and the polymer then undergoes block extension with vinyl acetate.⁵³ The process appears to work



Scheme 7 (a) Two strategies for the synthesis of block copolymers based on a PNIPAM block and a P(DMA-co-NAS) block by RAFT polymerization. (b) SEC traces of the first block P(DMA-co-NAS) and of the P(DMA-co-NAS)-b-NIPAM (left) and of the first block PNIPAM and of the PNIPAM-b-(DMA-co-NAS) (right). [Adapted with kind permission of Elsevier B.V. from Ref. 50.]



Scheme 8 (a) Universal switchable RAFT agents reported by the CSIRO group and F-RAFT agents that may function as universal RAFT agents. (b) Molecular weight distributions generated via the CSIRO universal RAFT agent concept: poly(methyl acrylate) $\bar{M}_n = 31\,100$ Da, PDI = 1.08) prepared using the protonated form of the universal RAFT agent (dashed curve) and the chain-extended poly(methyl acrylate)-*b*-poly(*N*-vinyl carbazole), $\bar{M}_n = 48\,000$ Da, PDI = 1.33 (solid curve). [Reprinted with permission from Ref. 52. Copyright 2009 American Chemical Society.]

well, although more in-depth studies are required to assess its full scope.

5.2 The Example of Block Copolymers: Convergent Synthesis

While sequential polymer design strategies have dominated living (radical) polymerization protocols, recently a paradigm shift⁵⁴ in how complex macromolecular architectures are constructed has occurred. By using high-yielding organic addition reactions that are orthogonal to the polymerization, polymer chemists can now design complex functional macromolecular architectures by following

a modular approach. In this convergent synthesis route, the polymer is built and subsequently reacted postpolymerization, to form the desired product in high yields. This approach has been employed to react either the end of the polymeric chains or the backbone of the polymer (by introducing the required functionality via the monomer). We have described above the use of functional monomers and will focus on the end-group chemistry in the current section. Macromolecules are either equipped with end groups or already carry suitable end groups as a result of the control process, which can be employed in macromolecular ligation, preferably under mild reaction conditions and without the use of toxic catalysts. One of the most employed conjugation protocols is the

copper catalyst 1,3-dipolar Huisgen cycloaddition between an azide and an acetylene. However, a host of other protocols—some of which specifically exploit RAFT chemistry, such as the RAFT–hetero Diels–Alder (RAFT–HDA) approach—are available. These are summarized under the term “click” chemistry and have been thoroughly reviewed.⁵⁵ Here, we focus on those conjugation protocols that have been employed in the context of the RAFT process to generate complex macromolecular designs.

The combination of RAFT chemistry with orthogonal polymer–polymer conjugation can be a convenient avenue to block copolymer structures in cases where no suitable RAFT agent for both monomers is available or where both homopolymers need to be analyzed and prepared separately. The advantage of the modular approach is thus that the individual building blocks can be characterized in depth before they are ligated. One of the earliest examples of conjoining RAFT homopolymers is the preparation of vinyl acetate/styrene block copolymers.⁵⁶ In this approach, two individual RAFT agents are prepared—one capable of mediating the polymerization of styrene (i.e., a dithiobenzoate) and carrying an (protected) acetylene group, the other capable of mediating the polymerization of vinyl acetate and equipped with an azide moiety. Both homopolymers are prepared separately with the desired molecular weight and subsequently conjugated via standard conditions of copper catalyzed [2 + 3] dipolar cycloadditions. Similar azide functional RAFT agents (in the form of trithiocarbonates and dithiobenzoates) have been prepared by Sumerlin and colleagues and were employed to mediate the polymerization of styrene and *N,N*-dimethyl acrylamide.⁵⁷ Subsequently, the resulting azide functional polymers have been reacted with a range of alkyne functional species to generate well-defined telechelic materials. Without doubt, the obtained azide-functional trithiocarbonate-based macro-RAFT agents can also be employed for conjugation reactions with polymers prepared via acetylene-capped RAFT polymers. Figure 4 provides examples of azide and alkyne functional RAFT agents as well as the general synthetic ligation strategy alongside an example conjugation of poly(vinyl acetate) and polystyrene. While the above approach often works very well, it has limitations. One, which was foreseen by the authors of Ref. 56, is the potential reaction

of propagating or primary radicals with acetylene moieties during the RAFT polymerization process. To minimize these interactions, the acetylene group can be protected with a trimethylsilyl group, which can be readily removed via hydrolysis, after the polymerization process. A similar protective approach can also be taken when monomers containing acetylene units are polymerized.⁵⁸ In the case of acetylene-functionalized RAFT agents, protection can be avoided, but temperatures must remain low, and monomer conversions must be limited to 80% or below.⁵⁹

In addition to complications with the acetylene group, the most significant of the potential limitations is the observation made by Perrier and coworkers that azides, when, for example, attached to a RAFT agent, can undergo 1,3-cycloadditions with monomeric vinyl bonds, in a similar fashion as they do during reaction with acetylene (Scheme 9).⁶⁰ This side reaction affects more significantly acrylates and acrylamides, since it depends on the electron-withdrawing properties of the vinyl bond substituent. Steric hindrance of the double bond, for instance in the case of methacrylates, limits the reaction. Monomers such as styrene, with delocalization of the double bond to the benzene ring, are less reactive. For instance, test reactions of methyl acrylate, dimethyl acrylamide, *N*-isopropyl acrylamide, methyl methacrylate, and styrene with benzyl azide at 60 °C (with a molar ratio monomer/azide of 4 : 1) have shown that conversions of 95.2, 89.4, 79.3, and 27.2%, respectively, are obtained within 20 h.⁶⁰ In order to limit these side reactions during polymerization, the reaction time should be kept short (e.g., under 5 h at 60 °C) and/or the temperature should be kept low.

While equipping RAFT agents with groups that allow modular conjugation chemistry can be a route to complex polymer architectures, an alternative possibility is to employ the dithioester functionality itself as one side of a linkage reaction. Such a concept was realized in the form of the RAFT–HDA concept, where highly electron-deficient dithioesters are employed to mediate the polymerization and are subsequently used in HDA reactions with suitable dienes. If the diene is judiciously chosen, very rapid reaction (minutes) to quantitative polymer–polymer conjugation can be achieved at ambient temperatures.⁶¹ A typical set of HDA-capable RAFT agents is depicted in Scheme 10. Best conjugation results

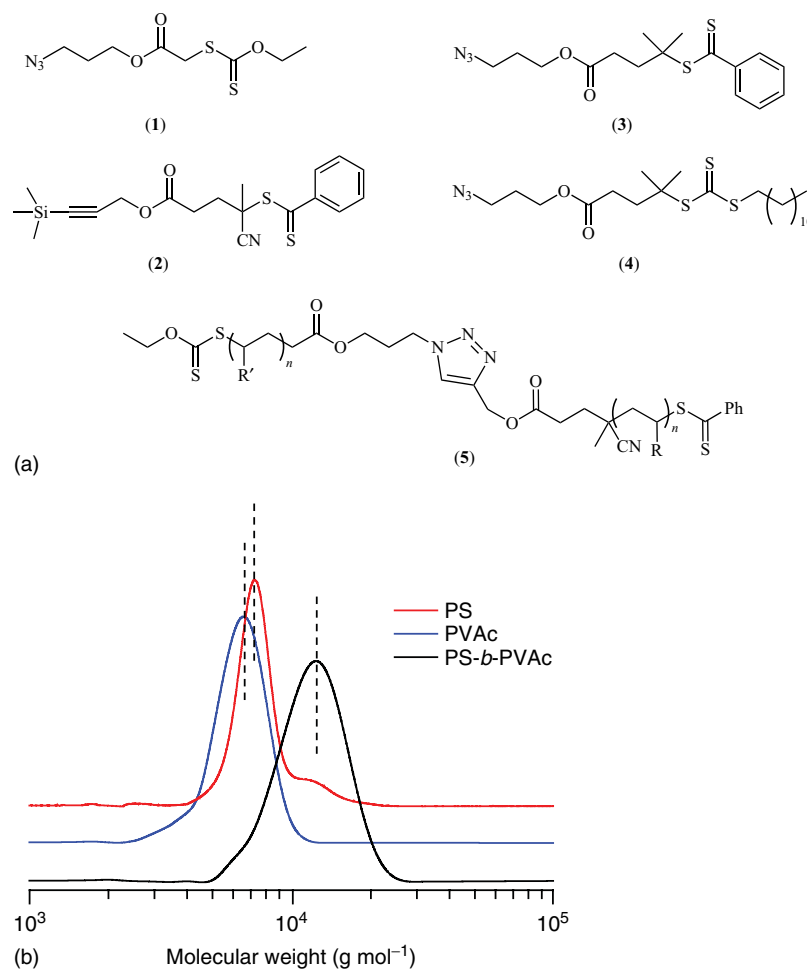
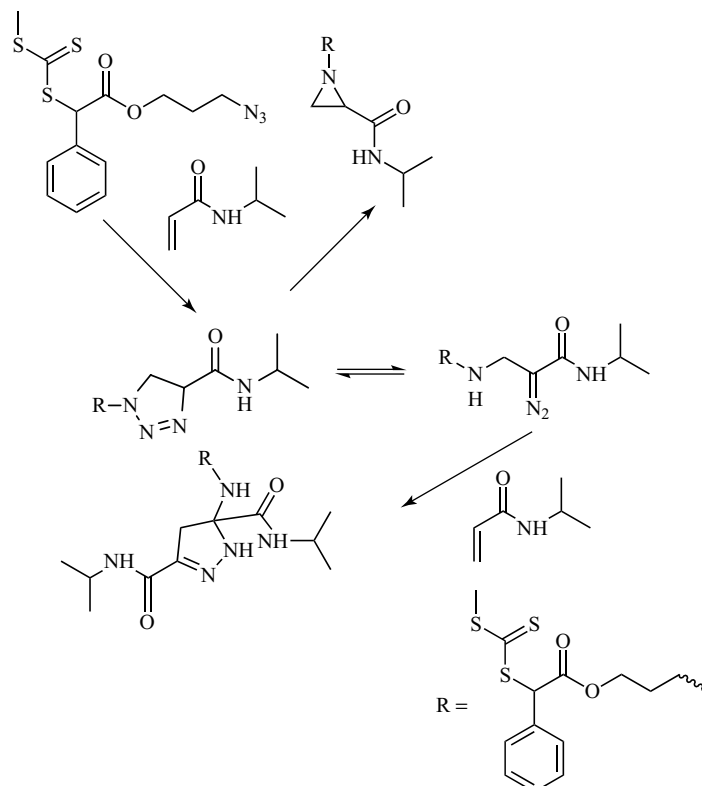


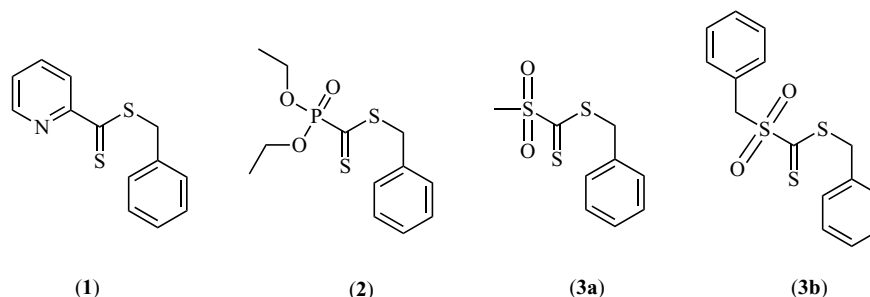
Figure 4 (a) Typical azide and acetylene functional RAFT agents (1) to (4) (according to Refs 54, 55) as well as a typical conjugation product (5). Note that acetylene functional RAFT agents are often employed with protected acetylene as in (2), since the carbon–carbon triple bond can react with radicals during the polymerization processes. (b) The example (taken from Ref. 56) demonstrates the coupling of two individual molecular weight distributions of poly(vinyl acetate) and polystyrene to form a block copolymer via [1 + 3] dipolar cycloaddition. The number average molecular weights of the constituting blocks is close to 7500 and 6800 Da, whereas the conjugate features a number average molecular weight of 15 200 Da.

and shortest reaction times are achieved when cyclopentadiene-capped polymers are employed as dienes. Preparing block copolymers using these systems can result in products with molecular weights over 100 kDa.⁶² If the dithioester is extremely electron deficient (as in sulfonyldithioformates), the reactivity of the C=S diene can become so high that it will react with monomers such as styrene or acrylates in Diels–Alder reactions, even breaking the aromaticity of the phenyl ring in styrene.⁶³ In such cases, only monomers that display a high degree of steric bulk (such as isobornyl

acrylate) can be polymerized. However, extremely electron-deficient dithioesters can find applications in surface conjugation approaches, where surfaces covered with styryl groups can be readily reacted with sulfonyldithioformate-capped poly(isobornyl acrylates) in an efficient fashion.⁶⁴ Conventional RAFT agents such as trithiocarbonates, dithioacetates, and dithioesters, as well as xanthates or carbamates without a Diels–Alder activating Z-group, will not—even with the most reactive dienes such as cyclopentadiene—function well in HDA reactions.



Scheme 9 Proposed mechanistic pathway for the 1,3-cycloaddition of an azide group (attached to a RAFT agent) to the vinyl bond of *N*-isopropylacrylamide. [Reprinted with permission from Ref. 60. Copyright 2008 American Chemical Society.]



Scheme 10 RAFT agents capable of undergoing RAFT–hetero Diels–Alder reactions in polymer–polymer conjugations. Note that the C=S double bond in sulfonyldithioformates (**3a,3b**) is of such high dienophilicity that it will readily react with diene structures present in many monomers (C=C–C=C or C=C–C=O), unless these feature a high degree of steric bulk preventing the [2 + 4] cycloaddition.

The RAFT–HDA concept relies strongly on the provision of diene-capped polymers, specifically those carrying the reactive cyclopentadienyl (Cp) group. Recently, a mild ambient temperature approach toward Cp-capped polymers was introduced by one of the authors. Employing nickelocene allowed the transformation of virtually

all ATRP-prepared polymers into Cp-capped entities in a quantitative fashion.⁶⁵ The RAFT–HDA approach is not only suited for the preparation of block copolymers (or more complex structures)⁶⁶ but stands to be exploited as a tool for the preparation of telechelic polymers by reacting the electron-withdrawing polymer termini with

small molecule dienes.⁶⁷ It goes without saying the RAFT–HDA chemistry also has limitations, such as the (at present) limited choice of RAFT agents that may be employed (see Scheme 10).

A further ligation protocol employs indirectly the thiocarbonyl thio-reactive group, which, after having controlled the growth of polymeric chains, can be transformed into a thiol and utilized as a handle for functionalization of the resulting polymer chain ends. The thiocarbonyl thio end group of a RAFT polymer is readily transformed into a thiol via either reduction (for instance with NaBH₄ in water) or aminolysis in the presence of primary amines.³ The chemistry of thiols is very well documented, especially in biology and biochemistry, for instance, via reactions on cysteine, a thiol-containing amino acid, to introduce conjugates or functional groups along the backbone of peptides and proteins. In macromolecular chemistry, the thiol functionality has proved to be a versatile handle to introduce functionalization onto polymeric materials, as it is capable of reacting in high yields and mild reaction conditions with other thiols, maleimides, iodoacetamides, alkenes, acrylates (via Michael addition), alkynes (via double addition to the triple bond), and isocyanates.⁶⁸ The selectivity, rapidity, and high yields of such reactions have led some researchers to classify them as *click* reactions. However, there are severe limitations—at least for the radical variant—of thiol-ene chemistry for polymer–polymer conjugation (see **Radical Thiol–X Click Chemistry**).⁶⁹ Thus, we classify thiol-ene and thiol-yne chemistries in here as convenient RAFT-derived conjugation protocols, specifically suited for the conjugation of small molecules, rather than as fully fledged click chemistries. The overall synthetic approach exploits the ubiquity of the thiocarbonyl thio group, which controls both polymer synthesis and postpolymerization functionalization, two orthogonal relay reactions. The key aspects of such an approach are that the polymerization mediator, that is, the thiocarbonyl thio moiety, also behaves as a protecting group for the thiol functionality and the resulting thiol can be used for a ligation reaction that is undertaken in very mild conditions (e.g., ambient temperature) and often does not require a catalyst.

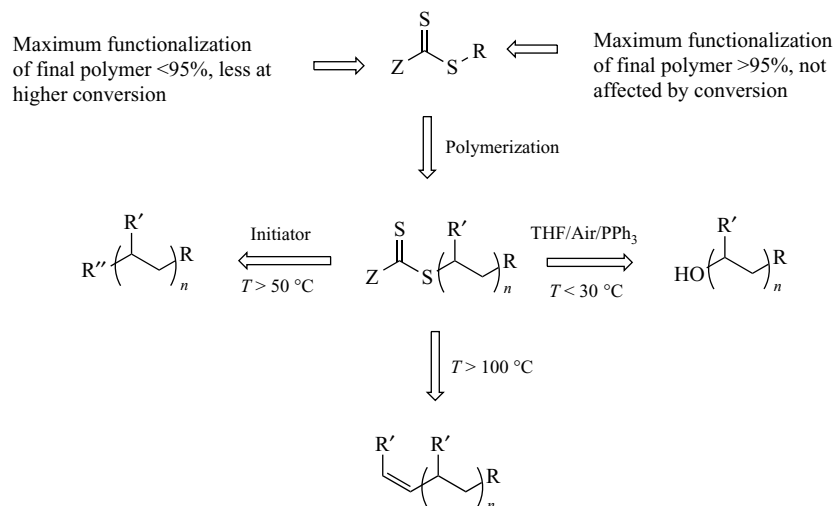
Drawbacks of the thiol-ene/yne approach include the typical issues associated with the use of the living end of the polymeric chains (termination events occurring during radical polymerization lead

to polymeric chains without ω -functionality); the fact that there will not be a quantitative transformation of the thiocarbonyl thio groups into thiols (although yields are high) and the potential for side reactions of the thiol end groups. Indeed, thiol–thiol coupling between two polymeric chains can occur in solution to form disulfide bridges. These side products are readily observed as shoulders at twice the molecular weight of the initial polymers on SEC analyses. Such side reactions are, in particular, preponderant for small polymeric chains. In the case of acrylic and methacrylic polymers, the terminal thiol group has also been observed to undergo intramolecular transesterification to yield terminal thiolactones at the polymer chain end.⁷⁰ A potential solution to prevent this problem, although not always practical, is to end-cap the polymeric chains with a small number of styrene units.

6 END-GROUP CHEMISTRY ON RAFT POLYMERS

End group chemistry can be finely controlled during the RAFT process based on the choice of the R- and Z-group. In addition, the thiocarbonyl thio end group can undergo a wide range of subsequent post-polymerization transformations, which have been reviewed previously in detail.^{71–74} Here, we will limit our discussion to those end group transformations that lead—in our view—to the most efficient removal of the RAFT group or introduce groups that can be effectively employed as starting points for the orthogonal conjugation of two polymeric chains or for the ligation of polymer strands to biomolecules. An overview of the most reliable and workable end group transformations is provided in Scheme 11. Note that transformations employing thiocarbonyl thio end groups themselves for end group modification are discussed in the section below on ligation protocols.

When functionality is to be introduced into a polymer via the RAFT process by virtue of the RAFT agent, this can either proceed via the Z- or R-group. Both approaches have been explored in detail. Introduction of functionality via the R-group provides a very efficient, and most importantly permanent, approach to end group functionalization. There is no danger of hydrolysis or elimination of the end group since it is tethered to the polymer terminus via a robust C–C single bond that is



Scheme 11 Reliable strategies to introduce end groups to or remove end groups from RAFT polymers. Note that the efficiency of the radical end group removal pathways depend on the individual RAFT agent as well as the leaving group ability of the polymer. The provided temperatures are typical values, which can vary in individual cases. The same holds true for the degrees of functionalization provided in the upper part of the figure for the Z- and R-group functionalization approaches.

formed during the reinitiation sequence. In addition, even those chains which do not carry a thiocarbonyl thio terminus can carry an R-terminus, allowing degrees of end group functionalization over 95% to be reached (the remaining 5% or less corresponds to those chains that have been initiated via an initiator-derived primary radical fragment and subsequently terminated in a bimolecular termination reaction). Introducing functionality via the Z-group consistently leads to lower degrees of functionalization, as the Z-group is attached to the thiocarbonyl thio moiety and can be the subject of elimination and hydrolysis reactions, especially at higher conversions. An interesting case, unique to the RAFT process, arises when the Z-group is attached to a solid support, either during or after polymerization. In this case, the products of the termination reactions (from either combination or disproportionation) lose their attachment to the support (since they lose their “living” end) and a simple filtration permits the separation of dead polymeric chains from living chains, which remain attached to the solid. Such an approach has been employed to generate highly pure living polymers⁷⁵ and multi block copolymers.⁴⁶ The most common types of functionalities introduced via the Z- and R-groups include carboxylic acids,⁷⁶ alcohols⁷⁷ and fluorescent markers,⁷⁸ but also carbohydrates⁷⁹ as well as proteins.⁸⁰

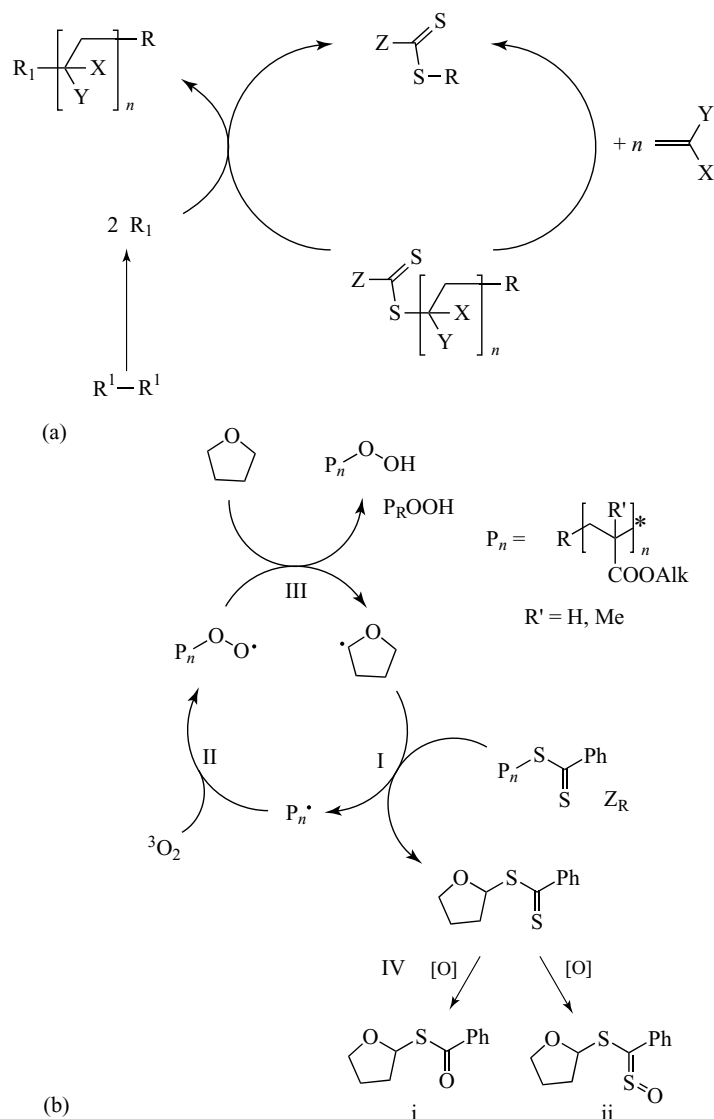
It is also possible to have an agent containing a long hydrophobic R-group which when polymerized with a hydrophilic monomer forms an amphiphilic system.⁸¹

The removal of the RAFT end group can be important for a range of applications as it gives the polymer a distinct color (ranging from red/pink to yellow). In addition, thiocarbonyl thio groups are always in danger of hydrolysis to thiols over longer periods in service, potentially giving rise to odor problems. Among the most efficient and reliable pathways for RAFT end group removal (i.e., the complete elimination of all sulphur from the polymer) are thermal elimination and radical reaction sequences.

Thermal elimination is the simplest removal tool, yet the macromolecular backbone has to withstand temperatures exceeding $100\text{ }^{\circ}\text{C}$. Several examples have demonstrated that thermolytic end group removal can be highly efficient with little effect on the molecular weight distribution.⁸² An added advantage is the fact that the resulting ω -end group functionalization can be employed in further reactions, including the use of the polymers as macromonomers. Removal of the thiocarbonyl thio end group via means of radical replacement has become very popular due to its high efficiency, generally low reaction temperature and

ease of use. The simplest approach merely involves the stirring of the RAFT polymer in a solution of tetrahydrofuran, in air, in the presence of a small amount of radical initiator, at low temperatures (see Scheme 12b).⁸³ During such a procedure, a hydroperoxide end group is initially generated,

which can be subsequently and readily be reduced to a hydroxyl group (using triphenyl phosphine or an alternatively suitable reducing agent). The transformations have been shown to be highly efficient with trithiocarbonate-capped poly(acrylates) as well as styrene, yet dithioesters also give



Scheme 12 Two principle mechanisms to remove the RAFT end group from the polymer. (a) Reaction sequence to recycle the thiocarbonyl thio end group of a RAFT-made polymer and yield an end-functional polymer via radical addition. In this procedure, the RAFT agent is recycled when $R^1 = R$. [(a) Reproduced with permission from Ref. 85. Copyright 2005 American Chemical Society.] (b) Reaction sequence for the transformation of RAFT-made polymer into hydroperoxy terminal species (which can be readily reduced to hydroxyl-capped polymers) via the addition of molecular oxygen to the freed macroradicals. [(b) Reproduced from Ref. 83a. © CSIRO Publishing, 2009.]

satisfactory results. If a symmetrical trithiocarbonate is employed, the molecular weight distribution of the polymer halves during the procedure. Problems and nonefficient transformations occur if poor leaving group chains are attached to the RAFT terminus (such as poly(vinyl acetate)). Occasionally the removal of the reducing agent can be difficult, depending on its nature (e.g., when it precipitates in the same solvent as the polymer). A detailed mechanistic description of the process can be found in Ref. 83. The provision of hydroxyl functionality using this procedure opens up an avenue for a range of follow-up chemical transformations, including the sulfur-free switch to other polymerization protocols.⁸⁴ A more versatile procedure is the introduced primary radical replacement process proposed by Perrier and coworkers that not only provides sulphur-free polymers but also allows for the recovery of the RAFT agent (see Scheme 12a). Addition of an excess of free radical initiator to a RAFT polymer leads to the preferred fragmentation of the intermediate radical to form a new RAFT agent (in which the R-group is the radical initiator) and a radical polymeric chain, which reacts in turn with the excess of initiator radicals by combination. The products of the reaction are therefore a new RAFT agent, ensuring the recycling of the thiocarbonyl thio group, and a polymeric chain, which is end-functionalized with the radical initiator.⁸⁵ In this approach, not only does the polymer product lose the color induced by the thiocarbonyl thio group but also it can be efficiently end-functionalized. To obtain optimal yields, care must be taken in the choice of the radical initiator, to favor the fragmentation of the polymeric chains from the intermediate radical. In cases where the recovery of the thiocarbonyl thio group is not required and/or the polymer end group functionalization is not sought, the removal of the thiocarbonyl end group can be achieved by using a source of radicals in association with a good H-donor molecule (e.g., isopropanol) to replace the thiocarbonyl thio end group with a hydrogen.^{82a} As in all radical processes, potential side reactions include the generation of polymeric chains from the termination (disproportionation and combination) of two macromolecules carrying a radical terminus. In the case of terminations by combination, these bimolecular termination fractions are evident as shoulders at twice the molecular weight of the initial polymer.

7 THE PROCESS OF RAFT POLYMERIZATION: HOMOGENEOUS AND HETEROGENEOUS POLYMERIZATIONS

One of the most advantageous aspects of RAFT polymerization is the versatility of the technique and thus its applicability to a wide range of reaction conditions. RAFT can successfully exert control over polymerization reactions in bulk (monomer), solution (both in organic or aqueous phase) as well as in heterogeneous systems. While RAFT reactions in bulk or organic solvents have been reported extensively since the inception of RAFT over a decade ago, it is the application of RAFT agents in heterogeneous media or aqueous phase that highlights the versatility of the process.

Homogeneous RAFT polymerization in bulk or solution can usually be performed under similar conditions as conventional free radical polymerization. Indeed, as long as the RAFT agent is fully soluble in the solvent, the RAFT agent can be expected to perform as required. In solution, RAFT polymerization has been conducted in a wide range of media from the more conventional organic solvents³ and water,⁸⁶ to less-conventional media such as ionic liquids⁸⁷ and supercritical fluids.⁸⁸

7.1 Aqueous RAFT Homogeneous Polymerization

The special case of aqueous homogeneous RAFT polymerization has received particular interest due to the ability to synthesize water-soluble polymers that can be useful for biomedical applications, for example. In addition, the environmental advantages of performing polymerizations in water (as opposed to organic solvents) have also been a driving force behind this research. However, in aqueous RAFT polymerization a number of factors must be considered. Thiocarbonyl thio compounds are susceptible to hydrolysis, both acid and base catalyzed. The hydrolysis has been shown to be more pronounced for the original RAFT agent (as a small molecule) than for a macro-RAFT agent, presumably due to protection of the RAFT group by the polymer chain in the later case.⁸⁹ This highlights the fact that in order to achieve a well-controlled polymerization and maintain high

end-group fidelity, the pH of the aqueous solution must be considered both before and during the polymerization.

In addition to the problems of RAFT agent hydrolysis in aqueous solution, aminolysis of the thiocarbonyl thio group can also occur to yield thiol-terminated polymers. This can become a problem if the monomers themselves are prone to hydrolysis and hence yield primary or secondary amines which then react with the RAFT agent. Of particular note are the acylamido monomers, which tend to show little control when polymerized by RAFT in water. These reactions have been studied extensively by the group of McCormick and equations have been developed to determine the extent and effect of both hydrolysis and aminolysis.⁹⁰ They demonstrated the degradation of dithiobenzoates by showing that in aqueous solutions buffered to pH 5.5 and 7.0, when the ammonia concentration was set at 5×10^{-3} M, the fraction of 2-cyano-pentanoic acid dithiobenzoate that remained after 8 h under such conditions was approximately 0.7 and 0.4, respectively. Nonetheless, as long as the reaction conditions are carefully considered before polymerization then water soluble polymers can be synthesized successfully using RAFT in aqueous solution.⁸⁶

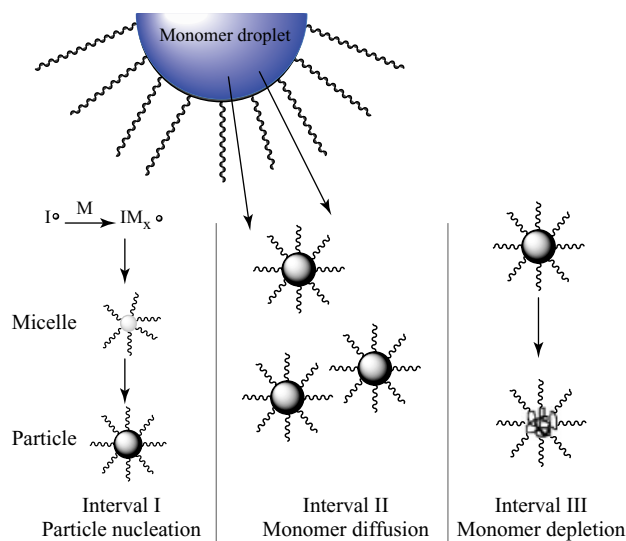
RAFT polymerization in dispersed systems provides a methodology for developing particles having well-defined size and size distribution, while simultaneously controlling the molecular weight and polydispersity of the (co)polymer. In this way, block copolymer particles can be formed that exhibit interesting microstructures which can be finely controlled by correct selection of reaction conditions. RAFT-controlled heterogeneous polymerization has been reported using a variety of techniques, namely emulsion, microemulsion, miniemulsion, dispersion, and precipitation polymerization.⁹¹ The application of RAFT, particularly in emulsion polymerization, has generated intense interest due to the challenges associated with RAFT and the enhancement of factors such as Ostwald ripening, so-called “super-swelling” and the importance of entry-exit kinetics in the RAFT process.⁹² In addition to the ability to form well-defined particles of potential industrial use (in applications, e.g., as coatings, adhesives, sealants, biomedical devices, and so on), heterogeneous polymerization conditions provide a unique environment in which to investigate aspects of the RAFT mechanism (e.g., the fate of intermediate radicals) and as such this has been the focus

of much research. The remainder of this section will look at each of these heterogeneous processes individually and highlight important aspects of the RAFT process in each section—particularly with regards to challenges and problems that have been encountered. Unless otherwise stated, water is the continuous phase.

7.2 *Ab Initio* Emulsion Polymerization

As the name suggests, *ab initio* emulsion polymerization involves incorporation of all components of the polymerization—water-insoluble monomer, water-soluble initiator, surfactant, and water—at the beginning of the reaction. Upon the application of shear, both monomer droplets stabilized as micelles (typically in the range of 20 nm) and large monomer pools are formed.⁹² Following initiation, the polymerization proceeds in the aqueous phase until the polymer chain reaches a critical molecular weight and the chain enters a monomer-swollen droplet, and propagation then freely occurs; this is termed *interval I* (as originally defined by Smith and Ewart⁹³) and refers to the nucleation stage of emulsion polymerization. The subsequent *interval II* refers to the particle growth regime when there are no more micelles in solution, but the monomer-swollen particles are continuously fed from the monomer pools. Finally, *interval III* refers to the point when there are no more monomer pools remaining and conversion slows due to consumption of the monomer within the droplets. These regimes are depicted schematically in Scheme 13 as originally described by Smith and Ewart (adapted from Ref. 94).

Entry and exit of the RAFT agent is of upmost importance if the molecular weight is to be controlled in emulsion polymerization. RAFT agents will typically reside on the chain end of polymers during most of the polymerization and hence partitioning into the aqueous phase becomes less likely during reaction; this is very different from nitroxides and metal complexes used in NMP and ATRP, respectively, which likely partition to a greater extent because of their smaller size. Additionally, nucleation of particles in emulsion polymerization using RAFT should occur in the same way as in standard free-radical polymerization. Nonetheless, considerable complications concerning colloidal stability have been encountered. The very first example



Scheme 13 Cartoon depicting the three intervals in standard emulsion polymerization. [Adapted from Ref. 94. © Elsevier, 1995.]

of RAFT being used in an emulsion was reported by CSIRO in their original RAFT patent.¹ Following this report, extensive investigations from many research groups have highlighted the importance of understanding the transport kinetics of the RAFT agent during reaction. Almost all reported successful RAFT-controlled emulsion polymerizations have involved the use of xanthates—the success being attributed to the much lower reactivity compared to other RAFT agents ($C_{tr} \sim 1$) and therefore decreasing the likelihood of colloidal instability due to superswelling. Unfortunately, the low C_{tr} of xanthates restricts the control over polydispersities.⁹⁵ Monteiro *et al.*⁹⁶ were able to partially overcome this issue by using a xanthate with a slightly higher C_{tr} and obtained $\overline{M}_w/\overline{M}_n$ of ~ 1.5 while maintaining colloidal stability. Numerous attempts to control *ab initio* emulsion using high- C_{tr} RAFT agents have been marred by poor colloidal stability and poor molecular weight control (and high PDI). Work by both Nozaria and Tauer⁹⁷ and Monteiro and colleagues⁹⁸ have highlighted the importance of RAFT agent hydrophilicity, *in situ* degradation of RAFT agent, and, of course, transport kinetics in controlling both the molecular properties of the polymer and the colloidal stability of *ab initio* emulsions.

7.3 Seeded Emulsion Polymerization

To overcome some of the issues associated with nucleation and stability in *ab initio* polymerization, a preformed latex “seed” can be used. In this way, the polymerization starts at intervals II or III. Numerous reports have been built on the original work by Monteiro *et al.*⁹⁹ and suggested that the transport of the RAFT agent to droplets must occur during the first few percent of conversion in order to obtain well-controlled polymerizations.¹⁰⁰ Others suggested that migration of the R-group from the droplet following fragmentation would also lead to poor control. Successful seeded emulsion polymerization was reported by Prescott *et al.*¹⁰¹ with good overall control of both molecular weight and colloidal stability; however, the inhibition and retardation effects typically associated with RAFT were exacerbated compared to the analogous reaction in a homogeneous solution. Georges and coworkers¹⁰² used acetone as an additive to aid particle formation via a precipitation mechanism. Acetone was removed from the mixture prior to polymerization. This approach yielded polymers with well-controlled molecular weight and polydispersity. Xanthates have also been used successfully in seeded emulsion polymerization in many instances.¹⁰⁰

7.4 Mini Emulsion Polymerization

RAFT-controlled mini emulsion polymerization has also been extensively investigated. Since the methodology minimizes the reliance on transport kinetics of the RAFT agent, good control has often been observed. The disadvantages of mini emulsions are the necessity for high concentrations of surfactant compared to *ab initio* emulsion polymerization as well as the requirement for cosolvents. The formation of a mini emulsion requires mixing of all of the components of the reaction followed by reduction of the droplet size using mechanical shear. This is often accompanied by ultrasonic homogenization to yield small droplets that are generally stabilized against particle growth (depending on the surfactant concentration). Polymerization is then started via conventional means.

In initial experiments, RAFT-controlled mini-emulsion polymerization tended to exhibit the same frustrating destabilization that was observed in *ab initio* emulsion polymerizations. Good control could generally be maintained only up to around 30% conversion for styrene and, while some other acrylates showed more promise, large polydispersities were still observed.¹⁰³ Luo developed a theoretical model to describe the inefficiencies of ionic stabilizers in RAFT mini emulsion polymerization.¹⁰⁴ They postulated that, in the absence of early equilibration of the chemical potential between droplets and particles, superswelling would occur leading to destabilization. This is a direct consequence of the lack of high molecular weight polymer in living polymerizations at low conversion, since RAFT-capped oligomers would be expected to swell to a much greater extent than high molecular weight polymer that would exist in conventional polymerization. Luo *et al.* suggested that more stable latexes could be formed in the presence of larger particles, higher cosurfactant levels, and lower concentration of RAFT agents.¹⁰⁴

It was later found that, if a nonionic surfactant was used (e.g., Brij 98), then polymers with well-defined molecular weight were formed with no loss of colloidal stability.¹⁰⁵ This was attributed to the ability of Brij 98 to stabilize a much greater surface area than SDS and also its ability to inhibit monomer transportation. As was observed with *ab initio* polymerization, rate retardation compared to reactions in the absence of RAFT was also observed.

This has been attributed to both intermediate radical termination and slow fragmentation.

In general, deviation from expected RAFT properties (i.e., control over molar mass and PDI) in mini emulsion is attributed to the superswelling theory and this can be mediated either by using a nonionic surfactant or by incorporating significant amounts of costabilizer into the reaction when ionic surfactants are used. Nonetheless, there have been extensive reports of successful, RAFT-controlled mini emulsion polymerizations that maintain acceptable colloidal stability using both ionic and nonionic surfactants; many of these are summarized in the literature.¹⁰⁰

7.5 Microemulsion Polymerization

Microemulsions are thermodynamically stable emulsions of two immiscible liquids with monomer-swollen droplets in the size range 5–10 nm. Typically, these droplets form spontaneously in the presence of stabilizer without the addition of shear. In theory, the polymerization is localized within the droplet and, as is the case for a miniemulsion, there is no need for transportation of controlling agents through the aqueous phase since the monomer droplets will form polymer particles. However, in practice it has been shown that the number of droplets far exceeds the number of particles that are formed and so microemulsions act more like standard emulsions (i.e., droplets feed nucleated particles). For the special case of controlled polymerization in microemulsions, it has been suggested that compartmentalization of RAFT agents may have an effect on the polymerization since different particles contain different numbers of RAFT agents—this is important owing to the small size of the droplets and can often lead to tailing in the molecular weight distributions.

The use of RAFT in microemulsion has only been briefly investigated. For example, Kaler and coworkers¹⁰⁶ showed that hexyl methacrylate could be conducted under microemulsion conditions to yield particles in the size range of 18–30 nm. Under carefully chosen reaction conditions, good RAFT characteristics were observed. However, once again, long inhibition times and rate retardation were observed if the RAFT concentration was high. Other recent publications have demonstrated

RAFT-mediated microemulsion polymerization of polystyrene¹⁰⁷ and inverse microemulsion polymerization of dimethylacrylamide.¹⁰⁸ Kaler recently investigated compartmentalization of various RAFT agents in microemulsion polymerization.¹⁰⁹

7.6 Dispersion Polymerization

RAFT-controlled dispersion polymerization has also been reported. In dispersion polymerization, the initial system is homogeneous and polymer particles are formed once the chains reach a critical molecular weight and are stabilized by the addition of a surfactant. Typically, micrometer- to submicrometer-sized particles are formed. The most commonly used solvents for dispersion polymerization are hydrocarbons (alkanes), and in some cases alcohols or alcohol/water mixtures have been employed.

Styrene has been polymerized via dispersion polymerization using RAFT by various research groups in numerous solvents.¹¹⁰ Typically, a two-stage reaction sequence is required in which the RAFT agent is added to the polymerization after particle nucleation. When the two-stage approach is used, polymers with narrow PDI and controlled molecular weight are obtained. If the two-stage approach is not used, then the RAFT agent acts to broaden the particle size distribution because of extended nucleation times; this is related to the fact that RAFT agents keep all chains at relatively low molar mass compared to dispersion polymerization by conventional free-radical polymerization. Scanning electron microscopy images shown in Figure 5 highlight the particle size distribution observed in standard styrene dispersion polymerization in ethanol using 12 wt% poly(*N*-vinylpyrrolidone) (PVP) as stabilizer and the effect of using the two-stage approach. Clearly, when the latter approach is used, the particle size distribution is much smaller than when just the normal dispersion approach is taken.

Howdle and coworkers¹¹¹ used supercritical CO₂ as a solvent to conduct dispersion polymerization of methyl methacrylate and showed that good control over molecular weight and PDI could be obtained while colloidal stability was maintained. This was achieved in the absence of the two-stage methodology.

Dispersion polymerization using macro-RAFT stabilizers has also become popular. This is mainly

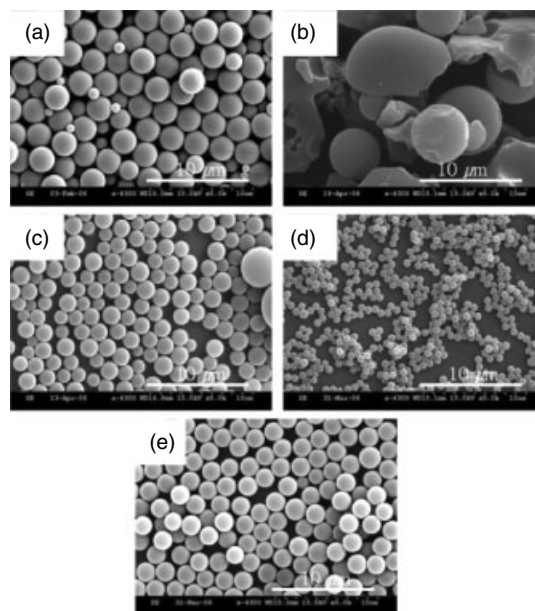
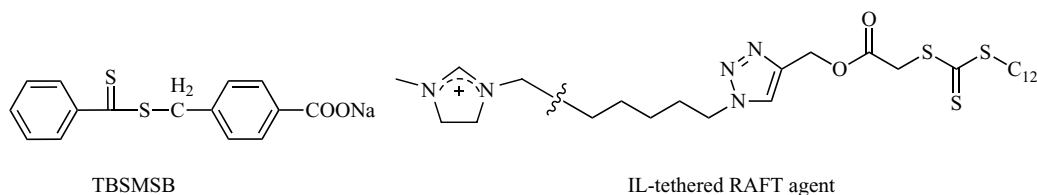


Figure 5 (a) Scanning electron microscopy images showing particles sizes and size distribution for dispersion polymerization of styrene in ethanol with PVP as surfactant in absence of RAFT agent; (b) with preaddition of RAFT agent at 4 h; (c) preaddition of RAFT agent at 24 h; (d) two-stage process at 4 h; (e) two-stage process at 24 h. [Reproduced with permission from Ref. 110b. © John Wiley and Sons, 2007.]

because the “surfactant” is covalently bound into the particles and cannot migrate and diffuse when the final polymer particles are used in future applications. In these experiments, the RAFT agent self-assembles into a particle *in situ*. Some notable examples have been demonstrated by the groups of Charleux,¹¹² Zheng and Pan,¹¹³ Bathfield *et al.*,¹¹⁴ and Youk.¹¹⁵ Additionally, Howdle and coworkers¹¹⁶ have shown that dispersion polymerization using macroRAFT is effective in supercritical CO₂ where CO₂philic macroRAFT agents containing polydimethylsiloxane or perfluoropolymers have been utilized. Other variations on this theme involve cross-linking of the dispersed polymer particles *in situ* to form insoluble particles.

7.7 Surfactant-Free Emulsion

RAFT polymerization in dispersed media was further improved by the team at the Key Centre for Polymers and Colloids,¹¹⁷ who developed an



Scheme 14 Structures of surface-active RAFT agent used by Choe *et al.*¹²¹ and IL-tethered RAFT agent used by Puttick *et al.*¹²²

approach to RAFT emulsion based on self-assembly techniques. In this approach, RAFT-terminated polymer chains of a hydrophilic species (e.g., acrylic acid) are initially formed in solution, followed by starved-feed of a hydrophobic monomer. This leads to the well-controlled growth of the hydrophobic monomer due to confinement of the RAFT group at the reaction locus upon formation of micelles. The authors were able to demonstrate a well-controlled polymerization with well-defined particles. The same group then showed that a block copolymer of styrene and acrylic acid that was terminated with a RAFT agent would also act to nucleate particles. They investigated the effect of hydrophobicity, for example, of the surfactant on block copolymer migration during particle nucleation.¹¹⁸ This approach revolutionized the development of RAFT emulsion polymerization, as it permits the manufacture of well-controlled polymeric particles exhibiting a range of morphologies and functionalities, including a route to efficiently encapsulate solids and liquids¹¹⁹ in a simple, surfactant-free process. Further developments exploiting this approach have led to numerous polymer systems being investigated and the formation of various core-shell particles. For example, Armes and coworkers recently used RAFT-terminated glycerol methacrylate as a steric stabilizer to form particles in the size range 20–100 nm with good size control.¹²⁰

7.8 Other Interesting Heterogeneous Systems

Choe and coworkers¹²¹ used a specially designed RAFT agent that acted as initiator, stabilizer, and chain transfer agent at 80 °C (4-thiobenzoyl sulfanylmethyl sodium benzoate (TBSMSB), Scheme 14). In these reactions, colloidal stability was maintained and polymers exhibiting good molecular weight control were observed (PDIs

ranging from 1.21 to 1.43). More interestingly, polymers exhibiting very high molar mass were observed (~400 kDa) while maintaining molecular weight monodispersity.

Thurecht and coworkers¹²² designed a surface-active RAFT agent to control heterogeneous polymerization in ionic liquids (ILs). In certain cases, poorly controlled RAFT polymerization was observed for methyl methacrylate in some ILs. An IL-tethered RAFT agent was synthesized (Scheme 14) and this facilitated much greater control over polymerizations yielding an experimental $\bar{M}_n$ much closer to the theoretical value. The authors postulated that the polymerization was occurring in a pseudomicroemulsion-type system and localization of the RAFT agent at the locus of polymerization was required.

In the realm of surfactant-free polymerization, RAFT polymerization employing the degassing technique has also received some recent interest. Following from the initial polymerization of styrene in the absence of the controlling agent, Hartmann *et al.*¹²³ showed that well-defined polymers with relatively narrow particle size distribution could be synthesized. The stable latex was formed by consecutive freeze-pump-thaw cycles and Ostwald ripening was minimized by addition of hexadecane. These authors attribute the stability of the system to the hydroxyl anions on the surface of the particles.

An interesting phase-inversion approach was reported by Charleux and coworkers¹²⁴ as a method of forming a stable emulsion. Bulk polymerization of styrene and acrylic acid (~80:20 molar ratio) was conducted to low conversion, followed by phase inversion by addition of aqueous sodium hydroxide. This generated a dispersed monomeric (organic) phase which could then be polymerized under “seed-like” conditions. Good control and colloidal stability were observed (PDI ~1.2, particle size = 140–180 nm).

7.9 Unique Morphologies from Heterogeneous Polymerization

RAFT control over heterogeneous polymerization facilitates the development of many interesting and useful morphological variations with applications ranging from impact modifiers in sheets to biomedical polymers. Importantly, the molecular weight control that RAFT imparts to any given polymerization can be used to tune the system for a desired morphology: for example, the development of core-shell, salami, or raspberry-type structures.¹²⁵

Klumperman and coworkers¹²⁶ utilized the miniemulsion technique to synthesize hollow-sphere polystyrene particles. These particles were formed because of the localization of polymerization at the interface of isooctane and water using an ionic potassium persulfate (KPS) initiator. The use of a RAFT agent that did not show retardation was required in order to achieve hollow particles. Numerous other authors have expanded upon this approach to develop hollow particles. For example, Luo and Gu¹²⁷ developed a dual control agent and surfactant that confined the RAFT to the surface of the particle. In Figure 6, the particles have been formed using SDS as a cosurfactant.

On the micrometer scale, Howdle and coworkers^{116b} developed a macroRAFT agent that acted as both CTA and stabilizer to undertake dispersion polymerization of MMA in

supercritical CO₂. The fluorophilic polymer 1*H*,1*H*,2*H*,2*H*-perfluorooctyl methacrylate was polymerized under bulk conditions using RAFT to a molecular weight of 8 kDa. This was then used as macroRAFT stabilizer in a dispersion polymerization. Transmission electron microscopy showed that the resultant particles had a clearly defined fluorine-rich shell.

8 CONCLUSIONS

The present article has highlighted the main strengths and limitations of RAFT chemistry. Key strengths of the RAFT process include its high tolerance to functional groups and reaction media, its non-rate-retarding nature, as well as its ability to control the molecular weight during a free-radical polymerization. The wide range of end groups and conjugation chemistries developed for thiocarbonyl thio-capped polymers allows it to be employed in efficient conjugation chemistries under mild and partially catalyst-free conditions. While there are a number of promising examples, there still exist substantial challenges in the form of the full development of a universal class of RAFT agents and their application toward a wide variety of monomer systems with disparate reactivities. For instance, exact control over the polymerization of ethylene under conditions of elevated pressure and temperature is highly desirable and, although notable attempts have been made, is still an important target of RAFT polymerization, as it requires RAFT agents that can not only form low-stability intermediate radicals upon the addition of high-reactivity ethylene propagating radicals but are also stable up to high temperatures ($T > 140^{\circ}\text{C}$) for extended periods. Of high importance, especially for the processability of the RAFT polymers, is a detailed understanding of their thermal stability, for example, of Z-group-generated star polymers. Such an understanding on a systemic level (via a variation of the RAFT agent structures in Z-group architectures) is still lacking to a large degree and may prove to be vital for the bulk processing of RAFT-made, complex-architecture polymeric materials.

Within the realm of modular polymer conjugation, the advent of transformations that exploit the presence of the RAFT end group in an atom-economical fashion has opened the possibilities for direct conjugation of RAFT polymers to

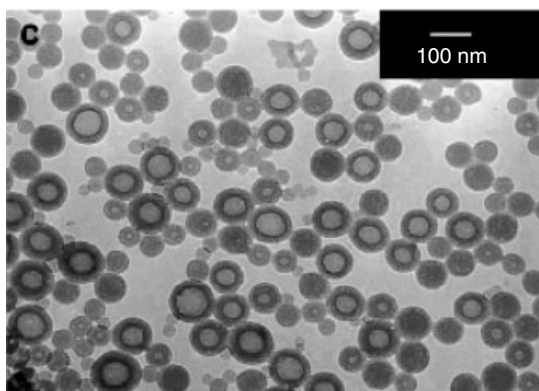


Figure 6 Hollow polystyrene particles formed by emulsion polymerization using a surface-active RAFT agent in the presence of additional SDS surfactant. [Reproduced from Ref. 127b, Copyright (2007), with permission from Elsevier.]

variable diene structures via [4 + 2] cycloadditions. Although these reactions can proceed with high rates at ambient temperature to quantitative yields, other conjugation protocols involving the RAFT end group might be feasible with similar ease. In terms of process, the versatility of RAFT enables it to be expanded to large-scale industrial processes and to become a commercial reality, both for homogeneous and heterogeneous polymerization systems. However, RAFT still requires further developments in terms of sustainability¹²⁸ and to lower the cost of the reagents.

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END NOTE

^a. See Ref. 1. The Rhodia process is referred to as macromolecular design via the interchange of xanthates (MADIX), yet its underpinning control sequence is identical to that of the RAFT process.

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Nitroxide-Mediated Polymerization and its Applications

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1 INTRODUCTION

Radical polymerization has been a tool for industry since the mid-twentieth century.¹ Nevertheless, controlled radical polymerization emerged during the last 3 decades, mainly as four techniques: degenerative transfer (see **Fundamentals of Controlled/Living Radical Polymerization**), atom transfer radical polymerization (ATRP, see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**), reversible radical addition transfer fragmentation (RAFT, see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**), and the stable free radical polymerization (SFRP).² This article is devoted to the kinetics and subsequent limitations of nitroxide-mediated polymerization (NMP) (one of the most popular SFRP techniques) as well as the various applications of advanced polymers prepared with this technique. Several sections are devoted to the kinetic behavior (homolysis, reformation, and side-reactions) of alkoxyamines (initiator/controller) and macroalkoxyamines (so-called “dormant species”). Although the term *living polymerization* is sometimes discussed,^{3,4} for the sake of simplicity and as this term is commonly used in the community, it is preferred to pseudo-living

polymerization.⁵ Clear and supporting arguments are provided by Rizzardo and Moad in their book in favor of the use of controlled/living radical polymerization.⁶ All alkoxyamines, nitroxides, and alkyl radicals mentioned in this article are gathered in Figure 1.

2 PRINCIPLE AND KINETICS OF NITROXIDE-MEDIATED POLYMERIZATION

Although the kinetic properties of alkoxyamines (R^1R^2NO-R) were reported in the mid-1970s,^{7–9} NMP was only discovered in 1985 by the Commonwealth Scientific and Industrial Research Organization (CSIRO) team,^{10,11} and was widely advertised by the seminal work of Georges in 1993.¹² Quickly, several authors pointed out the important role of the lability of the C–ON bond in alkoxyamines.^{13–15} In 1997, Fischer¹⁶ proposed that the kinetics of NMP was ruled by the unusual selectivities of radical reactions by internal suppression of fast modes¹⁷ *aka* persistent radical effect (PRE) (see **Nitroxides in Synthetic Radical Chemistry and Fundamentals of Controlled/Living Radical Polymerization**),¹⁸ and predictive

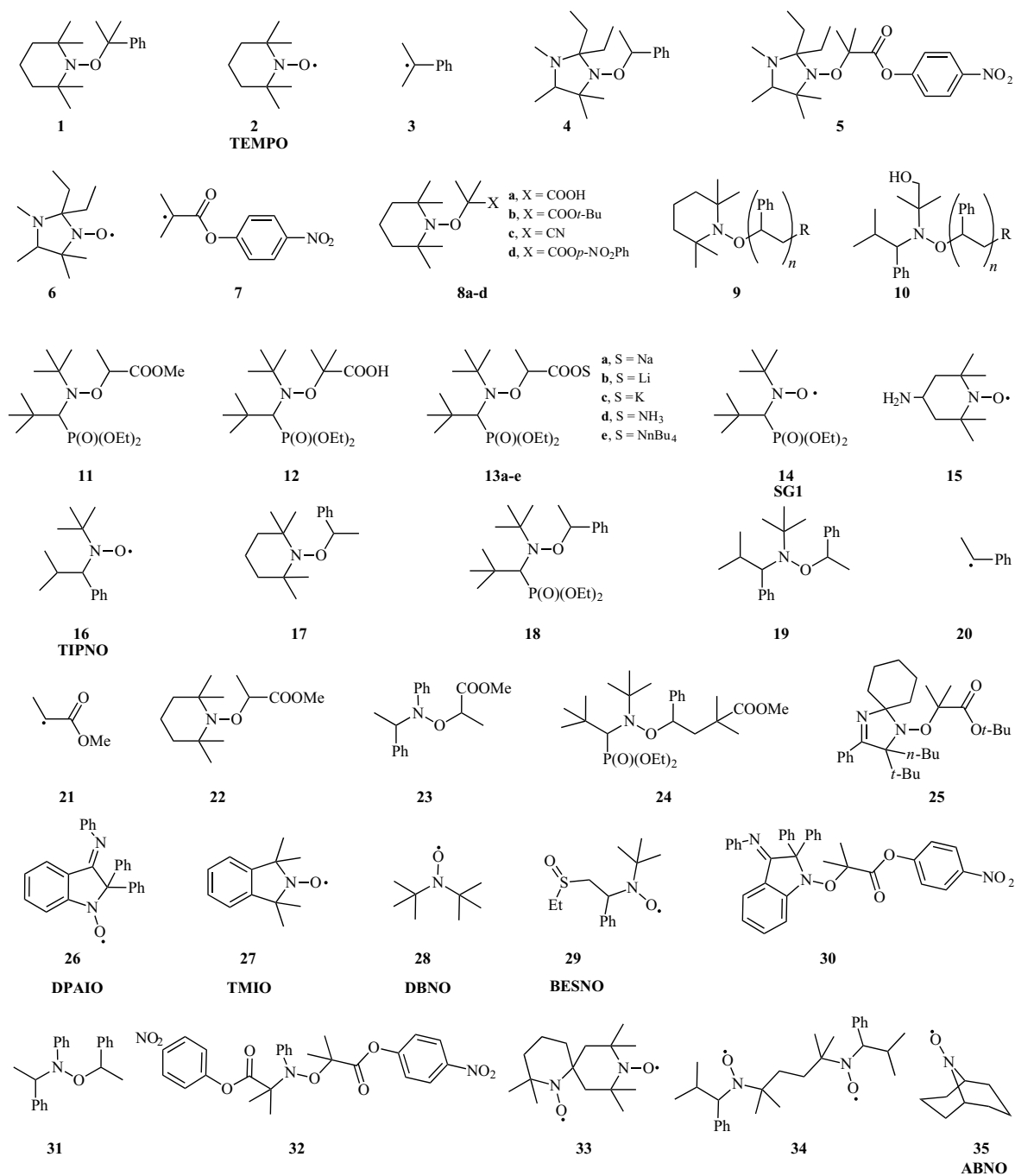
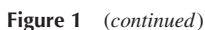
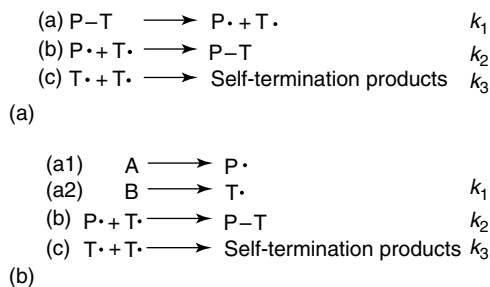


Figure 1 Species discussed in this article.



The PRE is a kinetic effect leading to unusual selectivities for radical reactions, that is, when several



Scheme 1 Persistent ($P\cdot$) and transient ($T\cdot$) radicals generated from a unique source (a), and from two sources (b).

types of radical are generated simultaneously, the fast reaction for coupling of (alkyl) radicals is suppressed, leading to observation of the predominance of the cross-coupling reaction up to a large extent or, in some cases, an unstable compound made to look stable. Even though this effect was first reported in 1936,²⁵ the kinetic equations describing this amazing selectivity were only developed in 1986 by Fischer (Scheme 1),¹⁷ and it found its first interesting applications in NMP.²⁶ The occurrence of this effect must comply with some of the following requirements¹⁷:

- two different types of radicals are involved;
- one must be more persistent than the other one;
- they must be generated at the same moment at the same rate (or very close rates).

It can be either a monocomponent (Scheme 1a) or a bicomponent (Scheme 1b) system.

Resolving the equations for these two systems leads to (1) showing that the concentration of persistent species obeys a $t^{1/3}$ law.

$$[P\cdot] = [PT]_0^{2/3} \times \left(\frac{3k_1^2 \times 2k_3}{k_2^2} \right)^{1/3} \times t^{1/3} \quad (1)$$

Unfortunately, recording this $t^{1/3}$ law is often a challenge because (i) it needs a persistent species readily monitored; (ii) the side-reactions readily spoil the ideal kinetic behavior; and (iii) the evolution of the diamagnetic species is too slow on time. One of the best models fulfilling all the kinetic requirements was reported in 1998, with alkoxyamine **1** as PT, k_d (k_1 in Scheme 1) as the C–ON bond homolysis rate constant, 2,2,6,6-tetramethyl piperidin-*N*-oxyl (TEMPO) **2** as

persistent nitroxide, cumyl radical **3** as transient radical, k_c as the cross-coupling rate constants between nitroxide and alkyl radicals (k_2 in Scheme 1), and k_t as the self-termination reaction rate constant of alkyl radicals (k_3 in Scheme 1).²⁷ It was shown that the decay of **1** was dramatically accelerated in the presence of a free alkyl radical scavenger (100% of **2** released in 3000 seconds at 79.2 °C, Figure 2a), whereas it was extremely slow in the absence of a scavenger (2% of **2** released in 30 000 seconds at 82.5 °C, Figure 2b) and **2** obeyed a $t^{1/3}$ law (1), as expected. Thus, experiments with scavengers showed fast homolysis of **1**, whereas experiments without scavengers showed that the recombination reaction was favored over the termination reactions (Scheme 1).

Then, it was possible to solve the kinetic equations for each species and to plot their evolution with time (Figure 3). The kinetic behavior of **1** exhibited three different regimes as follows:

- A first regime for less than 0.1 second where transient cumyl radical and persistent nitroxide are generated at the same rate obeying a law in t . During that time, the self-termination reactions for the transient radical occur, leading to an excess of persistent radical which is needed to set the quasi-equilibrium that rules the second regime.
- A second regime lasting around 175 days ($t \approx 10^7$ seconds) before significant decay of **1** (circa 20%) can be observed. During that time, the pre-equilibrium is set, and the growth of the persistent nitroxide obeys a $t^{1/3}$ law (1) and the decay of the transient cumyl radical obeys a $t^{-1/3}$ law.
- The third regime lasting around 4 centuries (!) to reach 99% decay of **1**. During that time, the decays of the alkoxyamine **1** (so-called dormant species) and of the cumyl radical obey a $1/t$ law.

More details on the development of the kinetic equations and the subsequent consequences are available in the reviews by Fischer,^{19–21,26} Goto and Fukuda,²⁴ and the recent update²⁸ made by Fukuda and Matyjaszewski.

2.1.2 Examples

Here is the (probably) first example reported by Bachman and Wiselogle²⁵ (Scheme 2a)

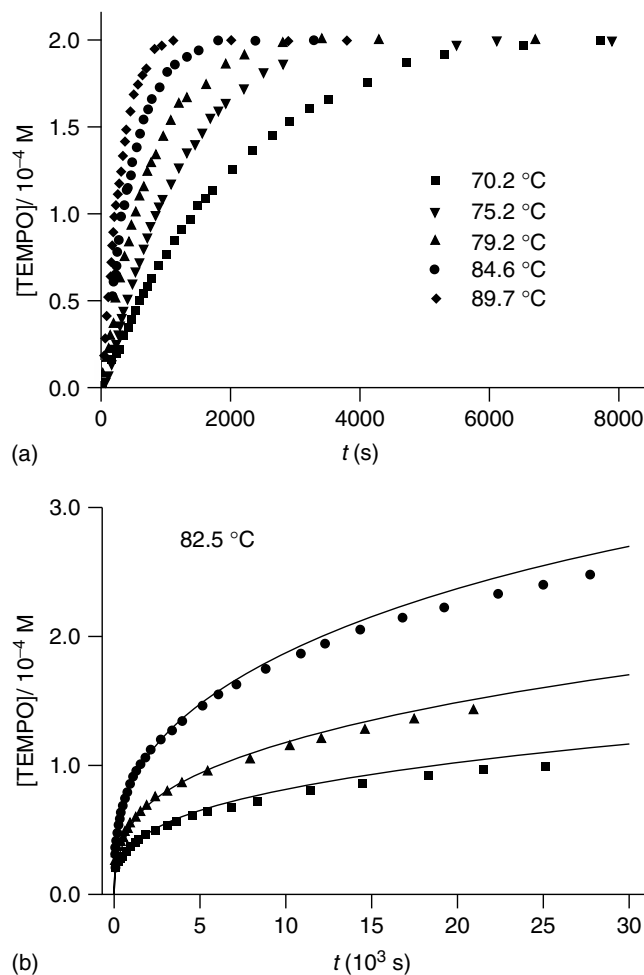


Figure 2 Thermolysis of **1** (a) in the presence of galvinoxyl as alkyl radical scavenger and (b) under PRE conditions. [Reproduced from Ref. 27. © Royal Society of Chemistry, 1998.]

highlighting the exceptional stability of pentaerythranes toward thermolysis. Note that several other reactions ruled by this effect were discovered during the last century as, for example, the famous Barton reaction.²⁹ An example of a bicomponent system exhibiting high selectivity is displayed in Scheme 2b. The photolysis of a *bis**tert*butylperoxide/*tert*butylhydroperoxide/1,4-cyclohexadiene solution³⁰ leads selectively to the formation of a mixed dialkylperoxide. The application of PRE to alkoxyamines is highlighted by the seminal report of Studer,³¹ and more examples are provided in the reviews by Fischer,²⁶ Studer,^{32–35} and Bertin *et al.*³⁶

2.1.3 Consequences

The examples reported and the kinetic evidence given by **1** exemplify nicely the importance of the PRE in controlling the reactivity and selectivity of highly reactive radical species. Recent applications in organic chemistry using alkoxyamines highlight how this effect can be applied to perform selective intermolecular reactions such as addition onto alkene^{37,38} or carbonylation (see **Nitroxides in Synthetic Radical Chemistry**).³⁹

Consequently, in an idealized case, such a long decay for an alkoxyamine makes it possible to perform polymerizations before significant loss of

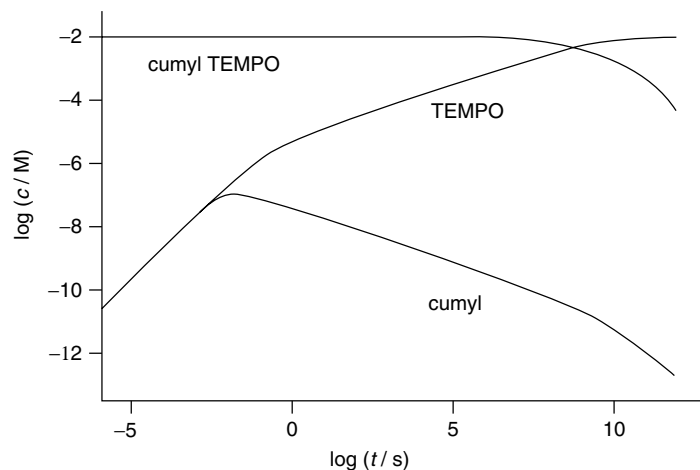
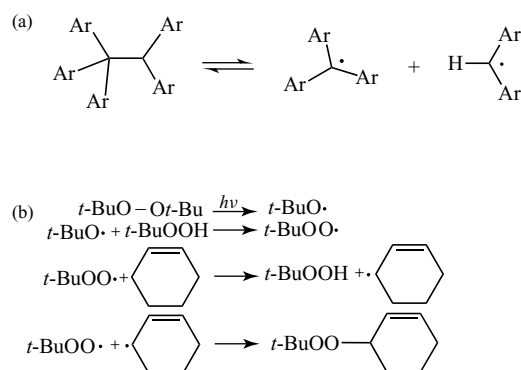


Figure 3 Evolution of **1** and its subsequent radical species in log plot. $k_d = 2.3 \times 10^{-3} \text{ s}^{-1}$, $k_c = 9.1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, and $2k_t = 2.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ were given at 83°C . [Reproduced from Ref. 27. © Royal Society of Chemistry, 1998.]



Scheme 2 Examples of applications of the PRE in synthesis.

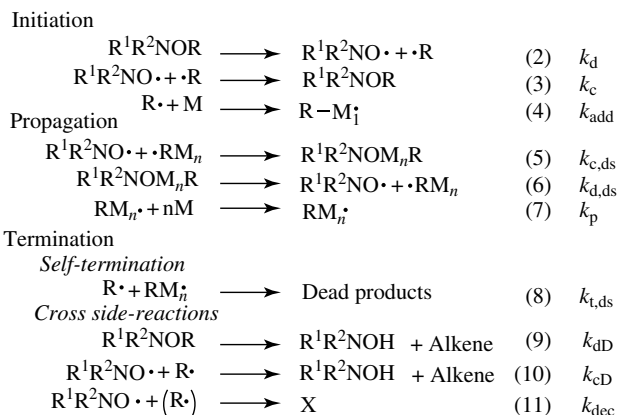
livingness is noticed. However, for polymerization, it should be mentioned that the typical kinetic behavior due to the PRE might be hidden by side-reactions such as thermal self-initiation of monomer,⁴⁰ and also by the use of an extra amount of nitroxide,⁴¹ of extra conventional initiators,⁴² or of nitroxide-reducing agents.⁴³

2.2 Nitroxide-Mediated Polymerization

2.2.1 General Scheme

As soon as NMP was discovered, Johnson *et al.*⁴⁴ using numerical analysis showed that the conventional three-stage—initiation, propagation, and

termination—radical polymerization was the most suitable description for the NMP process (Scheme 3). However, most researchers⁶ accepted that the homolysis of the initiator should not be slower than the homolysis of the dormant species (macroalkoxyamine $\text{R}^1\text{R}^2\text{NOM}_n\text{R}$ in (6)) and thus, the role of the initiation stage on the fate of NMP was disregarded. It facilitated the development of the analytical kinetic equations linking the features of the polymer (chain length M_n , PDI, conversion) to the rate constant values for the reactions of the propagation and termination stages (*vide infra*). However, recent studies showed that a description of NMP involving three stages was more suitable to get deep insight into each of the factors affecting the fate of NMP.⁴⁵ Thus, the complete kinetic scheme (Scheme 3) is composed of three stages, with k_d and $k_{d,ds}$ the homolysis rate constants of the initiator $\text{R}^1\text{R}^2\text{NOR}$ (2) and of the dormant species (6), k_c and $k_{c,ds}$ the cross-coupling rate constants between the alkyl radicals (the initiating one $\text{R}^\bullet$ and the propagating one $\text{RM}_n^\bullet$) and the controlling nitroxide $\text{R}^1\text{R}^2\text{NO}^\bullet$ ((3) and (5), respectively), k_{add} the addition rate constant of initiating alkyl radical $\text{R}^\bullet$ onto monomer M (4), k_p the propagation rate constant of propagating radical $\text{RM}_n^\bullet$ (7), $k_{t,ds}$ the self-termination rate constants for C-centered radicals (8), k_{dD} the intramolecular proton-transfer (Cope-type elimination, (9)) rate constants for the initiator and the dormant species, k_{cD} the intermolecular H-transfer rate constants between nitroxide and C-centered radical (10) for both the



Scheme 3 Scheme of three-stage NMP.

dormant species and the initiator, and k_{dec} the rate constant for the self-decay of nitroxide or alkyl radical (11).

is fulfilled for most of the alkoxyamines used in NMP.

$$K \ll \frac{k_{c,ds}[\text{initiator}]_0}{k_t}, \quad K \ll [\text{initiator}]_0, \quad k_{d,ds} \leq k_{t,ds}[\text{initiator}]_0 \quad (12)$$

2.2.2 Key Equations

Using the core equations of PRE and assuming that the initiation stage has a minor effect on the fate of NMP, Fischer^{19–21,26} developed a set of equations based on $k_{c,ds}$ and $k_{d,ds}$, making it possible to predict the region in which the quasi-equilibrium conditions are fulfilled (12), that is, the quasi-equilibrium constant $K = k_{d,ds}/k_{c,ds}$ holds, and hence to develop equations giving the control (PDI, (13)), livingness

$$PDI_\infty = 1 + \frac{[\text{initiator}]_0}{[\text{monomer}]_0} + \left(\frac{\pi k_p^3 [\text{initiator}]_0}{k_{d,ds} k_{c,ds} k_{t,ds}} \right)^{1/2} \quad (13)$$

$$\phi = \left(\frac{2k_{d,ds}k_{t,ds} \ln \left(\frac{1}{1-\text{conversion}} \right)}{k_{c,ds}k_p[\text{initiator}]_0} \right)^{1/2} \quad (14)$$

$$t_{\text{conv}} = \left(\frac{\left(2 \ln \left(\frac{1}{1-\text{conversion}} \right) \right)^3 \times k_{t,ds}}{9 \times k_p^3 \times [\text{initiator}]_0} \times \frac{k_{c,ds}}{k_{d,ds}} \right)^{1/2} \quad (15)$$

(ϕ , (14)), and polymerization time (t_{conv} , (15)). From this set of equations, it is possible to build the so-called phase diagram (*vide infra*) and to predict the fate of NMP. As initiator concentrations are never higher than 0.1 M, as $k_{t,ds}$ values are higher than $10^6 \text{ M}^{-1} \text{ s}^{-1}$ (except at very high conversions), and as $k_{c,ds}$ values are often larger than $10^4 \text{ M}^{-1} \text{ s}^{-1}$, the quasi-equilibrium condition

2.2.3 Phase Diagram

With the equations displayed above, it is now possible to plot a phase diagram which shows different sections leading to NMP experiments of various qualities (Figure 4).^{20,21} The line QE borders the zone where quasi-equilibrium is achieved, that is, above this line there can be no living and controlled

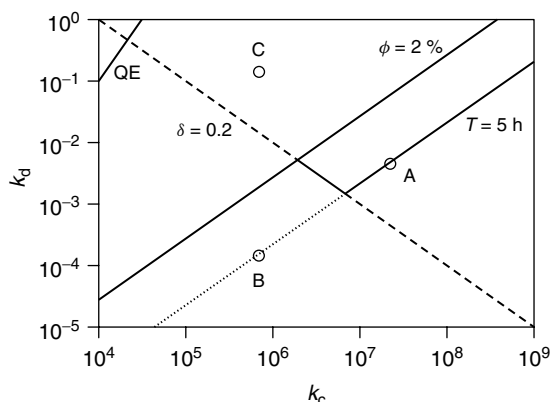


Figure 4 Range of rate constants $k_{d,ds}$ and $k_{c,ds}$ for optimized NMP experiments in $t_{90\%} = 5$ hours (15) for 90% conversion with less than 2% unreactive polymer and PDI ($\delta = \text{PDI} - 1$, (13)) smaller than 1.2. $k_p = 5000 \text{ M}^{-1} \text{ s}^{-1}$, $k_t = 10^8 \text{ M}^{-1} \text{ s}^{-1}$, and $[\text{initiator}]_0 = 0.1 \text{ M}$. [Reproduced from Ref. 21. © Wiley-VCH Verlag GmbH & Co. KGaA, 2001.]

polymerization. The bold lined zone, where point A lies, corresponds to the zone for which the polymerization exhibits an ideal control and targeted high livingness in the required polymerization time. The zone below the bolded line T and above the dashed line δ ($\delta = \text{PDI} - 1$) will provide a living and controlled polymerization in a longer time than aimed. The zone below the dashed line δ and the thick line ϕ will provide a poorly controlled but living polymer in a time depending on line T. On the other hand, the zone below the dashed line δ and above the thick line ϕ will provide a poorly living and poorly controlled polymer, indicating, unsuccessful NMP experiment. Interestingly, going from A to B, the product $k_{d,ds} \cdot k_{c,ds}$ decreases the K value constant being constant, which implies that the same livingness and conversion at the same time is reached for B as for A, except that the polymer obtained for B will exhibit high livingness but poor control. Indeed, the PDI of 1.1 for A increases to 3 for B, keeping the dead fraction smaller than 2%. Going from A to C, the K value increases, keeping the product $k_{d,ds} \cdot k_{c,ds}$ constant, implying that the same PDI and the same conversion is reached for C in a shorter time than for A, except that the polymer for C will exhibit good control but poor livingness. Indeed, the dead fraction of 2% for A increases to 50% for C, keeping the PDI close to 1.1. Obviously for NMP, the properties of livingness and control do not mutually imply each

other.^{20,21} Importantly, it must be stressed that the construction of this diagram is based on an ideal case with no additional initial nitroxide, no additional alkyl radical generation, no side-reaction, and assuming the nonimportance of the initiation stage. The effect of the last two terms on the fate of NMP is discussed in Section 2.2.4. The effect of the addition of extra alkyl radicals has been thoroughly discussed by Fukuda *et al.*^{22,24,46} It can originate from intentionally added initiators, residual peroxide impurities, or from the auto-initiation of the monomer.

In the case where the additional alkyl radical generation rate r is slow, the equations displayed above still hold. The main consequences are that the polymerization is faster, the $t^{1/3}$ law is not obeyed but the conversion follows the more conventional t law (16) and other equations are also modified.²⁶ When extra initial nitroxide is added, the kinetics are also modified. The $t^{1/3}$ law is not obeyed any longer and replaced by a t law. The polymerization is slowed down, which helps to control the monomer exhibiting high k_p values.^{26,47}

$$\ln \frac{[\text{monomer}]_0}{[\text{monomer}]} = k_p \sqrt{\frac{r}{k_t}} t \quad (16)$$

2.2.4 Initiation Stage

As will be discussed later, NMP can be performed in bulk, solution, or dispersed media. Whatever the conditions, only three types of initiations are possible: monocomponent initiating system, bicomponent initiating system, and *in situ* polymerization. It must be noted that the monocomponent initiating system in bulk polymerization has been the most thoroughly investigated because it is the simplest system, and the most suitable to test and exemplify the equations developed.

Monocomponent Initiating System for Bulk or Solution NMP

For cases exhibiting $k_d \gg k_{d,ds}$ (in the case of $k_d \ll k_{d,ds}$, polymerization went from poor control to no control or inhibition), the theoretical models developed by Johnson *et al.*,⁴⁴ Fukuda,⁴⁸ and Fischer²⁶ describe the experimental observations concerning the kinetics of the polymerization, and the

evolutions of the mass, PDI, and living fraction (LF). It was recently shown that the initiation stage plays a pivotal role, that is, the higher the k_d , the better the control.^{45,49} In a recent study, Bagryanskaya *et al.*⁵⁰ reported that NMP of styrene was successful when the slow initiator **4** was used, whereas it failed when the fast initiator **5** was used although the same nitroxide controller **6** was involved. Edeleva *et al.*⁵¹ reported that around 3% of H-transfer occurred during the cross-coupling reaction of **7** with **6**. This kinetic behavior was also reported for a series of TEMPO-based alkoxyamines **8a–d**.⁵²

Thus, alkoxyamines with high k_d can be used for initiation only when the H-transfer reaction ((10), Scheme 3) cannot compete with the reformation reaction ((3) in Scheme 3) when the first addition of the initiating alkyl radical onto the monomer ((4), Scheme 3) is slow. More details have been provided in a recent review.⁴⁵

The other key reaction in the initiation stage is the first addition of alkyl radical onto the monomer (k_{add} , (4) in Scheme 3). The factors controlling the later have been thoroughly investigated over the last 4 decades, and a comprehensive review was published by Fischer and Radom.⁵³ The comments developed in this subsection are likely to hold for other initiating systems.

Oil-Soluble Monocomponent Initiating System for Miniemulsion Polymerization

Both molecular and macromolecular oil-soluble alkoxyamines have been successfully employed in miniemulsion polymerization. For example, chain extensions with *n*-butyl acrylate from polystyryl-TEMPO⁵⁴ or polystyryl-TIPNO-OH (*N*-(1,1-dimethyl-2-hydroxypropyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl)**10**⁵⁵ macroinitiators afford an efficient route to the corresponding poly(*n*-butyl acrylate)-*b*-polystyrene diblock copolymer latexes. The more versatile SG1-based oil-soluble alkoxyamine **11** allowed better results to be obtained, as well-defined *Pn*BA homopolymers⁵⁶ and gradient copolymers⁵⁶ with styrene were obtained with solid contents up to 45 wt%.

Water-Soluble Monocomponent Initiating System for Miniemulsion Polymerization

Nicolas *et al.*⁵⁷ used the water-soluble BlocBuilder™ carboxylate salt alkoxyamine **12** to report the first example of a water-soluble

monocomponent initiating system in miniemulsion NMP.

Monocomponent Initiating System for Emulsion Polymerization

All successful results with molecular alkoxyamines concerned seeded systems in which the complex nucleation step has been circumvented. The first example was achieved when a polystyrene latex was allowed to swell with styrene and an oil-soluble, 2-based alkoxyamine.⁵⁸

A significant breakthrough has been witnessed with the use of water-soluble, **14**-based alkoxyamines **12** via a simple two-step emulsion process.^{59,60} The first step consists in obtaining low solid content seed latexes and preventing the formation of large droplet of monomer.⁵⁹ And the second step consists in the addition of a second load of monomer (either S or *n*-BA) in one part⁶⁰ or in a continuous fashion⁶¹ in order to target higher solid content by efficient chain extension.

Bicomponent Initiating System for Bulk and Solution NMP

On the other hand, an NMP experiment can be initiated using a system based on combination of nitroso^{62–67} compounds or nitrones^{62–64,68} and a conventional initiator. The *in situ* polymerization relies strongly on this approach and affords very good results concerning some monomers such as alkylmethacrylates.^{69,70} The conventional initiator releases radicals which add onto the monomer to generate second-hand alkyl radicals: one radical is scavenged by a nitroso compound or a nitron to afford a nitroxide which in turn scavenges another alkyl radical to yield an alkoxyamine which will play the final role of initiating/controlling species. The same approach is often applied using a bicomponent system combining nitroxide and conventional initiators. The important advantages of these approaches are the wide range of commercially available nitroso compounds, nitrones, and nitroxides, and the possibility of skipping the tedious step of preparation of alkoxyamines. Although the expected linear increase in M_n with the conversion has been reported, the unknown amount of *in situ* generated alkoxyamines makes it difficult to target a specific M_n .

Oil-Soluble Bicomponent Initiating System for Miniemulsion Polymerization

The first example that illustrates this approach, concerns the use of **2** in combination with benzyl peroxide for the polymerization of styrene at 125 °C and in the presence of camphorsulfonic acid as a rate accelerant.⁷¹ A good control was shown for M_n up to 40 000 g mol⁻¹ with PDIs in the 1.14–1.6 range. The use of **14** allowed the miniemulsion polymerization of styrene to proceed at a temperature below 100 °C.⁷²

Water-Soluble Bicomponent Initiating System for Miniemulsion Polymerization

In this case, the polymerization starts in the aqueous phase and leads to the formation of oligoradicals and oligomeric alkoxyamines which enter the monomer droplets, hence becoming the primary locus of polymerization. Macleod and coworkers achieved very fast polymerizations and low PDIs by selecting **2** and potassium persulfate (KPS) for the polymerization of styrene at 135 °C.⁷³ The success of miniemulsion NMP depends dramatically on the aqueous phase kinetics and on the partition coefficients of the nitroxides.⁷⁴ The use of the K₂S₂O₈/Na₂S₂O₅ redox initiating system in conjunction with **14** allowed the polymerization rate of styrene to be enhanced compared to its counterpart with azo-bis(isobutyronitrile) (AIBN) at 90 °C.^{72,75}

Bicomponent Initiating System for Emulsion Polymerization

The difficulties associated with an NMP process in a true emulsion systems were related to colloidal instability and/or poor control, mainly assigned to nucleation of the large droplets of monomer and nitroxide partitioning.⁷⁶

Among **2** and its derivatives under KPS initiation at 130 °C, only **15** led to stable latexes stabilized by sodium dodecyl sulfonate (SDS) with good control/livingness.⁷⁷ With K₂S₂O₈/Na₂S₂O₅ and **14** at 90 °C, the polymerization exhibited rather good control even though a certain percentage of coagulum was noticed.⁷²

2.2.5 Propagation Stage

The propagation rate constants k_p have been extensively and thoroughly investigated over the last

6 decades, and a comprehensive review has been recently published by Beuermann and Buback.⁷⁸ It does not deserve more comments, except that the k_p values will set $k_{c,ds}$ and $k_{d,ds}$ values through (13)–(15).

Using the core equations (12)–(15) shown above, it is possible to predict the control (PDI, (13)), livingness (ϕ , (14)), and polymerization time ($t_{90\%}$, (15)). From this set of equations, it is possible to build the so-called phase diagram and to predict the fate of NMP. For the sake of simplicity, $k_{d,ds}$ and $k_{c,ds}$ were assumed identical or close enough to the k_d and k_c of the corresponding alkoxyamine models (unimers) so that the predictive abilities of the phase diagram approach will not be altered. This held for macroalkoxyamines based on polystyryl chains, it was partly valid for poly-*n*-butylacrylate chains, and led to misleading prediction for polymethylmethacrylate (PMMA) chains as well as for random or statistical copolymers. As examples, phase diagrams for the NMP of styrene and *n*-butyl acrylate were plotted assuming no chain length effect (a plot taking into account chain length effect for poly-*n*-butyl acrylate-based alkoxyamine changed the figure slightly but did not modify the discussion and the conclusion drawn). Interestingly, the phase diagram (Figure 5a) predicts unsuccessful NMP of styrene at 120 °C with **14** (poor livingness), perfect NMP with **16**, and long time polymerization with **2** (but with the expected control and livingness). Experimentally, NMP was completely successful for these three controlling agents.^{41,49} In fact, side-reactions such as the instability of **14** and **16** modified the kinetic regime in a good way, and the auto-initiation of the styrene accelerated the reaction with **2**. On the other hand, successful NMP of styrene at 90 °C was only predicted for **14**. For **16** and **2**, control and livingness were predicted to be of good quality but with a dramatically long time of polymerization. Experimentally, the expected successful NMP with **14** was observed only when **12** was used as initiator (Figure 5a). For **2** and **16**, very sluggish polymerization has been reported.⁴¹

Unsuccessful NMP of *n*-butyl acrylate was predicted by the phase diagram for both temperatures and whatever the controlling agent (Figure 5b). This was confirmed experimentally and attributed to the high k_p value of *n*-butyl acrylate.^{10,41,49,79–81} This failure was overcome by adding a little amount of extra nitroxide^{41,82} or by developing new controlling

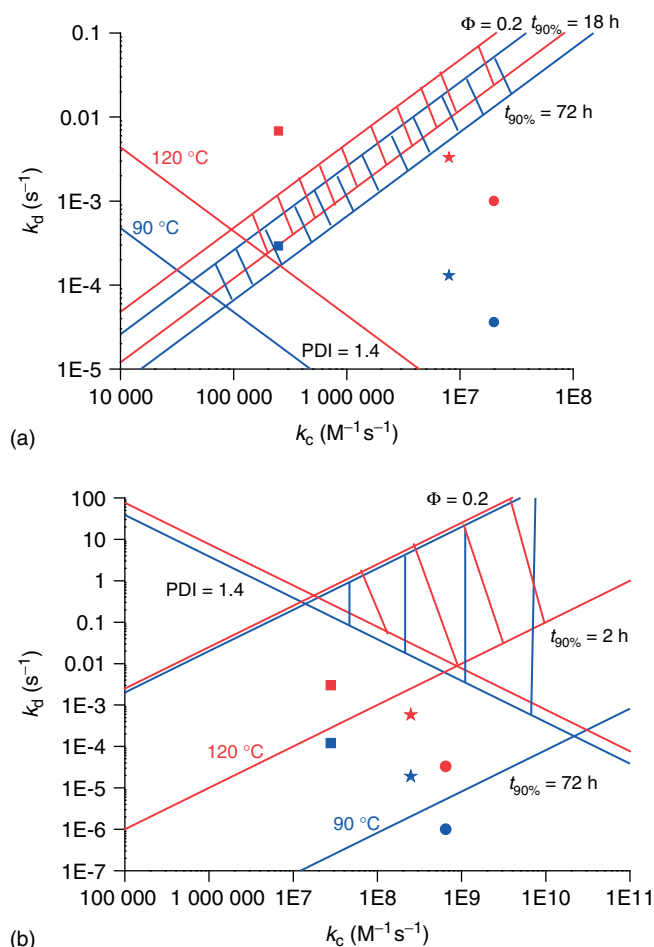


Figure 5 Phase diagrams for the NMP of styrene (a) and *n*-butyl acrylate (b) at 120 °C (red lines and symbols), and 90 °C (blue lines and symbols) with **2** (●), **16** (★), and **14** (■) as controlling agents. The dashed zone is where a perfect NMP experiment is expected. For (a) [alkoxyamine]₀ = 5 × 10⁻² M, $k_t(90 \text{ and } 120^\circ\text{C}) = 1.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $k_p(120^\circ\text{C}) = 2000 \text{ M}^{-1} \text{ s}^{-1}$, $k_p(90^\circ\text{C}) = 900 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{14} + \text{polystyryl radical}, 90 \text{ and } 120^\circ\text{C}) = 2.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{2} + \mathbf{20}, 90 \text{ and } 120^\circ\text{C}) = 2.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{16} + \mathbf{20}, 90 \text{ and } 120^\circ\text{C}) = 8.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, $k_d(\mathbf{46}, 90^\circ\text{C}) = 3.4 \times 10^{-4} \text{ s}^{-1}$, $k_d(\mathbf{46}, 120^\circ\text{C}) = 8.0 \times 10^{-3} \text{ s}^{-1}$, $k_d(\mathbf{45}, 90^\circ\text{C}) = 3.6 \times 10^{-5} \text{ s}^{-1}$, $k_d(\mathbf{45}, 120^\circ\text{C}) = 10^{-3} \text{ s}^{-1}$, $k_d(\mathbf{19}, 90^\circ\text{C}) = 1.3 \times 10^{-4} \text{ s}^{-1}$, $k_d(\mathbf{19}, 120^\circ\text{C}) = 3.3 \times 10^{-3} \text{ s}^{-1}$. For (b) [alkoxyamine]₀ = 5 × 10⁻² M, $k_t(90 \text{ and } 120^\circ\text{C}) = 7.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $k_p(120^\circ\text{C}) = 8.3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_p(90^\circ\text{C}) = 6.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{14} + \text{polyalkylacrylate radical}, 90^\circ\text{C and } 120^\circ\text{C}) = 2.8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{2} + \mathbf{21}, 90 \text{ and } 120^\circ\text{C}) = 6.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $k_c(\mathbf{16} + \mathbf{21}, 90 \text{ and } 120^\circ\text{C}) = 2.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $k_d(\mathbf{11}, 90^\circ\text{C}) = 1.2 \times 10^{-4} \text{ s}^{-1}$, $k_d(\mathbf{11}, 120^\circ\text{C}) = 3.0 \times 10^{-3} \text{ s}^{-1}$, $k_d(\mathbf{22}, 90^\circ\text{C}) = 10^{-6} \text{ s}^{-1}$, $k_d(\mathbf{22}, 120^\circ\text{C}) = 3.3 \times 10^{-5} \text{ s}^{-1}$, $k_d(\mathbf{23}, 90^\circ\text{C}) = 1.9 \times 10^{-5} \text{ s}^{-1}$, $k_d(\mathbf{23}, 120^\circ\text{C}) = 5.8 \times 10^{-4} \text{ s}^{-1}$.

agents.^{83,84} However, for **2**, the improvement was not enough because of the H-transfer side-reaction which spoiled the NMP.⁸⁵ It was also shown that successful NMP of *n*-butyl acrylate was observed when the fast homolyzing alkoxyamine **12** was used.⁴⁹

With the conventional assumptions, the phase diagram predicted successful NMP of methyl

methacrylate (MMA) with **14** at 45 °C (Figure 6a).⁸⁶ However, the experiment performed under the recommended conditions failed.⁸⁶ It was shown that it was due to dramatic differences between k_d and $k_{d,ds}$ and between k_c and $k_{c,ds}$, which favored the intermolecular H-transfer between **14** and **37** although in very low amount. Several authors showed that intermolecular H-transfer was occurring with **14** and **37**

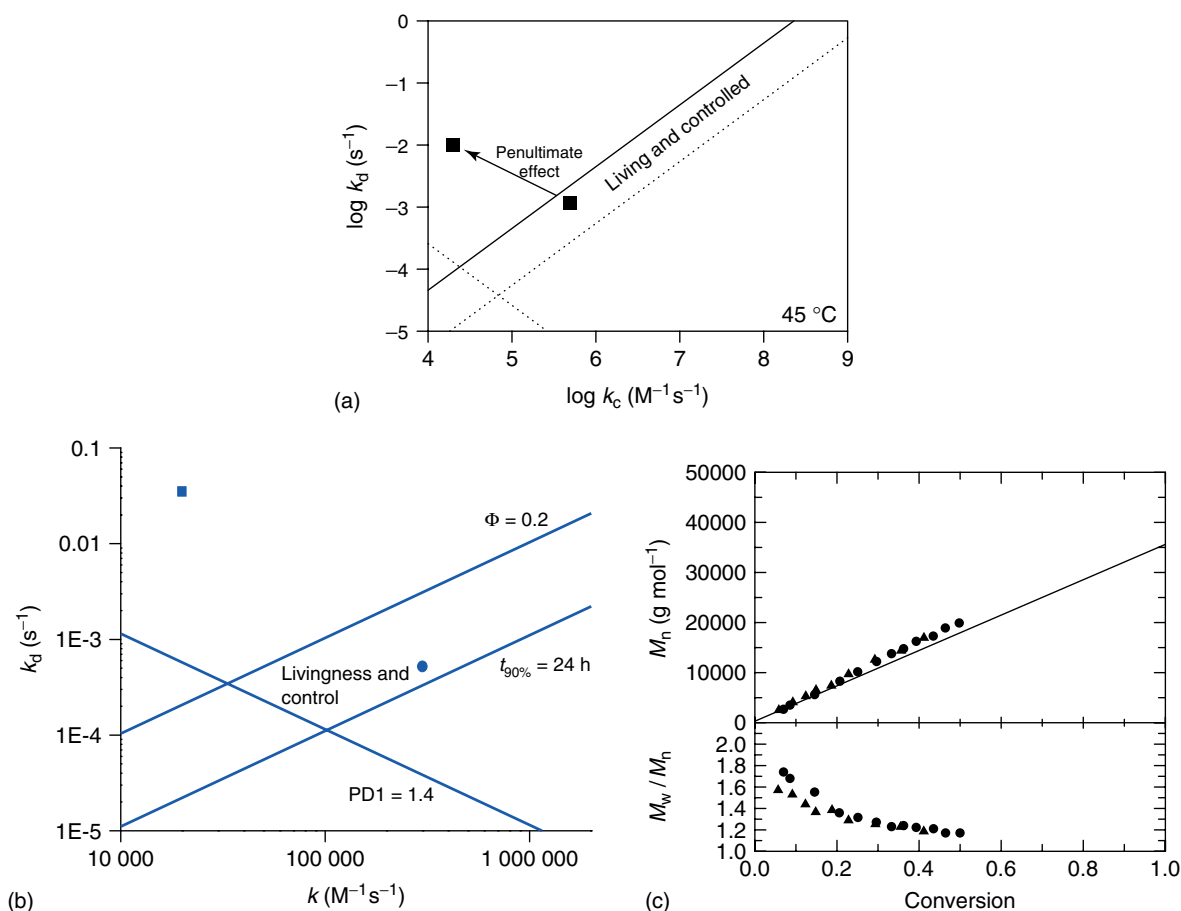


Figure 6 Fischer's phase diagrams for NMP of MMA: (a) controlled by **14** at 45 °C, (b) controlled by **14** at 75 °C with 8% of styrene, and assuming **24** as model of dormant species. (c) NMP of MMA with 8% of styrene controlled by **14** at 75 °C (● at 83 °C and △78 °C, $M_{n,th} \approx 35\,000$ g mol⁻¹). [(a) Reproduced from Ref. 86. © Wiley-VCH Verlag GmbH & Co. KGaA, 2006. (b) Reproduced from Ref. 45. © Royal Society of Chemistry, 2011. (c) Reproduced from Ref. 89. © American Chemical Society, 2006.]

although in very low amount (see Ref. 87). However, its occurrence plays a dramatic role during the NMP of MMA because due to very high k_d values and low k_c values, the H-transfer reaction becomes the preponderant termination reaction.^{86–88} In fact, when the chain length effect was taken into account (i.e., estimated for $k_{c,ds}$ and modeled for $k_{c,ds}$ using the penultimate unit effect (PUE) for $k_{d,ds}$, *vide infra*), the phase diagram predicted an unsuccessful experiment (Figure 6a), as experimentally observed.⁸⁶

It was reported that NMP of MMA was possible in the presence of some amount of styrene with **16**.⁴¹ Combining electron paramagnetic resonance

(EPR) investigations, kinetics analyses, and polymerization experiments, Charleux *et al.*⁸⁹ showed that **24** was the model for the dormant species. Furthermore, when a phase diagram was plotted with conventional assumptions, NMP of MMA with **14** was predicted to fail, whereas when the effect of the penultimate unit modeled by **24** was accounted for, NMP of MMA was predicted as being successful (Figure 6b,c). Consequently, to apply a phase diagram, it is strongly recommended to use $k_{d,ds}$ and $k_{c,ds}$ of the dormant species instead of k_d and k_c of the model alkoxyamine.

Unfortunately, only a few $k_{d,ds}$ and $k_{c,ds}$ are available in the literature. However, the chain length effect for $k_{d,ds}$ is mainly due to PUE, and can be

partly predicted. At this time, no trends are available for $k_{c,ds}$.^{58, 90–92}

2.2.6 Termination Stage and Side-Reactions

The conventional dimerization and disproportionation self-termination reactions of alkyl radicals were reviewed in the late 1980s,⁹³ and do not deserve more comments. The same termination reactions for polymeric radicals were reviewed a few years ago by Buback (see **Kinetics of Polymerizations**).⁹⁴ It is noteworthy that the termination rate constants k_t for polymeric radicals are in general several orders smaller than the corresponding ones for alkyl radicals. Importantly, these self-termination reactions are needed to set the PRE

Fischer.^{21,26,47,98} As a rule of thumb, 0.5% H-transfer has no influence on NMP which can tolerate up to 2% of H-transfer (80% conversion, 40% livingness). For a larger percentage of H-transfer, the NMP process is spoiled. Of course, these limits are modified depending on the conversion and the livingness targeted and the values of k_p , $k_{c,ds}$, and $k_{d,ds}$. When intermolecular H-transfer occurs, the decay of alkoxyamine is given by (17) with $f_{cD} = k_{cD}/(k_c + k_{cD})$ the disproportionation fraction, thus the maximal concentration C_{max} reachable, the optimal polymerization time t_p , and the LF are given by (18)–(20), respectively. Furthermore, the maximal f_{cD} tolerated to obtain a viable NMP experiment is given as a function of the conversion, LF, $k_{d,ds}$, $k_{c,ds}$, k_p , and k_t in (21).

$$[ds]_t = [\text{initiator}]_0 \times e^{-f_{cD} \times k_{d,ds} \times t} \quad (17)$$

$$C_{max} = 1 - \exp \left(-\frac{3}{2} \times k_p \left(\frac{[\text{initiator}]_0}{3k_{t,ds}(k_{c,ds} + k_{cD})k_{d,ds} \times f_{cD}^2} \right)^{1/3} \times 1.08 \right) \quad (18)$$

by generating an excess of nitroxide in the early stage, which in turn helps to maintain these termination reactions to a low level, leading to high livingness.^{20,24,26} To build a phase diagram, it is recommended to use the k_t values for the polymeric species when available.

The key termination reactions are the intramolecular (Cope-type elimination in Scheme 4 and (9) in Scheme 3) proton-transfer reaction,⁹⁵ which occurs during the thermal decomposition of the alkoxyamine, and the intermolecular (Scheme 4 and (10) in Scheme 3) H-transfer reaction,⁹⁶ which occurs during the cross-coupling between C-centered radicals and nitroxides.^{6,24,26,92,97} These reactions are most often invoked to explain why NMP failed.^{6,24,26,48}

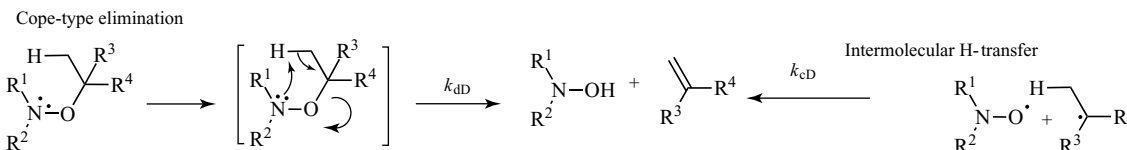
The influence of these reactions on the fate of NMP was theoretically investigated by

$$t_p = \frac{1}{f_{cD}k_{d,ds}} \ln \left(\frac{1}{2.59} \times \frac{2}{1-p} \right) \quad (19)$$

$$LF = \frac{[ds]_{t_p}}{[\text{initiator}]_0} = e^{-f_{cD} \times k_{d,ds} \times t_p} \quad (20)$$

$$f_{cD} < \frac{\ln \left(\frac{1}{LF} \right)}{(2 \ln \frac{1}{1-C})^{3/2}} \times 3k_p^{3/2} \sqrt{\frac{[\text{initiator}]_0}{k_{d,ds}k_{c,ds}k_{t,ds}}} \quad (21)$$

It was shown that the effect of the intramolecular proton transfer (Cope-type elimination) was the same as for the intermolecular H-transfer and, consequently, the equations displayed above are suitable to predict the fate of NMP, except that the decay of the alkoxyamine (dormant species) is



Scheme 4 Cope-type elimination and intermolecular H-transfer reactions.

given by (17) with $f_{dD} = k_{dD}/k_{d,ds}$. Consequently, although from a practical view point, it is difficult to differentiate between these side-reactions, this leads to the same consequence: lower quality NMP. Edeleva *et al.* provided a procedure to differentiate these processes and investigated the kinetics when both were occurring (22).^{51,99}

$$[ds]_t = [\text{initiator}]_0 \times e^{-(k_{dD} + k_{d,ds}f_{cD})t} \quad (22)$$

Owing to very complicated kinetics, only few results are available to confirm the set of equations developed by Fischer and are presented here.^{92,100,101}

Despite their importance, these side-reactions have not been extensively investigated and, thus, their occurrence is often considered as a random event and depends a lot on the structure of the nitroxide, the alkyl radical/fragment, and the experimental conditions (*vide infra*). However, some trends can be drawn: (i) in general in the case of styryl radical, the H-transfer is negligible and does not hamper the polymerization^{6,24,26,85}; (ii) the H-transfer is more favored in the case of acrylyl radicals and not all nitroxides can afford controlled polymerization of this type of monomer^{26,85,97}; (iii) *H-transfer in the case of methacrylyl radicals occurs for most of the nitroxides making the NMP of MMA a challenge for chemists.*^{6,24,26,102}

Another side-reaction, the instability of the nitroxide ((11) in Scheme 3), may play an important role on the fate of NMP. Several authors have noted that the removal of nitroxide due either to its self-decomposition or to the presence of an additive shortened strikingly the polymerization time with no alteration of both control and livingness.^{41,43,103} Equations describing acceptable limits for NMP were developed by Souaille and Fischer.⁴⁷ *The interesting outcome of this analysis is that a very unstable nitroxide (a few seconds of lifetime) can be used to control the polymerization.* Furthermore, the evolution of each parameter very much resembles the evolution observed when a conventional initiator is added, implying that the livingness is only slightly altered. Amazingly, the occurrence of the (self-) decay of the nitroxide might balance the detrimental effect of the H-transfer reactions when suitable conditions are gathered. This very surprising aspect was confirmed and highlighted by Edeleva *et al.*⁵¹ with **25**. On the other hand, such behavior makes

the monitoring of H-transfer reaction quite elusive in some cases and, thus, leads to controversial results.^{86–88,104,105}

In another case, between the self-decay of nitroxide and the intramolecular decay, side-reaction of alkoxyamine has been a little investigated: it is the CO–N bond homolysis which occurs, in general, for an alkoxyamine exhibiting bond dissociation energy (BDE)(C–ON) larger than 140 kJ mol^{–1}. Alkoxyamines based on **26** were successfully applied to the NMP of MMA which exhibited very good control up to 80% conversion and good livingness.¹⁰⁶ Surprisingly, such nitroxide did not undergo the conventional decay reactions affording hydroxylamine.⁹⁹ In fact, the occurrence of the N–OC bond cleavage,¹⁰⁷ despite a rather low BDE(C–ON) around 126.0 kJ mol^{–1},⁹⁹ is likely to moderate the occurrence of intermolecular H-transfer by decreasing the amount of nitroxide.

2.2.7 Copolymerization

Kinetic and Theoretical Studies

2-Mediated copolymerization of styrene in the presence of various comonomers has been essentially studied by Zaremski *et al.*^{108–111} The activation/deactivation equilibrium constants for many of those systems have been experimentally determined and various regimes depending on the ability or not of the second monomer to undergo a controlled/living NMP have been discussed. Charleux *et al.* investigated the theoretical features of the activation–deactivation equilibrium in nitroxide-mediated copolymerization and applied it to the SG1-mediated copolymerization of MMA with a low percentage of styrene (typically in the 4–8.8 mol% range). Using this approach, the MMA/styrene (4–8.8%) system exhibited all the characteristics of living/controlled polymerization, that is, (i) the concentration of propagating radicals and the level of irreversible termination reactions occurring with the MMA/**14** system were low; (ii) isolated styrene units were, time to time, incorporated into the macromolecular chains and at the chain end enabling the reversible deactivation by **14**, and (iii) additionally, the MMA PUE enhanced deactivation of the so-formed alkoxyamine **24**.^{89,112,113} This technique was later expanded to a series of methacrylate monomers

such as methacrylic acid,¹¹⁴ poly(ethylene glycol) methyl ether methacrylate,¹¹⁵ ethyl and *n*-butyl methacrylate,¹¹⁶ *tert*-butyl methacrylate,¹¹⁷ glycidyl methacrylate,¹¹⁶ and methacryloyl galactose.¹¹⁸

Reactivity Ratios

Despite the recent theoretical analyses reported above, reactivity ratios were determined experimentally for various systems and did not show significant differences with those found in classical radical copolymerization. The polymerizations were essentially carried out under controlled/living conditions either because both comonomers were easily controlled or because the composition was such that the major comonomer exhibited controlled NMP with the selected nitroxide. Many examples are based on styrene with a variety of methacrylate and acrylate comonomers, mostly in the presence of **2** or **14**.^{117, 119–131}

3 MAIN FAMILIES OF NITROXIDES

In this section, the main nitroxides are presented, as well as their efficiency in NMP. The main limitations of these nitroxides are their commercial availability and the preparation methods.

3.1 TEMPO, 1,1,4,4-tetramethyl isoindolin-*N*-oxyl (TMIO), and Other Cyclic Nitroxides

The first nitroxides to be used for NMP have been **27** and other isoindoline derivatives prepared beforehand by Moad and Solomon *et al.*^{10,11,13} It showed some efficiency for the NMP of styrene but was of poor efficiency in the case of other monomers. A few years later, Georges *et al.*¹² promoted the interest in the use of NMP to prepare polystyrene using the commercially available nitroxide **2**. It showed good efficiency to control the polymerization of styrene and its derivatives but was of poor efficiency for alkyl acrylate derivatives.¹³² The NMP of MMA failed with **2**¹³³ except under harsh acidic conditions^{134,135} or when random copolymerization conditions were applied.¹³⁶ Many other cyclic nitroxides with 5- to 8-membered rings carrying four alkyl groups on both positions α were prepared to overcome these limitations. Most of

them were efficient for NMP of styrene, whereas only a few of them^{83,137–139} were efficient for the NMP of alkyl acrylates. Interestingly, most of these radicals were rather stable for a long time at temperatures higher than 120 °C (for **27**, $t_{1/2} \gg 40$ hours, for **2**, $t_{1/2} \gg 15$ hours),¹⁴⁰ which may very much slow down the polymerization.

3.2 TIPNO, DBNO, SG1, and Noncyclic Nitroxides

Noncyclic nitroxides are divided into two families: one for which six groups are attached to the carbons in α of the NO moiety, and one for which five groups and one hydrogen atom are attached to the carbons in α of the nitroxide moiety. The first family was promoted by Catala's *et al.*⁴⁰ and Goto and Fukuda's⁹² groups who showed that **28** was efficient for the NMP of styrene and also of alkyl acrylate monomers. This efficiency was due to a low BDE(C–ON). The second family with **16** and **14** as heads of the series was promoted by Tordo's group.^{141,142} The versatility of **16**, carrying an aryl group and a hydrogen atom on the same carbon α , for the polymerization of styrene, alkyl acrylates, and random copolymerization of MMA with few percent of styrene was exemplified by the Hawker/Braslaw groups,⁴¹ whereas the versatility of **14**, carrying a phosphoryl group and an hydrogen atom on the same carbon α , was exemplified by Tordo's^{49,143,144} and Gnagnou's⁸² groups for the NMP of styrene and alkyl acrylates, and by Charleux's and Bertin's groups⁸⁹ for the random copolymerization of MMA. At the same period, Catala *et al.*^{84,145} developed **29**, a nitroxide carrying a hydrogen atom and an alkyl sulfoxide group on the same carbon α , which was as efficient as **16** and **14** and exhibited very low BDE(C–ON). Beside a very low BDE(C–ON), **14**, **16**, and **28** exhibit also low lifetime at 120 °C, that is, $t_{1/2} = 15$ hours, $t_{1/2} = 11$ hours, and $t_{1/2} = 3$ hours, respectively, which is an advantage when performing fast NMP.¹⁴⁰

3.3 DPAIO and Other Aryl Nitroxides

The use of **26** was promoted by Greci's and Bertin's groups for the NMP of MMA.¹⁰⁶ Twenty

years after the discovery of NMP, **26** was the first nitroxide able to control the homopolymerization of MMA by NMP up to 80% conversion with good livingness under mild conditions. Unfortunately, due to high BDE(C–ON) for other alkyl fragments than tertiary alkyl fragments ($E_{a,d} = 126.0 \text{ kJ mol}^{-1}$ for **30**)⁹⁹ and the competition between the C–ON and the C–ON bond cleavage,¹⁰⁷ the NMP of olefins other than 1,1-disubstituted olefins was uncontrolled. The potential of aryl nitroxides as controlling agents was confirmed by other aryl nitroxides such as **31** and **32** prepared by the Grubbs group.^{146,147}

3.4 Proximal Bisnitroxides

There are two types of bisnitroxides: those attached by a long flexible linker behaving as two independent nitroxides (e.g., **34** promoted by the Braslau's group)^{148,149} and the proximal binitroxides for which the two nitroxide moieties are maintained close enough for the occurrence of spin–spin interaction (e.g., **33** promoted by the Rassat/Vairon groups).¹⁵⁰ These types of nitroxide appeared to be unstable^{149,150} at the temperatures required for NMP, which might also be an advantage for performing fast polymerization.⁴⁷ Rassat/Vairon and Kaim's groups¹⁵⁰ reported that the proximity of the two nitroxide moieties had no significant effect either on the C–ON bond homolysis or on the polymerization outputs, whereas Braslau's group¹⁴⁹ reported a slight difference for the k_d of the C–ON bond homolysis and for the polymerization.

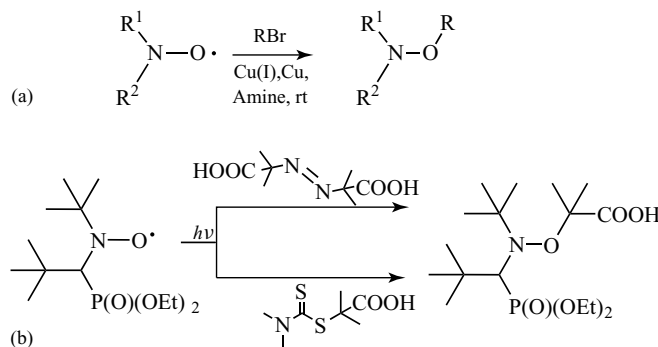
4 ALKOXYAMINES AND THEIR KINETIC BEHAVIOR

The kinetic behavior of alkoxyamines involves the homolysis of the C–ON bond releasing alkyl radical and nitroxide, the cross-coupling (reformation) reaction between the nitroxide and the alkyl radical, the Cope-type elimination and intermolecular H-transfer reactions, the CO–N bond homolysis, as well as the stability of the nitroxide (Scheme 3). The occurrence and the rate constants of all these reactions depend on the structures of the nitroxide, the alkyl radical, and the nitroxyl and alkyl fragments.

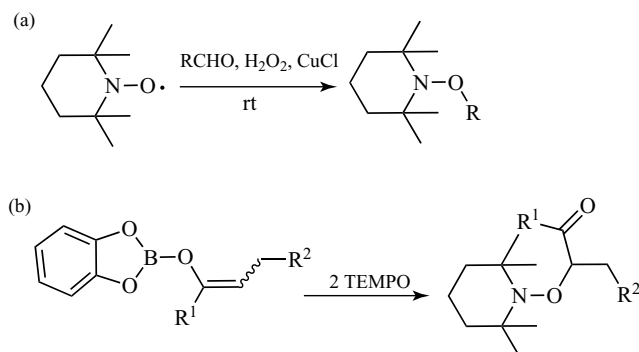
4.1 Preparation of Alkoxyamines

The preparation of alkoxyamines has been reviewed by Bertin *et al.*,³⁶ Nesvabda,¹⁵¹ and Greene and Grubbs¹⁵² and will not be discussed hereafter. In most of the cases, the preparation of alkoxyamines is performed through (3) (Scheme 3) which corresponds to the cross-coupling reaction between a nitroxide and an alkyl radical. Thus, the main outcome is the generation of alkyl radicals. Nowadays, the most applied procedure is the atom transfer radical addition (Scheme 5a) as developed by Matyjaszewski *et al.*¹⁵³ *In situ* preparation of alkoxyamines has been reviewed by Detrembleur *et al.*⁶⁹

Guillaneuf *et al.*¹⁵⁴ reported the preparation of a highly labile and functionalized alkoxyamine using the photolytic cleavage of an azo compound or alkyldithiocarbamate below room temperature (Scheme 5b). In many cases, yields ranged from



Scheme 5 Different routes for preparing alkoxyamines: (a) by atom transfer radical addition (ATRA), and (b) by irradiation.



Scheme 6 Different routes for preparing alkoxyamines (a) oxidation/reduction/ β -fragmentation of aldehydes, and (b) decomposition of alkyl catechol boron compounds.

good to quantitative. The drawbacks of this procedure are the cage effect occurring at low temperature and depending on the solvent leading to the low efficiency of azo compounds, and the availability of azo or alkyldithiocarbamate compounds.

Schoenig *et al.*¹⁵⁵ developed a very versatile and mild procedure for preparing alkoxyamines based on the oxidation of an aldehyde and its reduction/ β -fragmentation in the presence of catalytic amount of CuCl into an alkyl radical which was scavenged by a nitroxide (Scheme 6a). Except for a few cases (4 over 27 examples), good to excellent yields were reported. One drawback of this procedure is the use of an excess of hydrogen peroxide, which sometimes may lead to the formation of instable organic peroxides that may induce hazardous decomposition during the workup when not enough care is taken.

A more specific procedure for the preparation of acrylate-based alkoxyamines relying on the decomposition of catecholboron enolates in the presence of nitroxide (here **2**) was proposed by the groups of Studer of Renaud (Scheme 6b).¹⁵⁶ Yields varied from moderate to excellent.

4.2 C–ON Bond Homolysis

4.2.1 Measurement of the C–ON Bond Homolysis Rate Constant k_d for Alkoxyamines

As mentioned above, the decay of an alkoxyamine is governed by the PRE (Scheme 1a) and an accurate and reliable determination of k_d requires

the suppression of the cross-coupling reaction (back reaction), which is achieved either by scavenging the alkyl radical or by reducing the nitroxide into hydroxylamine. Consequently, in the presence of an excess of scavengers/reductants, k_d is obtained either by EPR monitoring of the growth of the nitroxide signal^{7–9,27} or by NMR monitoring of the typical signal of an alkoxyamine,^{157,158} or by monitoring the size exclusion chromatography (SEC) traces of a macroalkoxyamine,¹⁵⁹ or by monitoring changes in the fluorescence¹⁶⁰ of a labeled nitroxide. The limitations of each method, as well as the meanings and the reliability of frequency factors, have been discussed by Bertin *et al.*³⁶

4.2.2 Alkyl Fragment

The first report about the dependence of k_d on the structure of the alkyl fragment was made by Kovtun *et al.*⁷ Soon after, Howard and Tait^{8,9} reported a study on a larger series of compounds. However, the first relationship was provided by Mulder *et al.*,¹⁶¹ who showed that the activation energy E_a for the C–ON bond homolysis, that is, $\log k_d$, increased with decreasing BDE of the C–H bond of the released alkyl radical, meaning that the alkoxyamine homolysis is partly governed by the stabilization of the released alkyl radical. A few years later, Marque *et al.*³⁶ reviewed the various effects of the structure of the alkyl fragment on k_d . They are summarized in Figure 7.

The anomeric effect,¹⁶² which leads to striking decrease in k_d , was first reported by Ciriano *et al.*¹⁶¹ for alkoxyamine carrying O and N atoms,

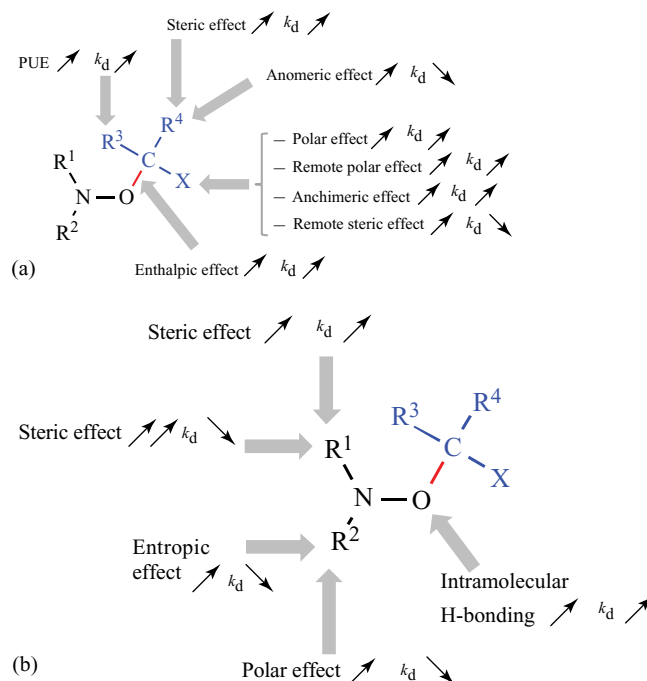


Figure 7 Various effects of the alkyl (a) and nitroxyl (b) fragments on the C-ON bond homolysis. [Reproduced from Ref. 45. © Royal Society of Chemistry, 2011.]

and for S atom and carbonyl group by Marque *et al.*¹⁶³ The steric effect, leading to an increase in k_d , is due to the size of R₁, R₂, and X groups and destabilizes the reactant.¹⁶⁴ The stabilization of the alkyl radical decreases the energy of transition state (TS) leading to an increase in k_d . As described by Pauling, the bond is composed of an enthalpic term and a polar term, that is, the difference ($\chi_O - \chi_C$)²,^{165,166} thus, a decrease in the difference in electronegativity χ between the carbon and oxygen atoms of the C-ON bond destabilizes the initial state, leading to an increase in k_d .¹⁶⁴ The anchimeric effect was probably observed for the first time with pyridyl and thiopyrrole groups carried by **2**-based alkoxyamines by Marque *et al.*¹⁶³ and proved for **14**-based alkoxyamines.¹⁶⁷ This effect destabilizes the initial state by donation of a lone pair of the heteroatom to the antibonding orbital of the C-ON bond, $n_X \rightarrow \sigma^*_{C-ON}$, leading to an increase in k_d . The remote polar effect was reported by Marque *et al.*^{168,169} for several series of **14**-based alkoxyamines as well as for a few examples of other types of alkoxyamines.⁵⁰ This effect plays the same role as the polar effect, that is,

it destabilizes the initial state leading to an increase in k_d . It must be noted that all the effects mentioned above are general to any type of alkoxyamine. On the other hand, the remote steric effect has only been observed for **14**-based alkoxyamines.¹⁷⁰ This effect probably involves some hindered rotations to reach TS from the initial state, leading to the destabilization of TS, and hence, to a decrease in k_d .

The two large series of alkyl fragments available for **2**- and **14**-based alkoxyamines gave the opportunity to develop structure–reactivity relationships describing the impact of the three main effects—stabilization (σ_{RS}), polar (σ_I), and steric (ν)—on k_d , as given by (23) and (24), respectively¹⁶⁴:

$$\log(k_d/s^{-1}) = -14.80 + 13.90 \times \sigma_{RS} + 13.60 \times \sigma_I + 6.60 \times \nu \quad (23)$$

$$\log(k_d/s^{-1}) = -14.33 + 15.30 \times \sigma_{RS} + 19.5 \times \sigma_I + 7.00 \times \nu \quad (24)$$

4.2.3 Nitroxide Fragment

Rizzardo and Moad were the first to report that k_d increased with the congestion around the nitroxyl moiety of the alkoxyamine.¹³ A few years later, Marque¹⁷¹ proposed a structure–reactivity relationship (25) for almost all types of nitroxyl fragments (except for aryl nitroxides) describing the impact of the ring size, the congestion around the nitroxyl moiety, the substitution on the ring, the presence of an H atom in position β , and the polar and the stabilization effects. First four effects were described by the Taft-type steric constants E_s , and, as the polar and stabilization effects were aliased, the Hammett polar constant σ_L was applied.

$$\log(k_d/s^{-1}) = -5.73 - 2.81 \times \sigma_L - 0.83 \times E_s \quad (25)$$

Several trends were observed as follows³⁶:

- The increase in k_d due to the release of steric strain which is due either to the relief of the ring strain, that is, increase in the $\langle \text{CNC} \rangle$ valence angle which in turn increases the congestion around the nitroxyl moiety, from 5- to 7-membered rings^{13,137,171,172} or to the change in hybridization of sp^2 to sp^3 of one of the atoms on the 7- or 8-membered ring.¹³⁷
- The increase in k_d due to the increase in the bulkiness of groups flanking the nitroxyl moiety, that is, increase in the congestion.^{13,36,83,138,164,165,172} However, this increase can be balanced by the leveled steric effect¹⁷³ (*vide infra*).^{36,171,174–176}
- The increase in k_d due to the presence of a substituent on the ring, which limits the number of possible conformations, that is, fewer conformations to “freeze” in TS and, hence, higher activation entropy $\Delta S^\ddagger$. However, this substituent effect depends on the position and the size of the ring.³⁶
- The increase in k_d due to the presence of intramolecular hydrogen bonding (IHB) which stabilizes the generated nitroxide, and, hence, lowers the energy of TS.^{163,172,177–179}
- The decrease in k_d with increasing electron-withdrawing capacity of the groups attached to the nitroxyl moiety (polar effect) which destabilizes the nitroxide and, hence, destabilizes TS.^{171,172}

- The decrease in k_d due to the entropic effect which increases with the size of the ring and depends on the substituents and their positions on the ring.^{36,172}

Interestingly, those effects are spread in enthalpic term—congestion around the nitroxyl moiety and relief of the ring strain (steric effect), IHB, polar effect—and entropic term—substituent effect, ring size, hybridization of the atom of the ring.

The leveled steric effect has been proved^{36,171,172} and invoked^{171,174} to include the noncyclic nitroxyl fragments into (25). However, results provided by Studer *et al.*¹⁷⁶ proved that the steric effect and strain relief are less obvious than described by (25), even though (25) provides often accurate and reliable k_d values for noncyclic nitroxyl fragments. Consequently, the data estimated for noncyclic nitroxyl fragments by (25) should be handled with caution.

4.3 C–ON Bond Reformation

A thorough survey discussing the methods of measurement of k_c , the Arrhenius parameters, the factors ruling the reformation reaction depending on the structures of both the nitroxides and the alkyl radicals, as well as a large collection of k_c values, is provided by Bagryanskaya *et al.* (E. G. Bagryanskaya and S. R. A. Marque, *Chem. Rev.* in preparation).

4.3.1 Measurement of the C–ON Bond Reformation Rate Constants k_c of Alkoxyamines

Laser flash photolysis-kinetic absorption spectroscopy (LFP-KAS) is the most popular and suitable technique to measure k_c values for the formation of unimolecular species. Several methods have been developed aiming to overcome the low absorption of some alkyl radicals and the difficulties in preparing suitable initiators. The kinetic analysis of the NMP experiment⁸² (26) and the radical nitroxide recombination-pulsed lamp photolysis-size exclusion chromatography¹⁸⁰ (RNR-PLP-SEC) are the only approaches and techniques available to estimate $k_{c,ds}$ values for polymeric radicals. Amazingly, many k_c values exhibit a reverted behavior with the

temperature, that is, k_c decreases with increasing temperature.¹⁸¹ Moreover, for many cases, k_c values also exhibit very weak temperature dependence, that is, k_c at 120 °C differs by less than a factor two from k_c given at room temperature.¹⁸¹ Those unexpected behaviors, due to an entropic effect, have been thoroughly discussed by Fischer *et al.*¹⁸¹

$$\ln \frac{[\text{monomer}]}{[\text{monomer}]_0} = \frac{3}{2} k_p \left(\frac{k_{d,ds}}{3k_{c,ds}} \times \frac{[\text{initiator}]_0}{k_{t,ds}} \right)^{1/3} \times t^{2/3} \quad (26)$$

4.3.2 Alkyl Fragment

Bowry and Ingold¹⁸² were the first to present a $\log k_c$ versus BDE(C–H) correlation and showed that the increase in the stabilization (enthalpic effect) of the alkyl radical led to a decrease in k_c . In a recent survey, Bagryanskay *et al.* applied a multiparameter analysis— σ_{RS} for the radical stabilization, σ_I for the polarity, and ν for the bulkiness at the radical center—to five nitroxides, **2**, **14**, **27**, **28**, and **35**, as given in (27) for **14**:

$$\begin{aligned} \log(k_c/l \times \text{mol}^{-1} \times \text{s}^{-1}) \\ = 10.72 - 6.72 \times \sigma_{RS} + 14.24 \times \sigma_I - 2.89 \times \nu \end{aligned} \quad (27)$$

Several of the following trends arose (Figure 8):

- k_c decreased with increasing stabilization, due to poor overlap of the singly occupied molecular orbitals (SOMO) of the nitroxide and alkyl radical at the TS. Furthermore, the impact of this effect increased with the bulkiness around the nitroxide moiety.
- k_c decreased with increasing bulkiness of the alkyl radical, which hampers the approach to the radical center.
- k_c increased with increasing polarity, which is related here to the change of sp^2 hybridization at initial state to partly pyramidalized sp^3 -type orbital at the TS. In general, an electron with drawing groups (EWG) attached to the radical center favors its pyramidalization.

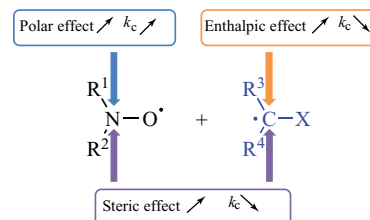


Figure 8 Different effects on k_c due to the structures of the nitroxide and alkyl radical. [Reproduced from Ref. 45. © Royal Society of Chemistry, 2011.]

Although they were investigated for the C–ON bond homolysis, the anomeric, anchimeric, remote steric, and polar effects were not investigated for the C–ON bond reformation because the initiators for the corresponding alkyl radicals were not available.

4.3.3 Nitroxide Fragment

Although k_c values were known for several types of nitroxides,^{181–184} Marqu $\acute{e}$ *et al.*^{185–187} were the first to report multiparameter analysis— σ_I for the stabilization/polarity (it was assumed that the polarity and stabilization effects were aliased and exhibiting the same trend), and E_s for the steric effects—for several alkyl radicals such as **3**, **20**, **21**, **36**, and **37**. A typical correlation is given as in (28) for **20**:¹⁸⁷

$$\begin{aligned} \log(k_c/l \times \text{mol}^{-1} \times \text{s}^{-1}) \\ = 10.07 + 0.52 \times \sigma_I + 0.45 \times E_s \end{aligned} \quad (28)$$

Several of the following trends arose (Figure 8):

- k_c decreased with increasing bulkiness of the group flanking the nitroxyl moiety.¹⁸⁵ However, the impact of this effect depended on the delocalization of the odd electron on the alkyl radical.
- k_c increased with the presence of an EWG attached to the nitroxyl moiety (polar effect).¹⁸⁶ However, the impact of this effect depended on the delocalization of the odd electron on the alkyl radical.
- The ring size, the hybridization of the atoms of the ring, the presence of substituents at other

positions than the positions α to the nitroxyl moiety had no influence.

IHB was investigated for **38** and no significant differences were observed.¹⁸¹

4.4 Side-Reactions

Although these side-reactions are crucial for the fate of NMP and their effects on NMP very much depends on the extent of their occurrence, they were not as carefully and intensively investigated as the C–ON bond homolysis and reformation.

4.4.1 CO–N Bond Homolysis

This reaction has been little investigated because it generally occurs for alkoxyamines exhibiting C–ON bond enthalpies higher than 140 kJ mol^{-1} ,^{13,26,140} whereas only alkoxyamines with BDE(C–ON) lower than 140 kJ mol^{-1} are interesting for NMP.^{20,24,26} However, Gimes *et al.*¹⁰⁷ observed CO–N bond homolysis for **26**-based alkoxyamines with BDE(C–ON) around 126 kJ mol^{-1} .⁹⁹ Furthermore, this side-reaction is likely to play a role in the nonoccurrence of the intermolecular H-transfer reaction.⁴⁷

4.4.2 Nitroxide Stability

The nitroxide stabilities have been investigated over the last 6 decades.^{188–192} There are two types of stability: the intrinsic stability which depends only on the molecular structure of the nitroxide, and the stability to reactants which depends on the structure of both the nitroxide and the reactant.

The intrinsic stability is related to three types of side-reactions as follows:

- the disproportionation reaction requiring the presence of at least one hydrogen atom in position β , and leading to the subsequent hydroxylamine and nitron;
- the α -fragmentation reaction leading to a nitroso compound and a radical species;

- the β -fragmentation reaction leading to a nitron and a radical species.

The occurrence of these fragmentation reactions depends on the bulkiness of the groups attached to the nitroxyl moiety, the stabilization of the released radical, and the thermodynamic stability of the diamagnetic compounds. Nilsen and Braslau¹⁹² carefully investigated the decomposition of **16** and showed that the main decay pathways were the fragmentation reactions. Marque *et al.*¹⁴⁰ investigated the kinetic stability of several nitroxides and showed that $t_{1/2}$ spanned from several hours to 20 minutes at 120°C and depended dramatically on the structure of the nitroxide and the experimental conditions.

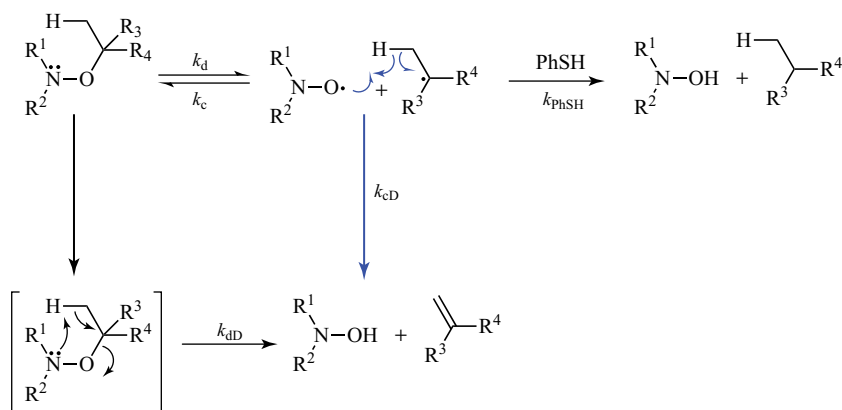
The stability toward reactants relies on both the congestion around the nitroxyl moiety, which hampers the approach of the H-atom donors such as thiol, phenols, metal hydrides,¹⁵⁷ and the redox potential of nitroxide controlling the reaction with reductant/oxidant such as sodium ascorbate.¹⁹³

4.4.3 H-Transfer Reaction and Cope-Type Elimination

As mentioned above, the occurrence of reactions affording hydroxylamine and alkene is crucial for the fate of NMP. These side-products are generated by the intermolecular H-transfer reaction between the nitroxide and the alkyl radical and/or the Cope-type elimination. Such reactions were investigated for phenylethyl radical **20** and homologs,^{85,96,105,194} alkoxy-carbonyl-ethyl radical,^{85,97,105} and alkoxy-carbonyl-2-prop-2-yl radical.^{51,85,97,99,105} It was shown for the cross-coupling between nitroxide and phenylethyl radical that the intermolecular H-transfer reaction is a minor event which does not impede the success of the NMP. For the two other radicals, these reactions can occur to large extent, spoiling the NMP.

Edeleva *et al.*^{51,99} provided a very simple and efficient procedure allowing discrimination between these two processes (Scheme 7):

- when the experiment is performed under scavenging conditions (k_{PhSH}) which completely and efficiently suppress the cross-coupling reaction k_c , any detected alkene is only due to the occurrence of the Cope-type elimination;



Scheme 7 Reactions occurring during the thermolysis of an alkoxyamine under various conditions.

- when the experiment is performed under PRE conditions, the detected alkene is generated by both processes. As the Cope-type elimination does depend on the procedure, each rate constant k_d , k_{cD} , and k_{dD} is readily determined.

Even though these side-reactions have been investigated for the decay of two series of alkoxyamines,^{51,97} no clear trends have emerged, and these events still look as if they occur randomly, for example, a large amount of alkene is observed for **22**⁸⁵ whereas no alkene is observed for **39** and **11**,¹⁰⁴ any is observed for **30**,⁹⁹ and a very small amount (<5%) is observed for **40**, and **41**.⁸⁷ Furthermore, their observation very much depends on the experimental conditions, that is, they were not detected by room temperature chemically induced dynamic nuclear polarization (CIDNP)^{186,195} but detected by high-temperature CIDNP,¹⁹⁶ and detected for **42** but not for **25**, because of the instability of the nitroxide and good kinetic circumstances,⁵¹ or because of the cancellation due to the presence of an acid as exemplified by **12**.

Indeed, the occurrence of these reactions is controlled by the following requirements of the TS:

- The intermolecular H-transfer reaction requires a linear TS, that is, the $\langle \text{NO}^\bullet \cdots \text{H}-\text{C} \rangle$ angle must be as close as possible to 180° .
- The Cope-type elimination requires a 5-membered cyclic TS exhibiting an $\langle \text{N}^\bullet \cdots \text{H}-\text{C} \rangle$ angle as close as possible to 150° .

Thus, predicting the occurrence of these reactions requires thorough calculations aiming to determine the accurate requirements for TS and how they are related to the molecular structures of products and starting materials.

4.5 Miscellaneous

4.5.1 Penultimate Unit Effect

The PUE for the C-ON bond homolysis has been little investigated because of the tedious work needed to prepare the starting alkoxyamines. Using 1,2-addition of radical onto alkene and the scavenging of the subsequent alkyl radical by **14**,³⁸ several models suitable for investigation were prepared.¹⁹⁷ It was shown that (24) developed for simple alkoxyamine models based on **14** holds for subsequent alkoxyamines carrying a penultimate fragment.¹⁹⁷ It was also shown that the PUE spans from weak (1.5-fold), from **18** to **43**, to strong (18-fold) from **18** to **44**.¹⁹⁷ Thus, some clear trends were drawn as follows:

- for the diads $\text{YCH}_2\text{CH}_2\text{MeZC-}$, $\text{YMeCHCH}_2\text{MeZC-}$, $\text{YCH}_2\text{CH}_2\text{ZHC-}$, and $\text{YMeCHCH}_2\text{ZH}_2\text{C-}$ only very weak PUE was reported;
- for the diad $\text{YMe}_2\text{CCH}_2\text{ZHC-}$, strong PUE was reported;
- for the diad $\text{YMe}_2\text{CH}_2\text{ZMeC-}$, very strong PUE is expected from (24)¹⁹⁷;

- for the triad $\text{YMe}_2\text{CCH}_2\text{ZHCCH}_2\text{ZHC-}$, no effect of the antepenultimate unit was observed;
- the PUE depends on the nitroxyl fragment, for example, no PUE for **43**¹⁹⁷ was detected, whereas clear PUE was detected for **45**¹⁵⁷;
- the importance of the PUE depends on the configuration of chiral carbons, as exemplified with **45**.¹⁵⁷

The PUE for C–ON bond reformation has been even less investigated than for the C–ON bond homolysis, because no suitable radical initiators were available. Developing a new procedure of k_c measurements, Lallevee *et al.*¹⁸⁴ were able to measure the PUE for a few dyads $\text{YMeHCH}_2\text{CHZ-}$ and $\text{YMeHCH}_2\text{CMeZ-}$. No significant differences have been observed as compared with the unimolecular models.

4.5.2 Chain Length Effect

The effect of the chain length on the C–ON bond homolysis rate constant has mainly been investigated for three nitroxyl fragments: **2**, **14**, and **28**. As mentioned above, Fukuda *et al.*¹⁹⁸ and Bon *et al.*¹⁹⁹ reported different values for the k_d of **9**, nicely accounted for by the PUE, compare to the model alkoxyamine **17**. Gnagnou *et al.*,⁸² Bertin *et al.*,⁹¹ and Goto and Fukuda⁴⁶ reported a roughly twofold increase in $k_{d,ds}$ for **46** compared to **18**.¹⁴⁰ Goto and Fukuda⁴⁶ reported $k_{d,ds}$ values for **47** similar to those¹⁴⁰ observed for **48**. On the other hand, for **49**, Marque *et al.*⁹⁰ reported a linear increase of $k_{d,ds}$ with the molecular mass M_n . Nonetheless, except for **49**, the effect of the chain length is weak and well accounted for by the PUE. For **49**, this chain length effect is likely due to the remote polar effect.

The effect of the chain length on the C–ON bond reformation rate constant $k_{c,ds}$ has not received as much interest as that on $k_{d,ds}$ because the required radical initiators were not available. Most values came from the kinetic analysis of the polymerization, providing that reliable k_d , k_p , and k_t values were available, providing that the system monitored complied with the requirements that the equations used held, and providing that side-reactions were minor on the experimental time. Although for most cases, the reported $k_{c,ds}$ were reliable, the

k_c for the unimolecular species were not measured, forbidding any comparison. To overcome these drawbacks, Guillaneuf *et al.*¹⁸⁰ developed a new procedure and applied it to the measurement of $k_{c,ds}$ for **50** with **2** ($k_{c,ds} = 1.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) and **14** ($k_{c,ds} \approx 2 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$), and for **51** with **14** ($k_{c,ds} = 6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$)⁸⁶ and **26**¹⁰⁶ ($k_{c,ds} = 1.4 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$). Consequently, the $k_{c,ds}$ reported for **9**^{23,180} (**52**,¹⁷⁸ **53**,⁴¹ and **54**¹⁷⁸) are of the same order of magnitude as for the unimolecular model.^{181,184} The $k_{c,ds}$ values reported for **46**,^{142,180} **49**,²⁰⁰ and **55**¹⁰⁶ are roughly one order of magnitude smaller than those reported for the unimolecular species.^{181,184} The $k_{c,ds}$ values reported for **56**⁸⁶ are roughly two orders of magnitude lower than those reported for the unimolecular species.^{181,184}

These few $k_{c,ds}$ values span over two orders of magnitude and depends dramatically on the molecular structure of the nitroxide and on the type of polymeric radical, in a such way that they cannot be predicted. Such a variation will play an important role in the fate of NMP.

4.5.3 Solvent Effect

For the C–ON bond homolysis, the solvent effect was investigated for two series^{13,90} and only a weak influence was reported, that is, a twofold increase for increasing solvent polarity from hexane to alcoholic solvents.¹⁶³ Interestingly, **13a–e** were reported to be soluble almost in any solvent from pentane to water.²⁰¹

For the C–ON bond reformation, the solvent effect was thoroughly investigated by Ingold *et al.*²⁰² who showed that k_c was decreased with the increasing polarity and viscosity of the solvent.

4.5.4 Acid and Salt Effects

Georges *et al.*²⁰³ and Marque *et al.*¹⁶³ showed that k_d was not modified by the presence of an acid but the later removed the nitroxide, and thus modified the kinetic behavior of NMP. However, these investigations were performed on an alkoxyamine without protonable functions close to the CON moiety. Under harsh conditions, Mazarin *et al.*²⁰⁴ showed that a **14**-based alkoxyamine was protonated and the C–ON bond was strikingly strengthened.

On the other hand, Bagryanskaya *et al.* reported a 10-times lower k_d value for the protonated form **57** than for the nonprotonated form **58**.²⁰⁵ Moreover, Brémond *et al.* reported a 15-fold increase in k_d for **59** upon protonation of the leaving alkyl radical of **60**.²⁰⁶

Marque *et al.* investigated the salt effect with **13a–d** alkoxyamines, and noted only a minor effect for one diastereoisomer.²⁰¹

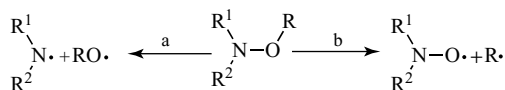
Scaiano *et al.*²⁰⁷ reported a very weak (twofold decrease) effect of the acidic conditions on k_c for the cross-coupling reaction between **2** and **36**. On the other hand, Bagryanskaya *et al.* reported a two times increase in k_c for the cross-coupling reaction of **61** with **37** upon protonation of **62**.²⁰⁵

4.6 Calculations

At the earlier stage of NMP, BDEs of alkoxyamines had been investigated using semiempirical and low cost methods.^{13,208–210} This provided good trends but the energies were not reliable and not accurate enough to investigate subtle effects. Thus, only calculations performed with methods using at least DFT will be discussed hereafter.

4.6.1 C–ON and CO–N Bond Dissociation Energies

As early as 1999, Marsal *et al.* showed that DFT afforded reliable BDE values for simple alkoxyamines in a reasonable time.²¹¹ With a large set of data, Coote *et al.* showed that, in general, the G3(MP2)-RAD method afforded better results than the DFT methods.²¹² They showed that BDE(CO–N) were not correlated to the BDE(C–ON). They noted that CO–N bond homolysis (unwanted reaction, Scheme 8, route a) is favored over the C–ON bond homolysis (Scheme 8, route b) when the aminyl radical generated is strongly stabilized.



Scheme 8 The two possible fragmentations of the C–O–N bond sequence.

4.6.2 Correlations

The analysis of k_d and k_c using a computational approach did not raise strong interest. However, as soon as in 1998, Iwao *et al.*²¹³ showed the suitability of calculations to describe steric and stabilization effects involved in the change in k_c . Some studies reported the correlation between k_d and BDE.¹⁶² Coote *et al.*²¹⁴ showed that computational tools are suitable to develop correlations both with k_d and k_c based on calculated parameters, and are able to describe the effects involved in the C–ON bond homolysis as it was done using empirical Hammett, Taft, and Charton parameters. Both experiments and computational approaches are in good agreement.

4.6.3 Miscellaneous

Calculations appeared to be very valuable to investigate anomeric,¹⁶² anchimeric,¹⁶⁷ remote steric,¹⁷⁰ and salt effects.²⁰¹ Indeed, they highlighted the $n \rightarrow \sigma^*$ interaction of the (N)O lone pair of oxygen to the antibonding orbital of the C–O(COME) bond (Figure 9a), which dramatically increases the strength of the C–ON bond in **63**.¹⁶² Calculations allowed the determination of the difference in k_d between the diastereoisomers of **11** due to the $n \rightarrow \sigma^*$ interaction of the (CO)OR lone pair of oxygen to the antibonding orbital of the C–O(N) bond (Figure 9b).¹⁶⁷ It was also of invaluable help to determine the origin of the effect of the penultimate unit for the diastereoisomers of **45**.²¹⁵

4.6.4 Reaction Pathway

As it is difficult to locate the TS of homolysis, no attempts were made to investigate the TS of the C–ON bond homolysis in alkoxyamines. On the other hand, few investigations on the TS of the cross-coupling reaction and the intermolecular H-transfer reaction were performed.^{216–218} Braslau *et al.*²¹⁶ investigated the cross-coupling reaction of some model reactions using DFT methods but did not find any TS. However, they noted that the angle between the alkyl radical and the nitroxide was around 110–120°, values close to that observed in the final alkoxyamine. A few years later, Kaim and Megiel^{217,218} investigated both the

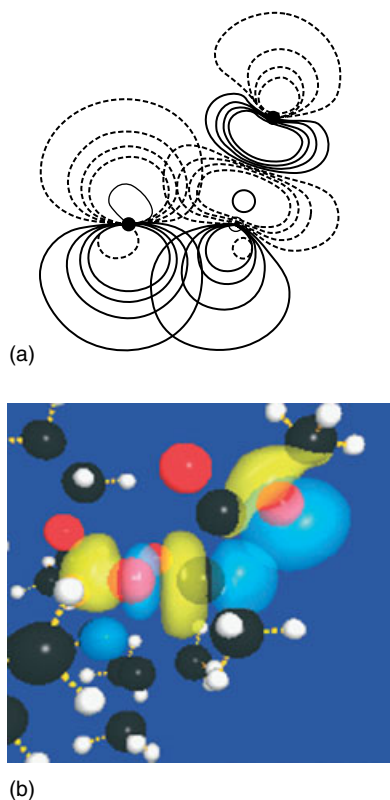


Figure 9 (a) Anomeric effect $n_O \rightarrow \sigma^*_{O-C}$. (b) Anchimeric effect $n_O \rightarrow \sigma^*_{C-ON}$. [(a) Reproduced from Ref. 162. © Wiley-VCH Verlag GmbH & Co. KGaA, 2006. (b) Reproduced from Ref. 167. © Wiley-VCH Verlag GmbH & Co. KGaA, 2006.]

cross-coupling reaction and the H-transfer reaction between TEMPO and homologs of radicals **20** and **64**. Using a lower method, they were able to locate TS for the cross-coupling reaction exhibiting the same features as reported by Braslau *et al.* They were also able to determine TS for the H-transfer reaction, except that the value of the C-H...O(N) angle (around 105°) is much smaller than the one conventionally accepted for intermolecular H-transfer (around 180°).

Nevertheless, these data provide some information about the structure of the activated complex at TS. For the homolysis of the C-ON bond (Figure 10a), a few requirements are expected:

- lengthening of the C-ON bond and shortening of the CO-N bond;

- flattening at the nitrogen and carbon atoms of the CON sequence, that is, changing from sp^3 hybridization to sp^2 hybridization;
- a dihedral $\langle OC \text{ insaturation} \rangle$ angle close to 90° .

These geometrical changes lead to interactions favoring the homolysis such as:

- $n_N \rightarrow \sigma^*_{O-C}$ interaction between the nitrogen lone pair and the antibonding orbital σ^* of the O-C cleaved bond;
- $\sigma_{O-C} \rightarrow \pi^*_{\text{insaturation}}$ interaction between the (N)O-C bonding orbital σ (nascent SOMO of the alkyl radical) and the antibonding orbital π^* of the insaturation bond to the nascent radical center.

Any other interactions occurring may either strengthen or weaken the C-ON bond (*vide supra*). As homolysis and reformation reactions of the C-ON bond share the same TS, for the reformation reaction converse requirements are expected (Figure 10b), namely:

- shortening of the $C \cdots ON$ distance and lengthening of the O-N bond;
- pyramidalization at the nitrogen and carbon atoms of the CON sequence, that is, changing from sp^2 hybridization to sp^3 hybridization.

These geometrical changes lead to interactions favoring the reformation of the C-O bond such as:

- $SOMO_C \rightarrow \pi^*_{O-N}$ interaction between the SOMO of the alkyl radical and the antibonding orbital π^* of the nitroxide, that is, its SOMO.

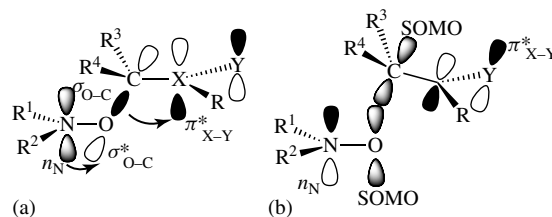


Figure 10 Expected interactions at TS for (a) the C-ON bond homolysis, and (b) for the cross-coupling reaction between nitroxide and alkyl radical.

5 POLYMERIZATION

NMP has been employed for the preparation of a large range of macromolecular architectures (Figure 11) and compositions allowing a fine tuning of their physico-chemical properties.

5.1 Homopolymerization

NMP of styrene and styrene-based monomers such as styrenes para-substituted with F, Cl, Br, CH₃, OCH₃, CF₃, CH₂Cl, 4-acetoxystyrene, 4-*tert*-butoxystyrene, or even *para*-(1-methylcyclohexyloxy)styrene has been successfully achieved.^{219,220} A large number of nitroxides including both cyclic such as **TEMPO**^{179,221–223} and its derivatives and non-cyclic ones such as di-*tert*-butyl-*N*-oxyl (**DBNO**),⁴⁰ **TIPNO**,^{41,142} and **SG1**^{82,142} were tested leading efficiently to precisely controlled polymer chains in terms of molar mass, PDI, and chain-end functionality.

TEMPO^{224–231} and **SG1**-mediated^{232,233} radical polymerizations were also successfully applied to vinylpyridine derivatives.

Owing to their particular high propagation rate constants, the NMP of acrylic esters is only achievable with sterically hindered analogs^{174,222} or with acyclic nitroxides such as **SG1**^{56,229,234} and **TIPNO**^{227,235,236} derivatives. It has to be mentioned that the best results were obtained with the development of the highly labile **SG1**-based alkoxyamines allowing an almost ideal building up of the PRE.⁴⁹

NMP of acrylic esters is now well established and applied with efficacy to a wide range of acrylic esters (*n*-butyl acrylate (BA), *tert*-butyl acrylate, 2-hydroxyethyl acrylate,²³⁷ *N*-acryloylmorpholine,²³⁸ 2-hydroxypropyl acrylate,²³⁹ 1,1,2,2-tetrahydroperfluorodecyl acrylate,

-(acryloyloxy)ethylbenzyltrimethylammonium chloride,²⁴⁰ 2-(dimethylamino)ethyl acrylate,^{241,242} trimethylsilyl propargyl acrylate,²⁴³ etc.) leading to well-controlled molar masses and high livingness.

Acrylonitrile and Acrylic Acid

The controlled homopolymerization initiated by a **TIPNO**-based alkoxyamine showed good control until high-molar masses.⁴¹ A deep investigation on polybutylacrylate-*b*-polyacrylonitrile (PBA-*b*-PAN) copolymer made with **SG1** by NMP showed that the use of PAN macroalkoxyamine to *n*-BA was less efficient than that from PBA macroalkoxyamine to acrylonitrile (AN) suggesting some difficulties to control AN properly in the presence of **SG1**.²⁴⁴

NMP of acrylic acid was performed in 1,4-dioxane solution at 120 °C in the presence of **SG1**-based alkoxyamine. However, the results showed a good control over the polymerization only when moderate molar mass polymers were targeted.^{245,246}

Acrylamide, *N*-Substituted, and *N,N*-Disubstituted Acrylamides

As for the *N*-substituted acrylamides, NMP has been used for the controlled polymerization of *N*-isopropylacrylamide (NIPAAm),²⁴⁷ *tert*-butylacrylamide,²³⁹ *N,N*-dimethylacrylamide (DMAAm),^{232,238,240,248–252} and *N,N*-diethylacrylamide (DEAAm).²³³

Dienes

NMP of butadiene and of isoprene in the presence of **TEMPO** was studied by Georges²⁵³ and Boutevin,^{254,255} respectively. Efficient controlled radical polymerization of butadiene and of isoprene was also demonstrated in the presence of **TIPNO**^{256–258} and more recently on isoprene with both **TEMPO** and **4-oxo-TEMPO 65**.²⁵⁹

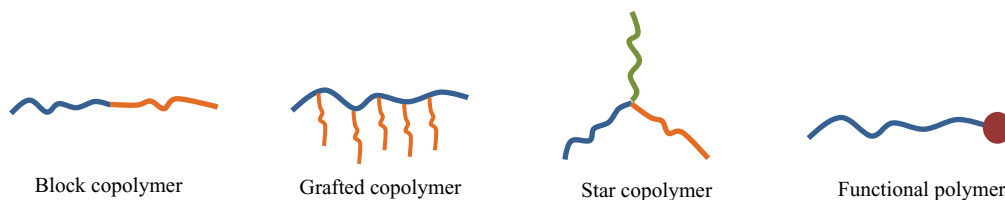


Figure 11 Some examples of the various polymer structures achievable by NMP.

Methacrylic Esters

Polyalkylmethacrylates represent an important class of material covering a broad range of applications. Therefore, many efforts have been focused on the NMP polymerization of alkyl methacrylate and more specifically MMA. A successful NMP of MMA has been a difficult achievement, mainly, owing to two different reasons closely related to the nature of the nitroxide used. For instance, it is assumed that NMP of MMA with **TEMPO** fails because of the occurrence of an undesired hydrogen atom abstraction from the nitroxide onto the propagating radical PMMA chain end to form the corresponding saturated polymer chain end and hydroxylamine.^{85,88,133,260} With **SG1**, the uncontrolled nature of MMA polymerization has been attributed to the too large activation–deactivation equilibrium constant which impedes a good quality of control and livingness.⁸⁶ In the case of high K_{eq} (12), the **SG1** acts as a spectator, therefore, the concentration of propagating alkyl radical is high enough to lead to a significant proportion of irreversible disproportionation reactions resulting in the loss of the control. The irreversible termination reactions mentioned above result directly in an accumulation of the stable **SG1** nitroxide in the sample. Obviously, at a given concentration, the **SG1** slows down dramatically the polymerization of MMA by reversible termination reaction with the propagating radical chains. When the concentration of **SG1** is too high, Charleux and coworkers detected the occurrence of both cross-disproportionation and bimolecular termination in **SG1**-mediated MMA polymerizations.⁸⁷

Up to now, several successful strategies have been developed to control the polymerization of methacrylate. Detrembleur *et al.*⁶⁹ demonstrated that the bulk polymerization of MMA and *tert*-butyl methacrylate (*t*BMA) conducted in the presence of methyl 2-methyl-3-nitro-2-nitrosopropionate (NMMA) was controlled when initiated by AIBN at 60 °C or using a mixture of NO/NO₂ mixtures. It has to be mentioned that this process, based on the *in situ* NMP, is intrinsically complex because several species are formed *in situ* as a result of the addition of both the initiating radicals and the propagating radicals. However, even if the polymerization control was not ideal (increase of the PDI along with increase of conversion), some encouraging results were obtained.

As mentioned earlier in this article, an alternative route consists in the copolymerization of a small percentage of a comonomer (styrene, acrylonitrile (4.4–8.8 mol%) with methacrylate to form not pure PMMA but PMMA-rich copolymers with low PDIs. In this case, it has been demonstrated that the K (12)) was increased positively, thanks to the presence of the comonomer used.^{89,261}

Regarding the control of the homopolymerization of MMA in the presence of nitroxide, the most successful route has been the use of *N*-arylnitroxides. It is thought that these nitroxides allow radical delocalization through the *N*-aryl moiety that could prevent the cross-disproportionation side-reaction, exhibit the proper kinetic parameters, and therefore allowing better control over MMA polymerization. For instance, it has been shown that the use of 2,2-diphenyl-3-phenylimino-2,3-dihydroindol-1-ylloxyl (DPAIO)-based alkoxyamines¹⁰⁶ and more recently *N*-phenyl nitroxide synthesized by *in situ* addition of carbon-centered radicals across the double bond of nitrosobenzene¹⁴⁶ or *N*-phenylalkoxyamine *N*-(1-methyl-(1-(4-nitrophenoxy)carbonyl)ethoxy)-*N*-(1-methyl-(1-(4-nitrophenoxy)carbonyl)ethyl) benzenamine¹⁴⁷ **66** allowed the NMP of MMA up to moderate conversions (50%). Unfortunately, even if some chain extension from the resulting PMMA macroinitiators has been achieved, the control of the polymerization of the second block was poor. This result suggests that the kinetic parameters of the macroalkoxyamines formed during the polymerization are only suitable for the MMA. Therefore, the NMP of methacrylates is still not completely achieved since more investigations are needed to find a nitroxide or a strategy to control efficiently styrenics, acrylate, and methacrylates and therefore to prepare in a convenient way, a wide range of tailor-made block copolymers.

Cyclic Ketene Acetals

Degradable aliphatic polyesters are receiving great attention. In this context, radical ring opening polymerization (ROP) turns out to be a very convenient and appealing technique to prepare such aliphatic polyesters.^{262,263} It has to be mentioned that 2-methylene-1,3-dioxepane was polymerized in the presence of **TEMPO**/di-*tert*-butyl peroxide at 125 °C.²⁶⁴

5.2 Random and Block Copolymerization

Living Random and Gradient Copolymers

Regarding the preparation of random or gradient copolymers, typically the same or very similar polymerization behaviors are observed when using either a conventional radical polymerization, or an NMP technique.^{112,265} The copolymers obtained when using the NMP technique exhibit very close compositions with obviously narrower PDIs.

A very interesting application of copolymerization consists in the control of various methacrylate derivatives^{89, 114–116, 118} using low amounts of comonomer such as styrene or acrylonitrile.²⁶¹

5.3 Polymerizations in Aqueous Dispersed Media

Radical polymerization can be conducted in various dispersed media,^{76,266,267} for example, emulsion, miniemulsion, microemulsion, precipitation, dispersion, and suspension. The continuous phase is usually water, but some examples also report the use of supercritical dioxide (scCO₂).^{268–277}

5.3.1 Aqueous Miniemulsion Polymerization

In miniemulsion system, monomer droplets are converted into polymer particles as the polymerization proceeds, and therefore, the transport of nitroxide or low molecular weight alkoxyamine in between the monomer droplets and the polymer particles in the aqueous phase (as in an *ab initio* emulsion polymerization) is not of any concern. Miniemulsion NMP can be broadly divided into two categories: (i) aqueous phase initiation and (ii) oil phase initiation. In general, miniemulsion polymerization requires the addition of a hydrophobe, such as hexadecane, to suppress Ostwald ripening.^{278,279} Interestingly, a nitroxide-terminated macroinitiator (for instance polystyryl-TEMPO) can be used instead of hexadecane.^{280,281} The addition of a small amount of high-molar mass polymers enhances droplet nucleation and stabilization.²⁸²

Typically, both oil- and water-soluble initiators have been investigated in miniemulsion NMP in the presence of TEMPO and SG1 nitroxides. Bicomponent systems were the first to be applied but improved systems were achieved using SG1-based water-soluble alkoxyamines.⁵⁹

5.3.2 Aqueous Emulsion Polymerization

Implementation of NMP in emulsion has proved to be a significant challenge. The main problems associated to this system were colloidal stability and high control/livingness. Indeed, to obtain successful emulsion NMP, several criteria have to be fulfilled. Typically, emulsion polymerization mainly involves large droplets (<1 μm) of hydrophobic monomer(s) and a large number of monomer-swollen micelles.²⁸³ Successful emulsion NMP implies that the polymerization takes place within small monomer droplets generated via diffusion of the monomer droplets through the aqueous phase. In contrast to miniemulsion, emulsion process requires the use of water-soluble radical initiators. Moreover, in order to ensure good control of the polymerization, the partitioning of nitroxide between the organic and aqueous phases allows the nitroxide concentration in the particles to be sufficiently high.

6 MACROMOLECULAR ADVANCED ARCHITECTURE AND COMPOSITIONS

6.1 Chain-End Functionalized Polymers from NMP

Various examples of α - and ω -functionalized polymers made from NMP have already been reported.²⁸⁴ Usually, α functionalization is obtained through the use of the corresponding functionalized alkoxyamine while ω functionalization is achieved after chemical transformation of the nitroxide moiety attached to the polymer chain end (Figure 12).

It has to be mentioned that the synthesis of functional polymers is the subject of intense research. Indeed a functional polymer exhibits specific properties valuable for the material application or in macromolecular engineering. The easiness of preparation of α,ω -functionalized polymers

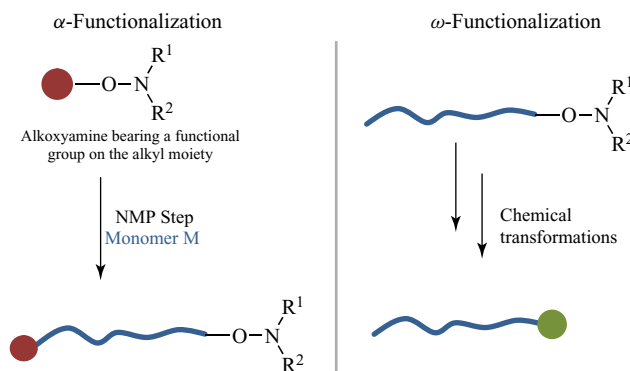


Figure 12 Possible routes for α and ω functionalization.

is strongly related to the polymerization technique used. α -Functionalization of the polymer chains is obtained by using the commercially available or beforehand prepared initiator. ω -Functionalization is by far more difficult to obtain since it usually requires at least one chemical step after the polymerization process.

6.1.1 α -Functional Polymers

A wide range of **TEMPO**, **TIPNO**,^{285–290} or **SG1** alkoxyamines³⁶ bearing a functional group on the alkyl moiety has already been reported. Most of the functionalized alkoxyamines prepared are based on a benzyl chloride moiety and its subsequent chemical transformation. Following this strategy, it has been possible to introduce azido, amino, or alcohol group on the alkyl moiety.^{290,291} Considering a styryl-type derivative as the alkyl moiety, some studies also report the introduction of a functional group at the sp^3 carbon in α position to the carbon linked to the oxygen atom of the nitroxide.^{292–294}

Tordo's group^{49,295} prepared alkoxyamine **12**, commercialized by Arkema under the trademark BlocBuilder MATM.²⁹⁶ The introduction of a carboxylic acid group represented a breakthrough in NMP, both in homogeneous and aqueous dispersed media, thanks to the good solubility of the corresponding sodium salt, for example, in water.⁵⁷ The coupling of this alkoxyamine with alcohols was investigated and it was shown that the combination of high steric hindrance and a high dissociation rate constant prevents

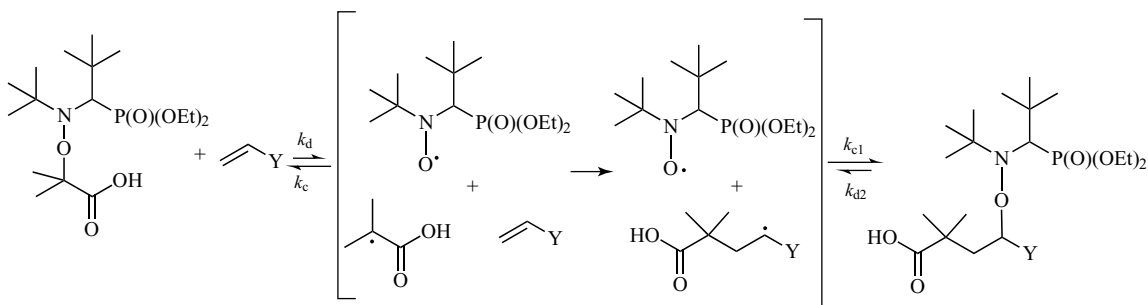
efficient coupling reactions.²⁹⁵ In contrast, the coupling of alkoxyamine **12** with amine-containing compounds was achieved either by preparing the activated ester derivative, **MAMA-NHS 67**,²⁹⁷ or by using a suitable coupling agent, that is, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP).²⁹⁸

A very efficient method for preparing functionalized alkoxyamines was recently proposed and this method relied on the low BDE of **12** to perform quantitative intermolecular radical 1,2-addition onto various olefins (Scheme 9).³⁸ In the case of activated olefins, the challenge consists in avoiding a multiple monomer addition. However, with alkoxyamine **12**, the resulting alkoxyamine after addition bore a less stabilized, bulky secondary radical moiety and to less than the 1-carboxy-1-methyl ethyl radical moiety of the starting alkoxyamine, which prevents further addition.

This reaction was successfully performed at 100 °C in solution with various olefins such as styrene,³⁸ *n*-butyl acrylate,³⁸ 2-hydroxyethyl-acrylate,³⁸ acrylic acid,³⁸ 4-vinyl pyridine,²⁹⁵ styrene sulfonate,²⁹⁵ and *N*-acryloylglucosamine.²⁹⁵ The intermolecular radical 1,2-addition is also useful to prepare di- or triblock copolymers by reacting **12** in the presence of multifunctionalized olefins such as butanediol diacrylate²⁹⁹ or pentaerythritol tri- or tetraacrylate.³⁸

ω -Functional Polymers

The removal or transformation of ω -end-groups of (co)polymers previously made by ATRP and RAFT has often been reported. In contrast, such transformations on ω -end-groups of NMP-made



Scheme 9 Mechanism of the intermolecular radical 1,2-addition.

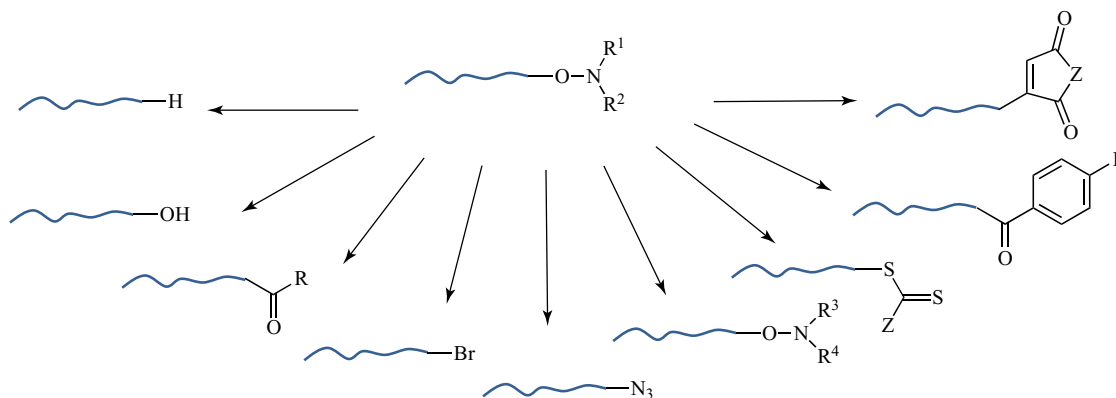


Figure 13 Various functionalized ω -end-groups accessible for NMP polymers.

macromolecules have not been extensively studied. However, some interesting transformations are now accessible (Figure 13).

The removal of the nitroxide moiety under a radical pathway is probably one of the easiest and most efficient transformations of an NMP-made polymer chain. Typically, the reaction consists in heating the macroalkoxyamine in the presence of an hydrogen donor such as a thiol derivative.^{10,158,261,300} Another famous example of one-step transformation is the reduction of a **TEMPO**-based macroalkoxyamine into the corresponding alcohol in the presence of a mixture of Zn/acetic acid¹⁰ or LiAlH₄.³⁰¹ Interestingly, it was also shown that the direct treatment of polymers containing a **TEMPO** end-group with an oxidant such as *meta*-chloroperbenzoic acid (*m*-CPBA), efficiently affords, at room temperature, the corresponding macromolecular chains bearing a ketone as ω -functional group.³⁰¹

O'Bryan and Braslau³⁰² developed a methodology allowing the preparation of ω -end alcohol, ether, or amide chain-end functionalized polymers

from the corresponding **TIPNO**-polystyryl-based macroalkoxyamines. The strategy consists in exploiting the reactivity of secondary benzylic cations toward various reactants, the latter being obtained after single electron oxidation of the **TIPNO**-polystyryl macroalkoxyamine in the presence of ceric ammonium nitrate.

The use of a non-self-polymerizable monomer (maleimide or maleic anhydride) as a radical trap to prevent multiple radical additions has also been reported as an efficient way to remove and functionalize at the same time an ω -**TIPNO**-polymer moiety.³⁰³

Various other radical traps were investigated. For instance, functionalized or nonfunctionalized tetraethylthiuram disulfide³⁰⁴ compounds were used with **TEMPO**-based polystyrene, whereas benzyl enol ether and ethanesulfonylazide were used with **TIPNO**-based polymers.^{305,306} With polystyryl-**SG1**, one can mention the formation, under radical reaction,³⁰⁷ of the corresponding azide using ethanesulfonylazide, of the corresponding

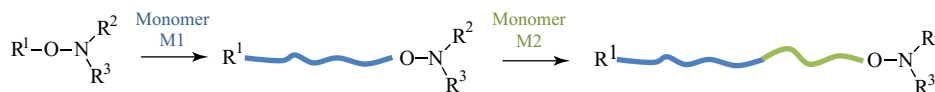


Figure 14 Synthesis of block copolymers from successive NMP steps.

bromide using ethyl 2-bromoisobutyrate, or of the corresponding polystyryl-macro RAFT agents using benzyl dithiobenzoate and benzyl trithiocarbonate.³⁰⁸

Nitroxide exchange was reported as an efficient tool in introducing valuable functional groups in ω position. For instance, Turro *et al.*,³⁰⁹ Scianio,¹⁵⁴ and Hawker *et al.*^{310,311} performed a direct exchange between **TEMPO**-terminated polystyrene and 4-substituted **TEMPO** derivatives. It should be mentioned that in such cases, the functional group is attached to the polymer chain via a nitroxide linkage that is thermolabile and therefore restricted to specific applications. Since the direct treatment of polystyryl-**SG1** with either Zn/AcOH, or LiAlH₄, or *m*-CPBA was not conclusive, Guilleaume *et al.*³⁰⁷ exploited the nitroxide exchange strategy to efficiently replace the **SG1** moiety by a **TEMPO** moiety. This approach combined with the methods already developed by Rizzardo¹⁰ and Pionteck³⁰¹ allowed hydroxyl- and keto-functionalized polymers to be obtained from polystyryl-**SG1** macroalkoxyamine.

6.2 NMP-Made Diblock and Triblock Copolymers

In order to fulfill specific criteria, novel polymeric materials exhibiting increasingly sophisticated properties and performances are desired. It is well established that a desired combination of physical and chemical properties, not achievable via homopolymers, can be obtained by designing tailor-made block, graft-, and other types of copolymers. In this context, intense efforts have been devoted to the development of novel strategies allowing the convenient synthesis of block copolymers. Indeed these materials whose access has been incredibly facilitated, thanks to the progress made in CRP, are obtained by covalent bonding of two or more chemically different polymeric chains that, in most cases, are thermodynamically incompatible, giving rise to a rich variety of microstructures in bulk and

in solution and therefore to a fine tuning of the associated materials properties.

Regarding the NMP technique, the most widely applied synthetic pathway for obtaining a block copolymer is the sequential polymerization of different monomers (Figure 14). After polymerization of the first monomer, the resulting macroinitiator could be either used *in situ* or purified/separated prior to further chain extension, the latter option being usually the most preferred one to achieve purity for the second block. Following this strategy, a wide range of block copolymers has already been prepared.

A number of specific techniques have also been developed for the preparation of block copolymers such as the coupling reaction or the use of a heterofunctional alkoxyamine (Figure 15).

Typically, heterofunctional initiators^{312–314} are designed for the synthesis of block copolymers composed of monomer units that require different polymerization mechanisms. The interest of this approach has been highlighted for the combination of NMP, with anionic polymerization, ROP, ring opening metathesis polymerization (ROMP), or other CRP techniques.

7 APPLICATIONS

The development of controlled radical polymerization techniques has enabled extraordinary opportunities in the synthesis of new materials such as block copolymers³¹⁵ mainly designed for a broad range of applications³¹⁶ specialty such as detergents, cosmetics, health, paints, coatings, adhesives, electronics, transport, or energy. As a consequence, strong efforts are devoted to building up precise correlations between composition/architecture of the micro and macroscopic properties and the development of analytical methodologies for the precise characterization of increasingly sophisticated polymer architectures and compositions.

Among the available controlled radical polymerization methods, NMP is of particular interest because of its tolerance of many functional groups,

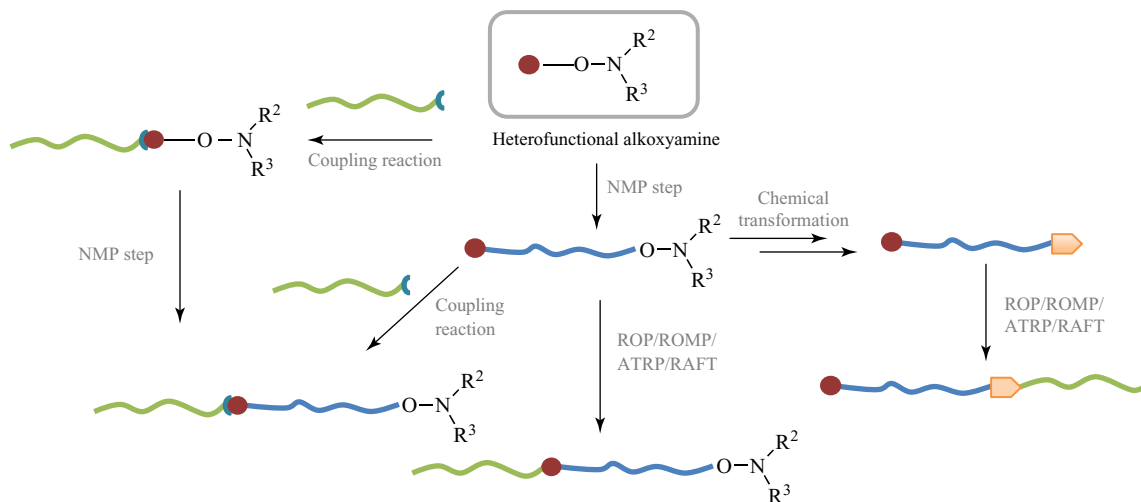


Figure 15 Possible synthesis of block copolymer from a heterofunctional alkoxyamine (with • = functional group such as OH, NH, SH, COOH, ...).

the absence of metal catalysts, as well as coordinating ligands, or sulfur-containing moieties. For instance and as highlighted by Fréchet *et al.*³¹⁷ such consideration is important when synthesizing electroactive from ligand-functionalized monomers, and the presence of catalyst residues might impair device performance. Interestingly, NMP is also well suited for the preparation of peptide–polymer conjugates.^{298, 318–321}

8 PERSPECTIVES

We can state that in only 25 years, the development of the CRP techniques including NMP has changed completely the rules in the field of polymer materials, opening up possibilities in both advanced polymer synthesis and polymer physics that until recently were either difficult or impossible to achieve. Thanks to both a deep investigation on the physico-chemical behaviors of various nitroxide/alkoxyamine^{6,26,45} and the synthesis of more efficient nitroxide/alkoxyamines,^{41,49,69,205,206,322–326} NMP has benefited from significant improvements since Rizzardo's pioneering work.^{10,11} However, NMP still suffers from some drawbacks and further improvements are highly desired. In order to reach this goal, fundamental mechanistic and kinetic studies of

NMP are still necessary. For instance, relationships between the nitroxide structure and the recombination rate constant of the macroradical have to be established. The presence and the effects of undesired side-reactions between the nitroxide and the propagating radical chain such as the hydrogen abstraction reaction need to be carefully investigated as they play a dramatic role on the fate of NMP.⁴⁵ Moreover, although NMP has been often investigated using semiempirical methods, a quantitative approach relying on more recent calculation methods is needed to get deeper insight on the effects of the alkoxyamine structure on each reaction involved for each stage.^{212,214}

On the polymer preparation side, an universal nitroxide/alkoxyamine allowing the preparation of block copolymers composed of styrene, acrylates, and methacrylates monomers (or any 1,1- and monosubstituted monomers) by NMP is still missing. In addition, homo NMP of vinyl acetate³²⁷ and *N*-vinyl pyrrolidone are not yet achieved and also represent exciting challenges that deserves to be investigated with respect to the importance of the applications of the polymeric materials based on poly-vinylacetate or poly-*N*-vinylpyrrolidone.³²⁸

Besides these works based on the NMP process initiated under thermal conditions, we can expect, in the near future, an intensification of studies focused on nitroxide-mediated photopolymerization

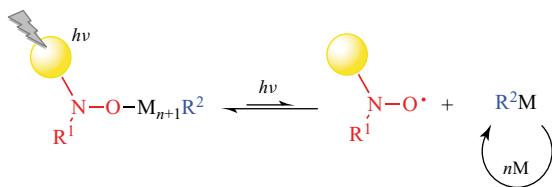


Figure 16 Principle of nitroxide-mediated photopolymerization (with • = chromophore group).

NMP2 (Figure 16). Indeed, Gigmes *et al.*^{329–331} showed very recently that by a careful selection and synthesis of photosensitive alkoxyamines, partial control of photopolymerization of *n*-butyl acrylate was possible. It has to be mentioned that photopolymerization represents a rapidly emerging field in material science, mainly due to the numerous advantages associated to UV irradiation (very fast polymerization <1 s, no volatile organic compounds released, etc.).³³² For coatings, inks, photoresists, or dual-cure systems, the photopolymerization is now recognized as particularly interesting and efficient.³³³ However, the main drawback of the photochemical processes is the lack of control of the polymer properties and the difficulty to prepare block copolymers. Therefore in this context, the development of NMP2 is very appealing and could represent a competitive alternative to photoiniferter technology, introduced by Otsu and Yoshida.^{334,335}

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Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications

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1 INTRODUCTION AND BACKGROUND

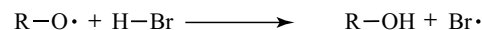
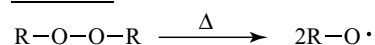
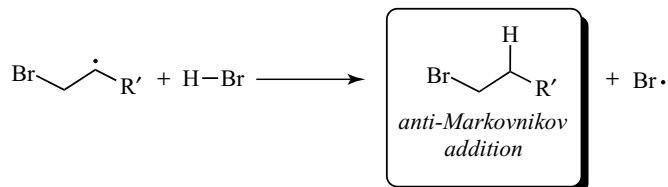
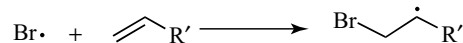
1.1 The Origins of Atom Transfer Radical Addition—"Peroxide Effect"

The origins of atom transfer radical addition (ATRA) can be traced back to 1937 when Kharasch and coworkers discovered "the peroxide effect" which accounted for anti-Markovnikov addition of HBr to unsymmetrical alkenes in the presence of peroxide initiators.¹ The generally accepted mechanism for this reaction involves free-radical intermediates, as outlined in Scheme 1. Soon after the discovery of the "peroxide effect," it was recognized that a variety of substrates such as hydrocarbons, polyhalogenated alkanes, alcohols, ethers, amines, aldehydes, ketones, aliphatic acids, and esters, as well as compounds of sulfur, phosphorous, silicon, tin, and germanium, can be used in the radical addition to alkenes. In particular, Kharasch investigated the addition of polyhalogenated alkanes (CBr₄, CCl₄, CBr₃Cl, and CCl₃Br) to alkenes in the presence of free-radical initiators or light (Scheme 2), in a reaction that is today widely referred to as the *Kharasch addition* or *atom transfer radical addition* (ATRA).^{2–4} Very high yields of the monoadduct were obtained in the case of

simple α -olefins (1-hexene, 1-octene, and 1-decene), but they were significantly low for more reactive monomers such as styrene, methyl acrylate, and methyl methacrylate (MMA). The principal reason for the decreased yield of the monoadduct was radical–radical termination and repeating radical addition to alkene to generate oligomers and polymers. Although radical–radical termination reactions by coupling and disproportionation could be suppressed by decreasing the radical concentration ($R_t \propto [\text{radicals}]^2$), telomerization reactions could not be avoided because of the low chain transfer constant (k_{tr}/k_p , Scheme 2). The research was thus shifted in the direction of finding a means to selectively control the product distribution.

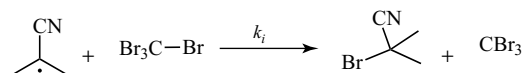
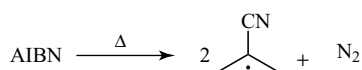
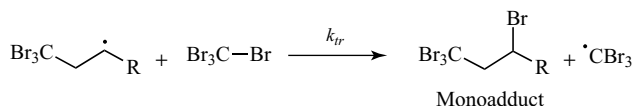
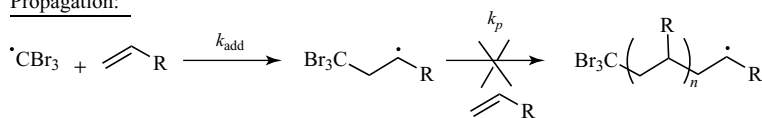
1.2 Fundamentals of Transition-Metal-Catalyzed Atom Transfer Radical Addition (ATRA)

The principal drawback of nontransition-metal-catalyzed (TMC) ATRA was the inability to control the chain transfer constant (k_{tr}/k_p , Scheme 2). This resulted in significantly lower yields of the monoadduct for monomers that are highly active in free-radical polymerization, such as styrene, methyl

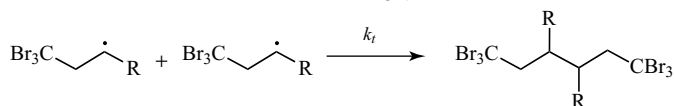
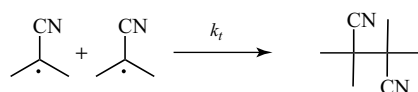
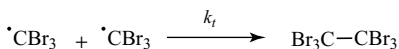
Initiation:Propagation:Termination:

Radical–radical coupling+disproportionation

Scheme 1 Anti-Markovnikov addition of HBr to unsymmetrical alkenes in the presence of peroxide initiators.

Initiation:Propagation:Termination:

Radical–radical coupling+disproportionation



Scheme 2 Kharasch addition of CBr₄ to alkene in the presence of free-radical initiator AIBN.

Table 1 Chain transfer constants for CCl₄ in free-radical polymerization at 60 °C.^{5,6}

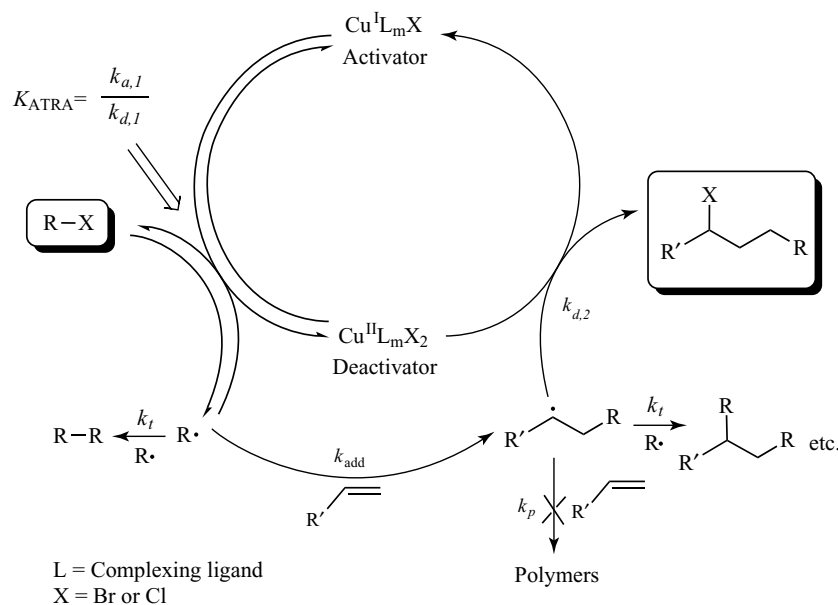
Alkene	$k_{tr}(M^{-1} s^{-1})$	$k_p(M^{-1} s^{-1})$	k_{tr}/k_p
Ethylene	259	79	3.28
1-Hexene	320	87	3.68
Vinyl acetate	2400	8 300	0.289
Acrylonitrile	0.17	3 200	5.31×10^{-5}
Methyl acrylate	0.26	28 000	9.30×10^{-6}
Methyl methacrylate	0.12	821	1.46×10^{-4}
Styrene	1.8	331	5.44×10^{-3}

acrylate, MMA, and acrylonitrile (Table 1). Clearly, a search for a better halogen atom transfer agents was needed.

In 1956, Minisci *et al.* attempted thermal polymerization of acrylonitrile in CCl₄ and CHCl₃ in a steel autoclave and observed considerable amounts of monoadduct (CCl₃–CH₂–CHClCN with CCl₄ and CHCl₂–CH₂–CHClCN with CHCl₃).⁷ These results were unexpected because the chain transfer constants (k_{tr}/k_p) of CCl₄ (Table 1) and CHCl₃ are not high enough to prevent polymerization of acrylonitrile. In 1961, on the grounds of analogous redox haloalkylations of acrylonitrile, the same authors proposed a mechanism in which iron chlorides (arising from corrosion of the autoclave) played a major role in this process by increasing the chain transfer

constant.^{8–13} This reaction marked the beginning of TMC ATRA. Since the seminal report by Minisci *et al.*, a number of species were found to be particularly active in the ATRA process, which included the complexes of Cu, Fe, Ru, and Ni,^{14–19} as well as metal oxides^{20,21} and zero-valent metals such as Cu(0)^{22,23} and Fe(0).^{24–26} Great progress has been made in not just controlling the product selectivity, but also in utilizing a variety of halogenated compounds (alkyl and aryl halides,^{12,27,28} *N*-chloroamines,¹² alkylsulfonyl halides,^{29–34} and polyhalogenated compounds^{29,34–36}). Furthermore, it was also demonstrated that a variety of alkenes (styrene, alkyl acrylates, and acrylonitrile) could be used as the source of reactive unsaturation. Therefore, TMC ATRA became a broadly applicable synthetic tool.^{15–17,37,38}

Based on chemo-, regio-, and stereoselectivity, it is generally accepted that the mechanism of TMC ATRA involves free-radical intermediates.^{12,29,39,40} The proposed mechanism in the case of copper complexes is shown in Scheme 3. Homolytic cleavage of an alkyl halide bond by a copper(I) complex generates a corresponding copper(II) complex and an organic radical ($k_{a,1}$). The radical may terminate (k_t) or add to an alkene (k_{add}) in an inter- or intramolecular fashion or it can abstract the halogen atom from the copper(II) complex and return to the original


Scheme 3 Proposed mechanism for copper-catalyzed ATRA.

dormant alkyl halide species ($k_{d,1}$). If the abstraction of the halogen atom occurs after the first addition to an alkene, the desired monoadduct will be formed ($k_{d,2}$). This step regenerates the corresponding copper(I) complex and therefore completes the catalytic cycle. There are several guidelines that should be followed in order to increase chemoselectivity of the monoadduct. Firstly, the radical concentration must be low in order to suppress radical termination reactions (rate constants of activation [$k_{a,1}$ and $k_{a,2}$] $\ll$ rate constants of deactivation [$k_{d,1}$ and $k_{d,2}$]). Secondly, further activation of the monoadduct should be avoided ($k_{a,1} \gg k_{a,2}$, ideally $k_{a,2} \approx 0$). Lastly, formation of oligomers should be suppressed, indicating that the rate of deactivation ($k_{d,2}[\text{Cu(II)L}_m\text{X}]$) should be much larger than the rate of propagation ($k_p[\text{alkene}]$). Alkyl halides for copper-catalyzed ATRA are typically chosen such that, if addition occurs, then the newly formed radical is much less stabilized than the initial radical and will essentially irreversibly react with a copper(II) complex to form an inactive monoadduct.

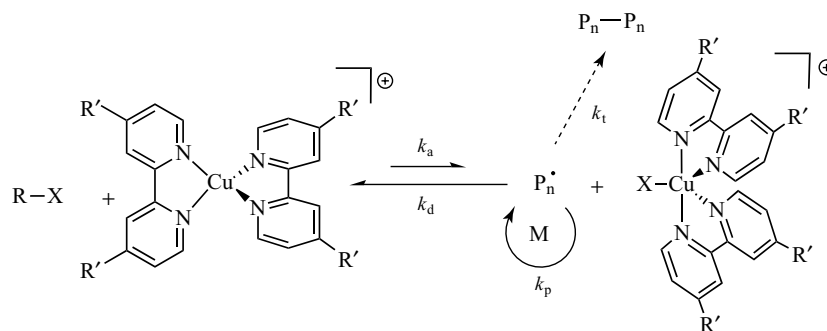
TMC ATRA reactions can also be conducted intramolecularly when alkyl halide and alkene functionalities are part of the same molecule. Intramolecular TMC ATRA or atom transfer radical cyclization (ATRC) is a very attractive synthetic tool because it enables the synthesis of functionalized ring systems that can be used as starting materials for the preparation of complex organic molecules.^{17,38,41–43} Furthermore, the halide functionality in the resulting product can be very beneficial because it can be easily reduced, eliminated, displaced, converted to a Grignard reagent, or, if desired, made to serve as a further radical precursor.³⁹

1.3 Fundamentals of Transition-Metal-Catalyzed Atom Transfer Radical Polymerization (ATRP)

In 1995, a new class of controlled/“living” radical polymerization method was reported by the groups of Wang and Matyjaszewski⁴⁴ and Sawamoto.⁴⁵ This new process, named *atom transfer radical polymerization* (ATRP),⁴⁴ has had a tremendous impact on the synthesis of macromolecules with well-defined compositions, architectures, and functionalities.^{46–63}

Mechanistically, copper-catalyzed ATRP is similar to ATRA with the exception that the reaction conditions are modified in such a way that more than one addition step occurs. As indicated in Scheme 4, a homolytic cleavage of an alkyl halide bond (RX) by a copper(I)/2,2'-bipyridine complex generates an alkyl radical and a corresponding copper(II)/2,2'-bipyridine complex. The newly formed radicals can initiate polymerization by addition across a double bond of a vinyl monomer, propagate, or terminate by either coupling or disproportionation, or be reversibly deactivated by the copper(II) bipyridine complex. In ATRP, formation of radicals is reversible and the stationary radical concentration is low because the equilibrium between the activation (k_a) and deactivation (k_d) processes, $K_{\text{ATRP}} = k_a/k_d$, is strongly shifted to the left-hand side ($k_a \ll k_d$). This in turn minimizes radical termination reactions and enables synthesis of polymers with predetermined molecular weights, narrow molecular weight distributions, and high functionalities.⁴⁷

Copper-catalyzed ATRP is well suited for the preparation of copolymers with controlled



Scheme 4 Proposed mechanism for copper(I)/2,2'-bipyridine-catalyzed ATRP.

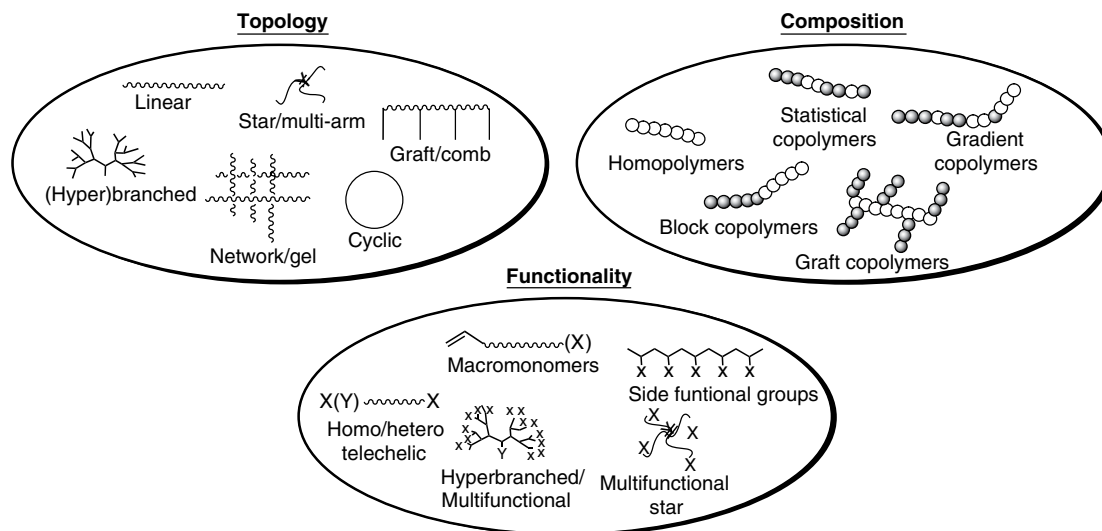


Figure 1 Schematic representation of polymers with controlled topology, composition, and functionality synthesized using copper-catalyzed ATRP. [Reproduced from Ref. 64. With permission of Springer Science + Business Media.]

topologies, including star- and comb-like polymers, as well as branched, hyperbranched, dendritic, network, and cyclic type structures.^{46,47,53,55,56} The basic strategies for producing polymeric materials by ATRP are illustrated in Figure 1 and more specific examples will be discussed later. Similarly, particularly with recent advances in catalyst regeneration techniques, copper-catalyzed ATRA and intramolecular version ATRC are becoming synthetically useful for the construction of small organic molecules (see below).

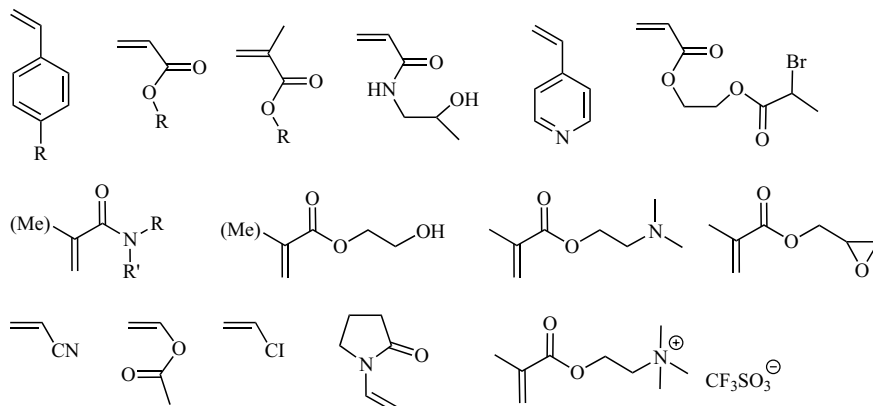
2 BASIC COMPONENTS OF ATRP

Copper-catalyzed ATRP is a multicomponent system, and it is composed of the monomer, an initiator with a transferable (pseudo)halogen, and a copper complex (composed of a copper(I) and copper(II) (pseudo)halide and usually nitrogen-based complexing ligand). Sometimes an additive is used. For a successful ATRP, other factors, such as solvent and temperature, must also be taken into consideration.

2.1 Monomers

Copper-catalyzed ATRP is applicable to a wide range of monomers that contain an α -stabilizing

substituent adjacent to the transferable atom or group (Scheme 5). Such substituents provide efficient reactivation of the dormant chains. The initial range of monomers that could be polymerized by ATRP included styrenes,⁴⁴ (meth)acrylates,⁶⁵ meth(acrylamides),^{66,67} and acrylonitrile.^{68–72} Subsequently, ATRP was expanded to include several functional monomers, including 4-vinylpyridine,^{73–76} monomers containing OH-group, such as 2-hydroxyethyl acrylate (HEA),⁷⁷ 2-hydroxyethyl methacrylate (HEMA),^{78–80} and glycidyl acrylate,^{70,80–82} and precursors of ionic monomers⁸³ including dimethylamino methacrylate (DMAEMA),^{84–86} 2-(trimethylammonium)ethyl methacrylate trifluoromethanesulfonate, and 2-(dimethylammonium)ethyl methacrylate bromide.⁸⁷ Glycidyl acrylate⁸³ has also been copolymerized by ATRP, yielding well-defined polymers containing the reactive glycidyl group which can be used as a precursor for other functional groups.⁸² Furthermore, both neutral and ionic water-soluble monomers can be polymerized in a controlled fashion by ATRP in protic (aqueous) media.⁶² Some representative examples of monomers, including those with polar groups, are shown in Scheme 5. Additionally, simple alkenes have been copolymerized by ATRP with polar monomers.^{88–91} Recent improvements in catalysis and expansion of suitable transferable atoms or groups have also



Scheme 5 Examples of functionalized monomers that can be polymerized by ATRP.

allowed successful ATRP of *N*-vinylpyrrolidone,⁹² vinyl acetate,⁹³ and vinyl chloride.⁹⁴

The major differences between the polymers prepared by ATRP and conventional free-radical polymerization are the additional degrees of control over the architecture, molecular weight, molecular weight distribution, and telechelic functionality. In addition to low molecular weight monomers, a broad range of macromonomers have been copolymerized with low molecular weight monomers to form graft copolymers^{95–97} and even homopolymerized to form bottle-brush polymers.^{98–100}

2.2 Initiators

The polymer growth in ATRP starts by homolytic cleavage of a carbon–halogen bond in an initiator, commonly denoted as R–X (Scheme 4). The initiator in ATRP can be a small molecule, a macromolecule, or a functionalized surface of any topology, with one or more radically transferable atoms or groups.¹⁰¹ The best results have been obtained when X has been either a chlorine or bromine, but iodine has also been successful with acrylates, vinyl acetate, and vinyl chloride.^{93, 102–105}

For a successful ATRP, appropriate combination of the initiator, catalyst, and reaction conditions must be selected. The primary reason is to provide control over the efficiency of the initiation reaction.¹⁰⁶ Shown in Figure 2 is the variation between the activation rate constant (k_a , Scheme 4) and structure of the initiator and transferable atom. Generally, the activation rate constants are highest for

tertiary alkyl halides, followed by secondary ones. Primary alkyl halides typically have very low activation rate constants and are generally poor initiators for ATRP. The activity of alkyl bromides is several times larger than that of the analogous alkyl chlorides in reactions mediated by the same catalyst complex. Additionally, polymers prepared by other polymerization processes can be functionalized at the termini or along the backbone and incorporated into an ATRP as macroinitiators.^{107–110} Such methodology leads to the preparation of well-defined block and graft copolymers comprising a broader range of monomers. Furthermore, the initiator(s) can be attached to any type of polymer, or a solid surface¹¹¹ (particle,¹¹² fiber,¹¹³ porous material,¹¹⁴ etc.), leading to chain growth in several directions. A functional initiator may carry a second noninitiating functionality, in addition to a radically transferable atom or group, to yield hetero-telechelic materials.¹¹⁵ Since ATRP is a radical process, many functional groups can be tolerated in the initiator molecule, including hydroxy, epoxy, amino, amido, cyano, and azido groups. Additionally, several other ones can be incorporated in a protected form.

2.3 Complexing Ligands in Copper-Catalyzed ATRP

The primary role of the complexing ligand in ATRP is to solubilize the copper salts and tune the catalytic activity to optimally conduct a well-controlled polymerization. Neutral nitrogen-based complexing ligands are typically used in copper-catalyzed

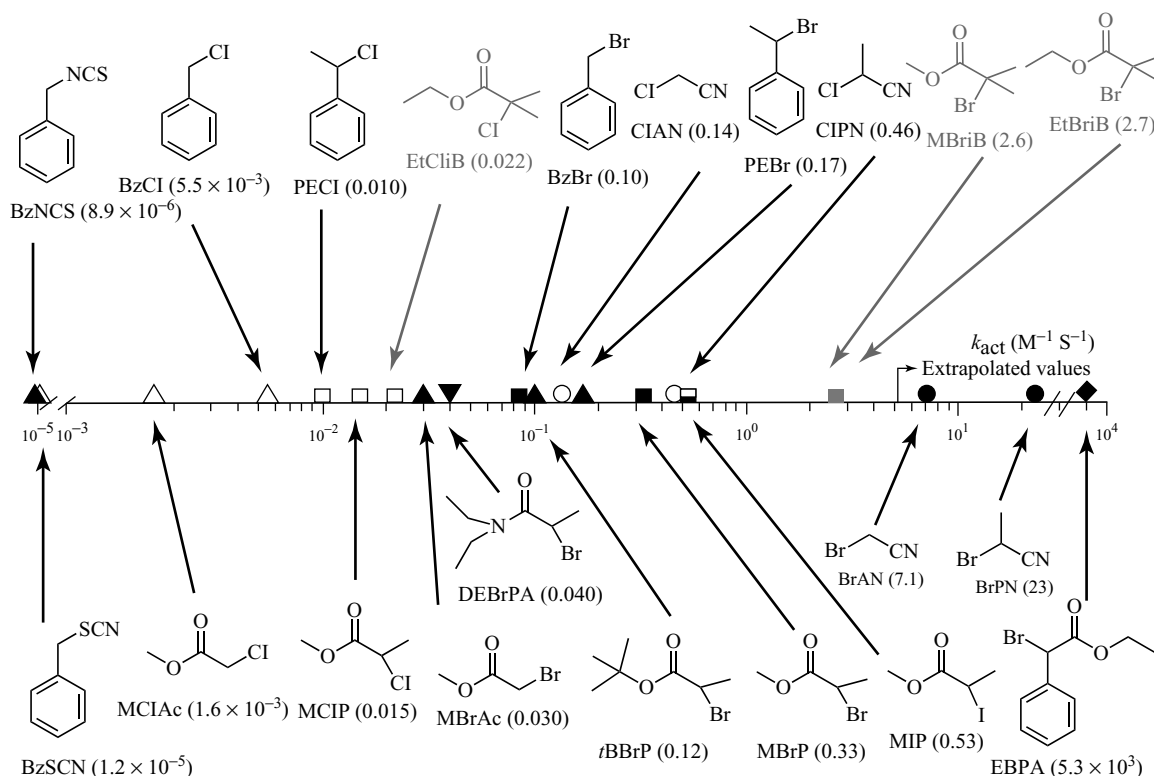


Figure 2 Variation of activation rate constants (k_a in $\text{M}^{-1} \text{s}^{-1}$) based on structure of initiator and transferable atom. [Reproduced with permission from Ref. 116. Copyright 2008 American Chemical Society.]

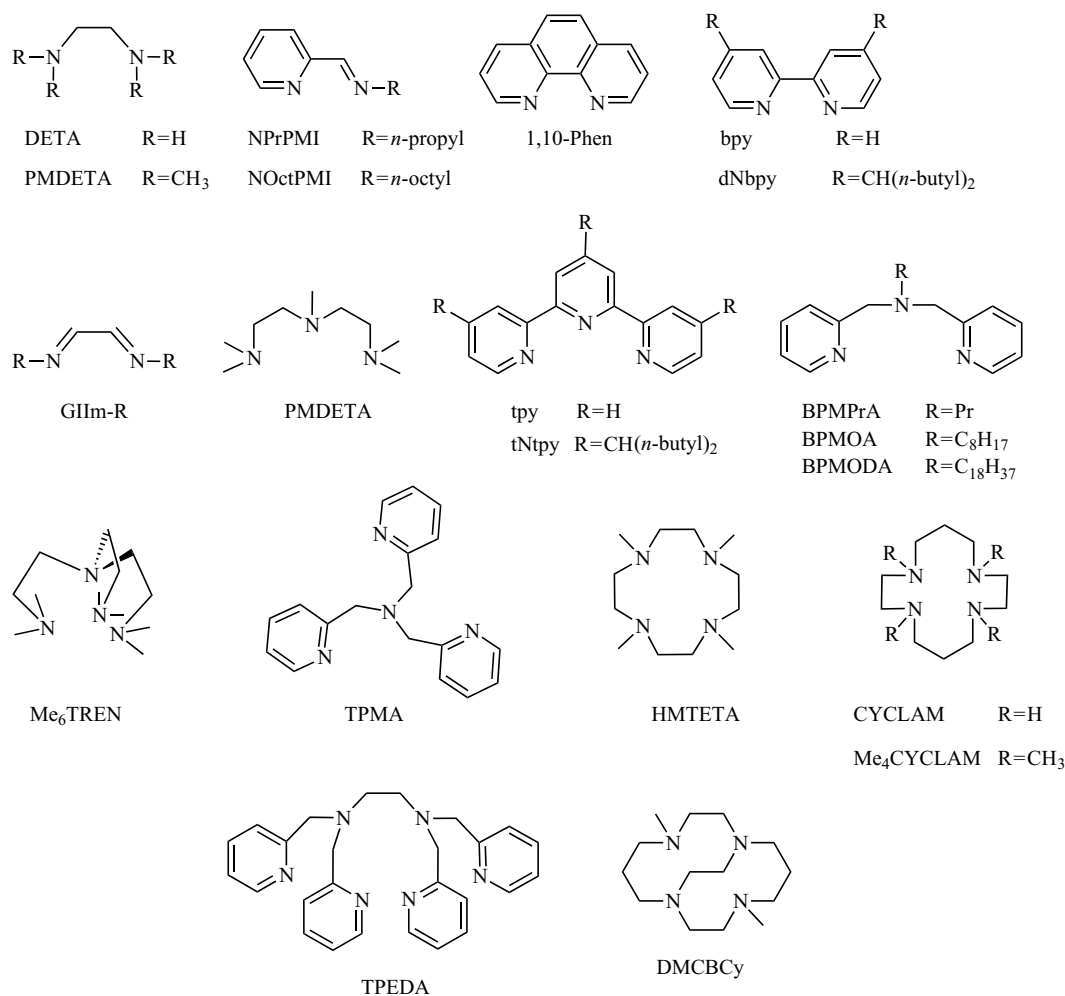
ATRP. Some representative examples are shown in Scheme 6. Depending on the type of amine ligand, the complexes are either neutral (triamines) or ionic (bpy and tetramines).¹¹⁷ The counterions in the case of the ionic complexes are either a bromide anion (Me_4CYCLAM and HMTETA) or the linear Cu(I)Br_2^- (dNbpy), but this also depends strongly on the solvent. No direct correlation was found between the Cu(II)-Br bond length and the deactivation rate constant (k_d , Scheme 6) in ATRP, which suggested that other parameters, such as the entropy for structural reorganization between the copper(I) and copper(II) complexes, might play an important role in determining the overall activity of the catalyst in ATRP.¹¹⁷

As discussed in the kinetic section (see below), the ratio of activity for the copper(I)/ligand and initiators each spans over seven orders of magnitude. The general order of activity of the copper complex formed with specific type of ligand is Cyclam > N4-branched > N4-linear > N3 > N2. Anionic

ligands form stable and active neutral copper complexes, but their deactivation rate constants are low.^{118,119} Because of the high stability of copper(I) and copper(II) complexes with TPMA, this catalyst is particularly suitable for activators regenerated by electron transfer (ARGET) and initiators for continuous activator regeneration (ICAR) ATRP (see below).¹²⁰ More detailed information about structural and mechanistic aspects of copper-catalyzed ATRA and ATRP can be found in several recently published review articles.^{40,59,60,64,121}

2.4 ATRP with Other Transition Metals

ATRP has been successfully mediated by a variety of metals, including those from groups IV (Ti¹²²), VI (Mo^{123–125}), VII (Re¹²⁶), VIII (Fe^{127–130}, Ru^{45,131} and Os^{132,133}), IX (Rh¹³⁴ and Co¹³⁵), X (Ni^{136,137} and Pd¹³⁸), and XI (Cu^{44,57,139}). Copper complexes have been the most thoroughly

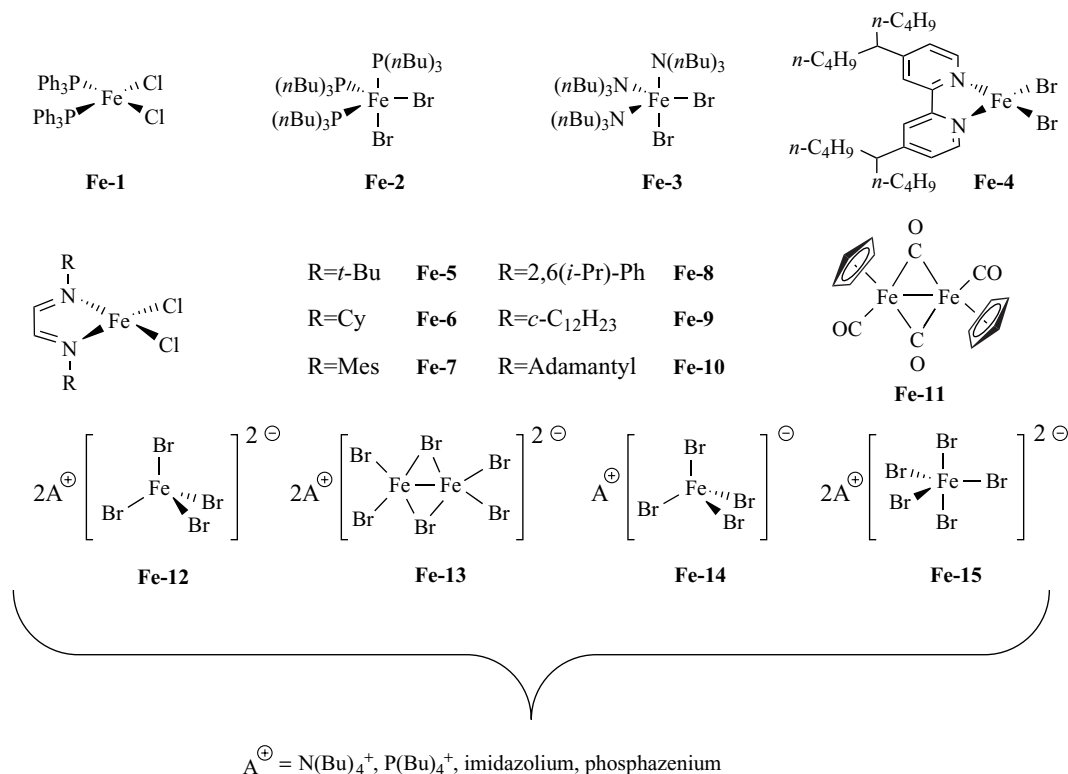


Scheme 6 Examples of neutral nitrogen-based complexing ligands suitable for preparing copper-based catalysts for ATRP.

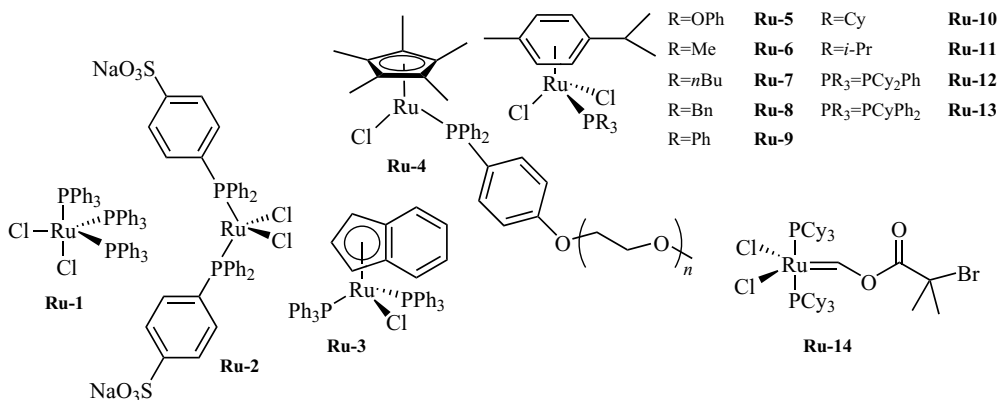
investigated in ATRP and are perhaps the most efficient catalysts based on a broad range of monomers and applicability to diverse reaction media.^{59,64} Some complexes based on Co, Mo, and Os form reversibly organometallic species and usually do not operate via the halogen atom transfer mechanism.¹⁴⁰ However, several complexes based on Fe (Scheme 7) and Ru (Scheme 8) will also be briefly discussed in this section. Iron attracts large attention because it is the least toxic and expensive transition metal. Ruthenium complexes, together with copper, were first used in ATRP and also ATRA reactions.

Iron complexes were first used with monodentate ligands such as phosphines, phosphites,

and amines (**Fe-1** to **Fe-3**). Iron complexes with bidentate ligands such as bipyridines and α -diimines were also successfully applied (**Fe-4** to **Fe-10**). The activity of iron α -diimine complexes depends strongly on the nature of R groups. Generally, with electron-donating substituents well-controlled ATRP was observed. However, with electron-withdrawing groups, oligomerization and transfer were detected.^{141–143} Computational, reactivity, and mechanistic studies indicated that this switch in polymerization mechanism correlates with a change in the metal spin state in the corresponding Fe(III) complexes, with electron-withdrawing groups stabilizing the intermediate-spin state ($S = 3/2$) complexes and



Scheme 7 Examples of iron complexes used in ATRP.



Scheme 8 Examples of ruthenium complexes used in ATRP.

electron-donating groups supporting the high-spin ($S = 5/2$) species.^{144,145} The observed transfer is caused by β -H elimination from a postulated Fe(III)–R intermediate.

Complexes most active in ATRP are based on half-metallocenes (**Fe-11**). They were successful in

polymerization of various monomers. With ethyl 2-iodoisobutyrate as the initiator, they were active even in polymerization of vinyl acetate, presumably by degenerative transfer mechanism.¹⁴⁶

Fe(II)X₂ together with ammonium or phosphonium chloride, bromide, or iodide salts induced

the controlled polymerization of both styrene and methacrylates.¹³⁰ Structures **Fe-12** to **Fe-15** represent iron complexes that may be involved in the polymerization process. This has been the first example of negatively charged ATRP activators. The reverse ATRP initiated by AIBN/FeBr₃/onium salts led to a controlled polymerization of both methyl methacrylate and methyl acrylate. Recently, an improved version of the system using phosphazanium halides with FeBr₂ for the polymerization was reported.¹⁴⁷ The best catalytic performance was found when an equimolar mixture of ligand and metal salt was used, which is indicative of the formation of a 1 : 1 anionic complex.

ATRP of methyl methacrylate catalyzed by FeBr₂ with several ionic liquids bearing various counterions in absence of added organic ligand was also successful.¹⁴⁸ In mixtures with toluene, at 60–70 °C and with EBiB (ethyl 2-bromoisobutyrate) as the initiator, molecular weights increased linearly upon conversion. In the presence of small amounts of FeBr₃, an enhanced control of the polymerization was observed. The ionic liquids containing the transition-metal salts could be efficiently separated from the polymerization media and regenerated. This has been the first example of an ionic liquid acting as a true catalytic species.

Recently, ATRP of methyl methacrylate in polar solvents was successfully catalyzed by FeBr₂ in the absence of any additional ligand.¹⁴⁹ The polymerizations were well controlled in *N*-methylpyrrolidone (NMP), dimethylformamide (DMF), and MeCN. The molecular weights agreed well with the theoretical values and molecular weight distributions were relatively narrow ($M_w/M_n < 1.3$). These solvents might play the role of efficient ligands for FeBr₂. However, there was no control in dimethylsulfoxide (DMSO), which may coordinate to Fe too strongly. The concentration of NMP in methyl methacrylate can be as low as 10% (v/v), leading to a relatively fast polymerization at 60 °C. The conversion reached 55% in 100 min, providing poly(methyl methacrylate) with a molecular weight of $M_n = 5200$ g/mol and $M_w/M_n = 1.21$. Addition of a small amount of FeBr₃ improved the level of control in these systems.

Apart from copper and iron, ruthenium complexes have also been extensively used in ATRP. The first application of Ru-based catalysts in ATRP was with phosphine ligands, as an extension of

similar ATRA systems. Typically, they are soluble in nonpolar media (**Ru-1**) but complexes **Ru-2** have been also used in aqueous media. There are several Ru catalysts with carbon-based ligands, such as half-metallocene (**Ru-3**), which are also water soluble (**Ru-4**). Many Ru-based catalysts require some additives/cocatalysts, such as Al compounds or amines that increase their activity. However, air-stable complexes [RuCl₂(p-cymene)(PR₃)] (**Ru-5** to **Ru-13**) promote the controlled radical polymerization (CRP) of several vinyl monomers without the presence of a cocatalyst.¹³¹ The highest catalytic activity with a narrow molecular weight distribution was obtained with phosphines that were strongly basic and with a well-defined steric bulk ($160^\circ < \theta < 170^\circ$, θ = cone angle of the phosphine). In fact, typical ROMP (ring-opening metathesis polymerization) catalysts are also active in ATRP, and a catalyst (**Ru-14**) successfully mediated three different reactions (ROMP, ATRP, and hydrogenation of olefins) at the same time.^{150,151} This allowed preparation of various block copolymers without need of end group transformation.

2.5 Additives

Additives are sometimes added to ATRP reactions in order to modify the reaction kinetics and control over molecular weight and molecular weight distribution. In addition to various reducing agents, including sugars, phenols, tin(II) compounds, copper(0), or free-radical initiators initially added to activate and reactivate copper(II) complex in activators generated by electron-transfer (AGET), ARGET, and ICAR initiating systems (see below), one can also include the addition of specific agents to modify the equilibrium constant for atom transfer ($K_{\text{ATRP}} = k_a/k_d$), including solvents such as tertiary amines,¹⁵² pyridine,¹⁵³ malonitrile,¹⁵⁴ phenol,¹⁵⁵ antioxidants,¹⁵⁶ water,¹⁵⁷ or inorganic halides.⁸⁷

3 INITIATING ATRP

A successful ATRP process should meet several requirements. Firstly, the initiator should be consumed in the early stages of polymerization and

generate propagating chains leading to polymers with degrees of polymerization (DPs) predetermined by the ratio of concentrations of the converted monomer (M) to the introduced initiator (I), $DP = \Delta[M]/[I]_0$. Secondly, the number of monomer molecules added during one activation step should be small, resulting in polymers with low polydispersity index ($PDI = M_w/M_n$). Finally, the contribution of chain-breaking reactions, such as transfer and termination, should be negligible, enabling the synthesis of polymers with high degrees of end functionality.

According to Scheme 6, neglecting the termination reactions due to the persistent radical effect and using a fast equilibrium approximation, the rate law for ATRP can be derived as follows:

$$-\frac{d[M]}{dt} = k_p[M][P^*] = \frac{k_p K_{ATRP}[M][PX][Cu(I)]}{[X-Cu(II)]} \quad (1)$$

where $K_{ATRP} = k_a/k_d$. According to (1), the polymerization rate in ATRP depends on the equilibrium constant for ATRP (K_{ATRP}), concentrations of the dormant species [PX] and monomer [M], propagation rate constant of monomer (k_p), and the ratio of the concentrations of activator [Cu(I)] and deactivator [X-Cu(II)]. On the other hand, the molecular weight distribution or PDI in ATRP depends on the propagation rate constant (k_p), deactivation rate constant (k_d), monomer conversion (p), and the concentrations of dormant species, monomer, and deactivator [X-Cu(II)] according to (2):

$$\frac{M_w}{M_n} = 1 + \left(\frac{[PX]k_p}{k_d[X-Cu(II)]} \right) \left(\frac{2}{p} - 1 \right) \quad (2)$$

Shown in Figure 3a is a typical linear variation of conversion with time in semilogarithmic coordinates observed in metal-mediated ATRP. The plot indicates that there is a constant concentration of active species in the polymerization and first-order kinetics with respect to monomer. Furthermore, a plot of polymer molecular weight versus conversion is linear, indicating constant number of polymer chains (Figure 3b). Also, the molecular weight distribution (M_w/M_n) or PDI typically decreases with conversion, and in a well-controlled process it approaches the value that is usually less than 1.10 (Figure 3c).⁵⁷

There are presently several different ways to set up ATRP equilibrium shown above in Scheme 4, and they are discussed in detail below.

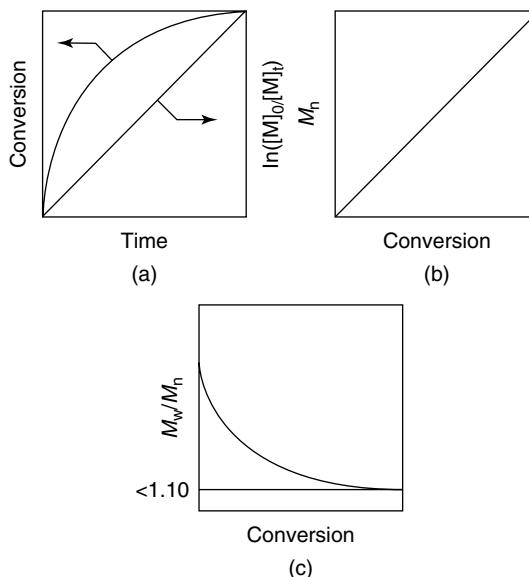
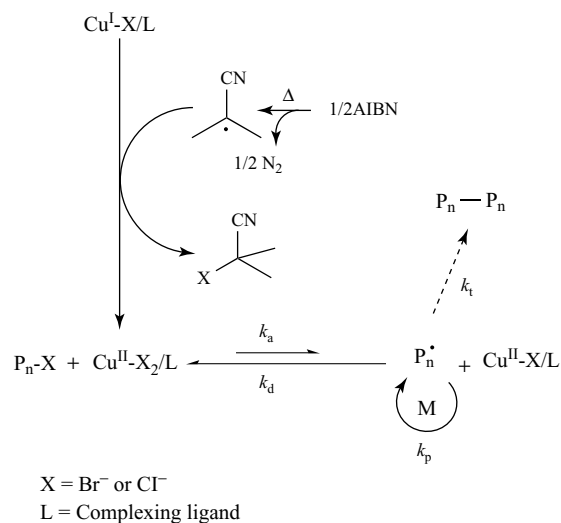


Figure 3 Typical kinetic features of copper-catalyzed ATRP. [Ref. 120 - Reproduced by permission of The Royal Society of Chemistry, 2008.]

3.1 Reverse ATRP

In 1995, it was established that ATRP equilibrium can be approached from both sides. A standard or “normal” ATRP process starts with an initiator and a transition-metal complex in the lower oxidation state.^{44,65} This combination can sometimes present a problem, specially if highly active complexes are used that can be easily oxidized if traces of oxygen are present in the reaction mixture. However, the spontaneous oxidation can also increase the efficiency of initiation from RX because radical termination reactions required to form the persistent radical or transition-metal complex in the higher oxidation state can be avoided or reduced.¹⁵⁸

In the initial example of reverse ATRP process,⁶⁵ the reduction of the deactivator (copper(II) complex) by the radicals generated from thermal decomposition of conventional free-radical initiators, such as 2,2'-azobis(isobutyronitrile) (AIBN)¹⁵⁹ or benzoyl peroxide (BPO),¹⁵⁹ was used to regenerate both the activator (copper(I) complex) and ATRP initiator. The proposed mechanism is shown in Scheme 9. Free radicals that are initially present in the system can also initiate polymerization; however, growing polymer chains are rapidly deactivated by the copper(II) complex to form dormant chains and



Scheme 9 Proposed mechanism for reverse ATRP.

copper(I). Thereafter, the reaction proceeds as normal ATRP. In another variation of this process, copper(0) metal can also be used as a reducing agent.^{160–162} One of the main advantages of reverse ATRP is the ability to start the reaction with oxidatively stable copper(II) complex, which allows a simple experimental setup and eliminates problems associated with oxidation of highly active copper(I) complexes.

3.2 Simultaneous Reverse and Normal Initiation

An improved reverse ATRP was developed to take advantage of the ability to use more active or readily oxidized complexes.^{163,164} This procedure was named simultaneous reverse and normal initiation (SR&NI) because the activator and a small fraction of initiating chains were formed in a “reverse” ATRP reaction, while the majority of the growing polymer chains were initiated from the added normal ATRP initiator molecule.

3.3 Activators Generated by Electron Transfer ATRP

The limitation of normal and simultaneous reverse initiation in copper-mediated ATRP is evident in

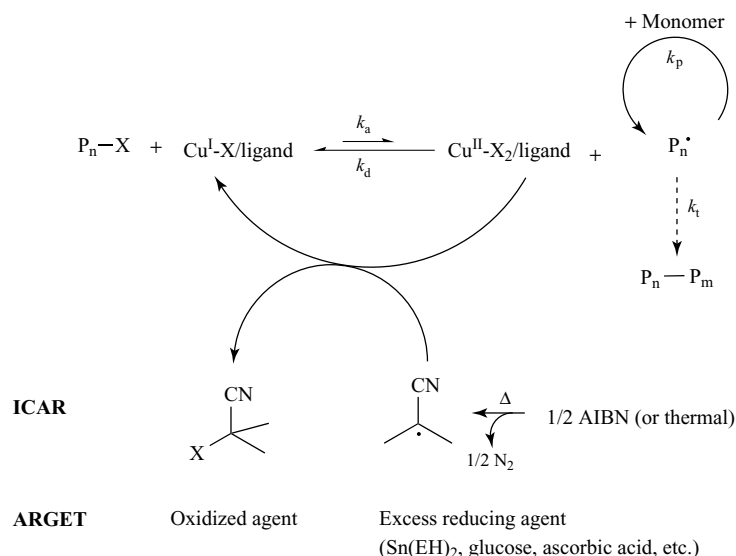
the inability of these techniques to produce clean block copolymers. In AGET ATRP, stoichiometric amounts of the reducing agents are added to the reaction mixture containing alkyl halide, monomer, and the air-stable deactivator (X-Cu(II)) to regenerate the activator (Cu(I)). After the regeneration of the activator (Cu(I)), the polymerization kinetics resembles that of conventional ATRP. AGET ATRP utilizes reducing agents that are unable to initiate new polymer chains, such as zero-valent copper, tin(II) 2-ethylhexanoate, ascorbic acid, or triethylamine.^{62,160,161,165,166} This technique has been shown to be particularly useful in aqueous and mini emulsion systems.^{165,167–169}

3.4 Activators Regenerated by Electron Transfer ATRP

An ATRP catalyst that is sufficiently stable and active can be used at very low concentrations. However, it is very important to realize that the lower oxidation state of the catalyst (the Cu(I) complex in the case of copper-mediated ATRP) is constantly being converted to a higher oxidation state complex (X-Cu(II)) as a result of unavoidable radical termination reactions. Therefore, the deactivator (X-Cu(II)) will accumulate in the system as the reaction proceeds. The amount of lost Cu(I) complex due to termination is equal to the amount of terminated chains, as shown by (3).

$$\begin{aligned}
 -\Delta[\text{Cu(I)L}_m] &= \Delta[\text{X-Cu(II)L}_m] \\
 &= \Delta[\text{P}_{\text{dead}}] = k_t[\text{P}^{\bullet}]^2 t \quad (3)
 \end{aligned}$$

Furthermore, the accumulation of the deactivator (X-Cu(II)) results in the slowing down of the polymerization rate, which in turn limits high monomer conversions. ARGET ATRP is similar to AGET ATRP, with the exception that it utilizes much smaller concentrations of the activator (Cu(I)) and consequently large excess of the reducing agent.^{170–172} As a result, copper(II), which accumulates as a persistent radical during ATRP, is continuously reduced to the corresponding copper(I) complex. Copper(I) complex is needed to homolytically cleave the alkyl halide bond (R-X). As indicated in (1), the rate of monomer consumption in ATRP depends on the absolute ratio of the concentrations of the activator (Cu(I)) and deactivator



Scheme 10 Proposed mechanism for regeneration of copper(I) complex in ARGET and ICAR ATRP.

(X–Cu(II)). Therefore, the absolute amount of copper catalyst in ATRP can be decreased under normal ATRP conditions without affecting the rate of polymerization. In ARGET ATRP, the presence of a large excess of the reducing agent ($Sn(EH)_2$, glucose, or ascorbic acid) enables the polymerization to be conducted using very small amounts of copper catalysts (Scheme 10). Furthermore, the excess of reducing agent can also be used to consume oxygen and other inhibitors from the reaction mixture and eliminate deoxygenation step. Apart from homo- and copolymerizations, this process can also be applied to grafting from various surfaces.¹⁷³

3.5 Initiators for Continuous Activator Regeneration

As discussed earlier, radical termination reactions lead to the irreversible accumulation of persistent radical or deactivator (X–Cu(II) complex) under typical ATRP conditions. In other words, if the initial catalyst concentration is too low, all of the activator will eventually be consumed as a persistent radical and polymerization will only reach limited conversions. A new technique known as *initiators for continuous activator regeneration* in ATRP can be used to both scavenge oxidants and also decrease the amount of catalyst.¹⁷⁴ In

ICAR ATRP, free radicals are slowly and continuously generated by conventional radical initiators (e.g., AIBN) throughout the polymerization to constantly reduce the copper(II) complex that accumulates as a persistent radical (Scheme 10). With this technique, controlled synthesis of polystyrene and poly(meth)acrylates ($M_w/M_n < 1.2$) can be conducted with catalyst concentrations between 5 and 50 ppm levels, at which removal or recycling of the catalyst would be unnecessary for many applications. The reaction is typically driven to completion with low concentrations of added standard free-radical initiators. Computer simulations confirmed that the rate of polymerization in ICAR ATRP is governed by the rate of free-radical initiator decomposition, while the degree of control, the rate of deactivation, and molecular weight distribution are controlled by K_{ATRP} , as in ATRP.¹⁷⁴ This method of catalyst regeneration has also been utilized with great success in mechanistically similar ATRA and ATRC.^{39,40,120,175–181}

4 ATRP THERMODYNAMICS AND KINETICS

Mechanistically, ATRP is a complex process based on several elementary reactions. Similarly to conventional free-radical polymerization, elementary reactions in ATRP consist of initiation,

propagation, and termination, which are systematically evaluated using pulse laser polymerization techniques and electron paramagnetic resonance (EPR) measurements.^{6,182} Perhaps, the most important reaction parameters in ATRP are activation (k_a) and deactivation (k_d) rate constants, and consequently equilibrium constant for atom transfer ($K_{\text{ATRP}} = k_a/k_d$). They strongly depend on the structure of alkyl halide, monomer, solvent, temperature, and, more importantly, the copper complex. Systematic evaluation of K_{ATRP} , k_a , and k_d is crucial in further understanding of the ATRP mechanism and can provide information about the nature and reactivity of active intermediates, as well as factors needed to design more active catalysts that can be used in smaller concentrations and also polymerize currently inactive monomers. The following paragraphs will outline the strategies in mechanistic understanding of ATRA and ATRP reactions.

4.1 Equilibrium Constants in ATRP

The equilibrium constant for ATRP ($K_{\text{ATRP}} = k_a/k_d$) provides critical information about the position of dynamic equilibrium between dormant and active species during polymerization (Scheme 4). The value of K_{ATRP} can be easily accessed from the polymerization kinetics using the $\ln([M]_0/[M]_t)$ versus t plots with a slope $K_{\text{ATRP}}k_p[\text{RX}][\text{Cu(I)}]/[\text{Cu(II)}]$. If sufficient initial excess of Cu(II) species is used, then its concentration, as well as that of the other reagents, does not change, and K_{ATRP} value can be determined by knowing k_p . Alternatively, K_{ATRP} can be obtained from model studies using modified analytical solution of the persistent radical effect,¹⁸³ originally developed by Fischer^{184–186} and Goto and Fukuda.¹⁸⁷

Values of K_{ATRP} strongly depend on the complexing ligand, halogen, alkyl group, as well as the solvent and the temperature.

4.2 Activation Rate Constants in ATRP

It is not possible to determine from K_{ATRP} alone whether the polymerization will be controlled; fast activation and, more importantly, fast deactivation are required to achieve good control

over polymer molecular weights and molecular weight distributions. Therefore, precise measurements of the activation (k_a) and deactivation (k_d) rate constants should be used for correlation with catalyst, alkyl halide, and monomer structures.

Activation rate constants (k_a) in ATRP/ATRA are typically determined from model studies in which copper(I) complex is reacted with alkyl halide in the presence of radical trapping agents such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO, see **Physical Properties of Thiazyl Radicals Toward Conductive and Magnetic Materials and Nitroxide-Mediated Polymerization and its Applications**).^{188–190} Rates are determined by monitoring the rate of disappearance of alkyl halide in the presence of a large excess of the activator (Cu(I)X/L) and TEMPO. Under such pseudo-first-order conditions, the activation rate constant can be calculated from $\ln([RX]_0/[RX]_t)$ versus t plots (slope = $-k_a[\text{Cu(I)C/L}]_0 t$). The activation rate constants are very dependent on the structures of the complexing ligand, initiator, and monomer. In a recent study of a variety of copper(I) complexes with nitrogen-based ligands, values of k_a were found to span more than six orders of magnitude.¹⁹¹ Representative examples are shown in Figure 4. Generally, the activation rate constant in ATRP/ATRA will depend on the topology of the complexing ligand (cyclic $\sim$ linear $<$ branched), nature of the N-ligand (aryl amine $<$ aryl imine $<$ alkyl amine $\sim$ pyridine), steric bulk around the metal center, and the linking unit between the nitrogen atoms ($\text{C4} \ll \text{C3} < \text{C2}$) or the “bite” angle. Compounds that contain halogen atoms activated by α -carbonyl, phenyl, vinyl, or cyano groups make efficient ATRP initiators (Figure 2). The reactivity of these initiators can be correlated with bond dissociation energy (BDE).¹⁹² The activation rate constant in ATRP (k_a) generally depends on (i) the degree of initiator substitution (primary $<$ secondary $<$ tertiary), (ii) the leaving atom/group ($\text{Cl} < \text{Br} < \text{I}$), and (iii) radical stabilizing groups ($-\text{Ph}-\text{C}(\text{O})\text{OR} \ll \text{CN}^-$). Representative examples are given in Figure 5. It was recently shown that the penultimate monomer unit can also have a strong effect on k_a .^{193,194} For example, k_a for dimeric alkyl halide H-MMA-MA-Br is approximately five times higher than for H-MA-MA-Br. This can be attributed to the back-strain effect. Furthermore, the rate of activation of a dormant chain end with an

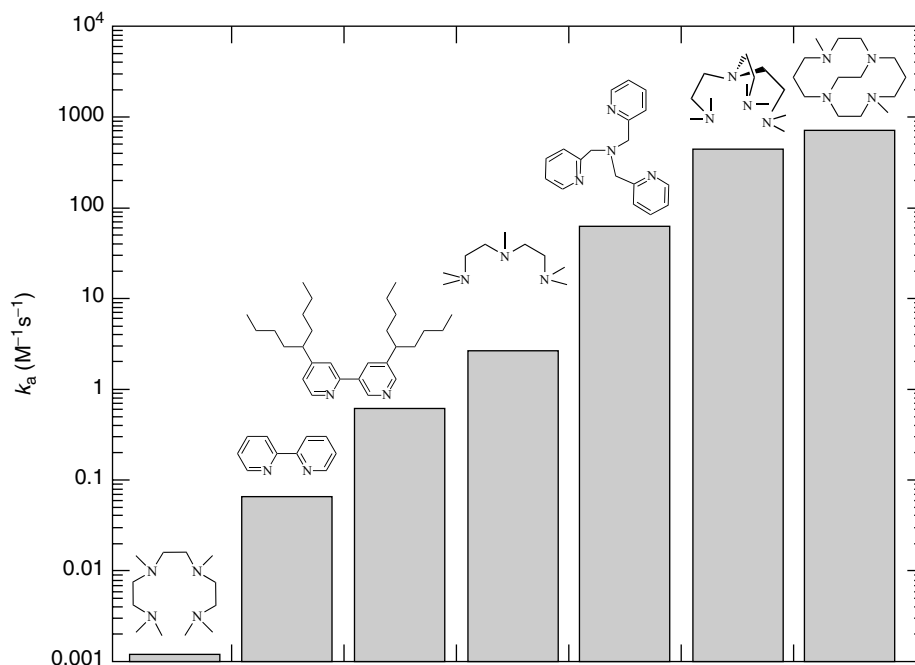


Figure 4 Rate constant of activation (k_a in $\text{M}^{-1} \text{s}^{-1}$) for various ligands with ethyl 2-bromoisobutyrate (EBriB) in the presence of Cu(I)Br in CH_3CN at 35°C .¹⁹¹ [Reproduced from Ref. 64. With permission of Springer Science + Business Media.]

MMA–Br terminal unit is approximately 20 times higher than with a MA terminal unit containing the same penultimate unit. This effect is induced by the formation of the thermodynamically more stable 3° radical when compared to the less stable 2° radical. Lastly, the combined effects of back-strain and radical stability result in a ~ 100 -fold increase of k_a for H–MMA–MMA–Br.

Other investigations include the effect of solvent, counterion, temperature, ligand/catalyst ratio, presence of monomer, and copper(II) complexes on the activation rate constant.^{195–202}

4.3 Deactivation Rate Constants in ATRP

Deactivation rate constants (k_d) have been much less studied in ATRP. The principal reason is the lack of experimental techniques for measuring the relatively fast deactivation process. One of the methods includes the clock reaction (see **Radical Kinetics and Clocks**) in which the generated radicals are simultaneously trapped with TEMPO and the deactivator $\text{Cu(II)X}_2/\text{L}$

Table 2 Deactivation rate constants (k_d) for 1-phenylethyl radicals measured under various conditions at 75°C .¹⁸⁹

Complex	Solvent	k_d ($\text{M}^{-1} \text{s}^{-1}$)
$\text{Cu(II)Br}_2/\text{dNbpy}$	CH_3CN	2.5×10^7
$\text{Cu(II)Br}_2/\text{PMDETA}$	CH_3CN	6.1×10^7
$\text{Cu(II)Br}_2/\text{Me}_6\text{TREN}$	CH_3CN	1.4×10^7
$\text{Cu}^{\text{II}}\text{Br}_2/2\text{dNbpy}$	Ethyl acetate	2.4×10^8
$\text{Cu(II)Cl}_2/2\text{dNbpy}$	CH_3CN	4.3×10^6

complex (Scheme 11).¹⁸⁹ Results for 1-phenylethyl radicals generated by thermal decomposition of 1-(*N,N*-(2-methylpropyl-1)(1-deithylphosphono-2,2-dimethyl-propyl-1)-*N*-oxyl)-1-phenylethane (PESG1) alkoxyamine are summarized in Table 2. In the deactivation process, the $\text{Cu(II)Br}_2/\text{dNbpy}$ complex was more active in ethyl acetate than in acetonitrile. Deactivation was also slower with Cu(II)Cl_2 than Cu(II)Br_2 complexes.

Furthermore, $\text{Cu(II)Br}_2/\text{dNbpy}$ complex appeared to have higher activity than either $\text{Cu(II)Br}_2/\text{PMDETA}$ or $\text{Cu(II)Br}_2/\text{Me}_6\text{TREN}$.

Additionally, deactivation rate constants (k_d) for more active catalysts such as $\text{Cu(I)X}/\text{Me}_4\text{CYCLAM}$

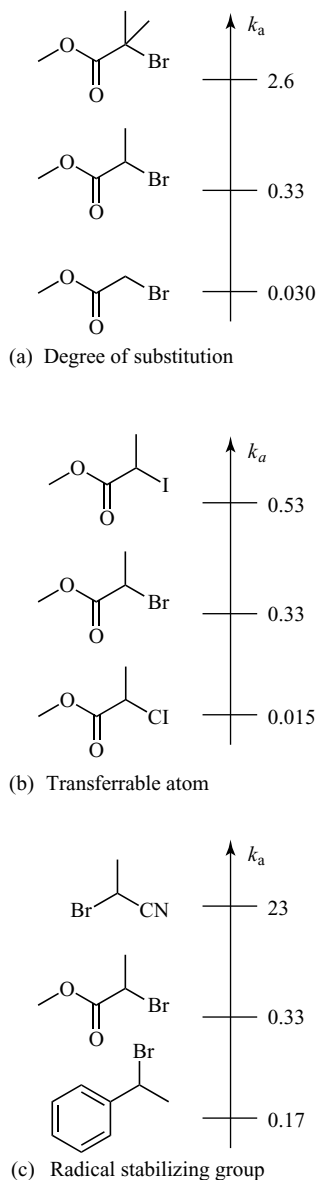


Figure 5 Values of k_a ($\text{M}^{-1} \text{s}^{-1}$) for various initiators with Cu(I)X/PMDETA in CH_3CN at 35°C .¹⁹³

have been estimated from the initial degree of polymerization without reactivation, end functionality, and molecular weight distributions.^{200,203,204}

With recent advances in the determination of the equilibrium constant for atom transfer ($K_{\text{ATRP}} = k_a/k_d$), deactivation rate constants ($k_d = k_a/K_{\text{ATRP}}$) can now be easily obtained from readily accessible activation rate constants (k_a).¹⁸³ Figure 6a shows the

correlation of activation (k_a) and deactivation (k_d) rate constants with equilibrium constant (K_{ATRP}) for various Cu(I)Br/L complexes with EBrIB at 22°C in CH_3CN . The k_a values were extrapolated from those at 35°C .^{191,195} Generally, the equilibrium constant increases as a consequence of an increase in k_a accompanied by a decrease in k_d . Figure 6b indicates the trend with various initiators in the presence of Cu(I)/TPMA catalyst under identical reaction conditions. As is evident, the more reactive dormant species generate less reactive radicals (lower k_d); however, k_d is generally less dependent on K_{ATRP} for initiators than for complexing ligands.

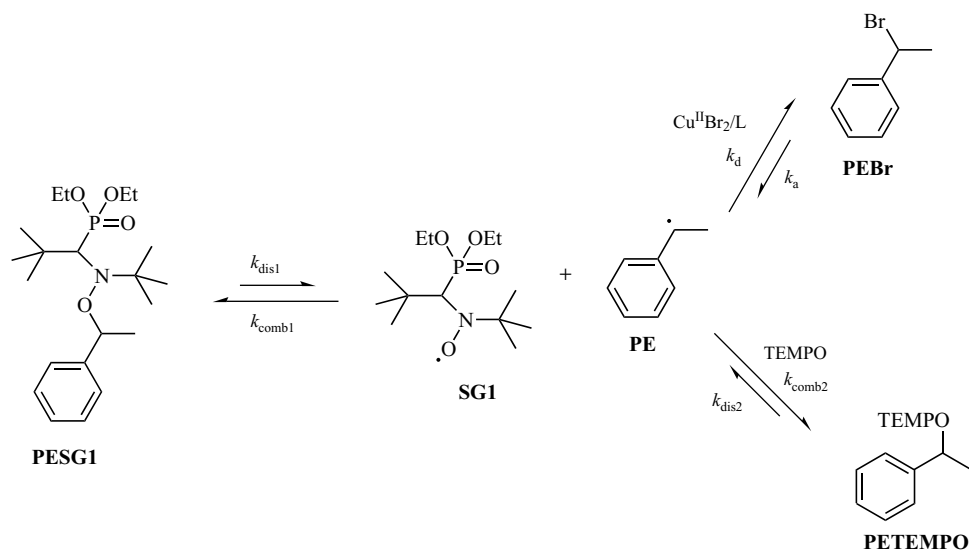
4.4 Correlating Redox Potential with Equilibrium Constant for Atom Transfer

One approach to developing a greater understanding of the overall ATRP equilibrium is to examine the reactions that formally contribute to it. The equilibrium constant for atom transfer ($K_{\text{ATRP}} = k_a/k_d$) can be expressed as a combination of several contributing reversible reactions (Scheme 12)^{59,60}:

1. Electron transfer or oxidation of metal complex (K_{ET});
2. Electron affinity or reduction of halide radical to halide anion (K_{EA});
3. Bond homolysis of alkyl halide (K_{BH});
4. "Halophilicity" or association of halide anion to metal complex (K_{HALIDO}).

Generally, these equilibrium constants are very solvent-dependent. In particular, the values of K_{EA} are expected to be relatively high in protic solvents because halide anions can be stabilized through solvation in such media.²⁰⁵ Also, on the other hand, K_{HALIDO} values will be likewise affected with changes in solvent polarity.⁶⁰ Low values of K_{HALIDO} in polar and protic media have direct implications on the degree of polymerization control because of the decreased amounts of deactivator ($\text{Mt}^{n+1}\text{X/L}$), as a result of halide anion dissociation from the metal center.

Catalyst activity (in terms of K_{ATRP}) is also intrinsically dependent on the redox potential of the metal complex. The latter, in turn, depends on the relative stability of the higher (Mt^{n+1}/L) and lower (Mt^n/L) oxidation states. For the case of



Scheme 11 Model reactions for deactivation rate constant measurements.

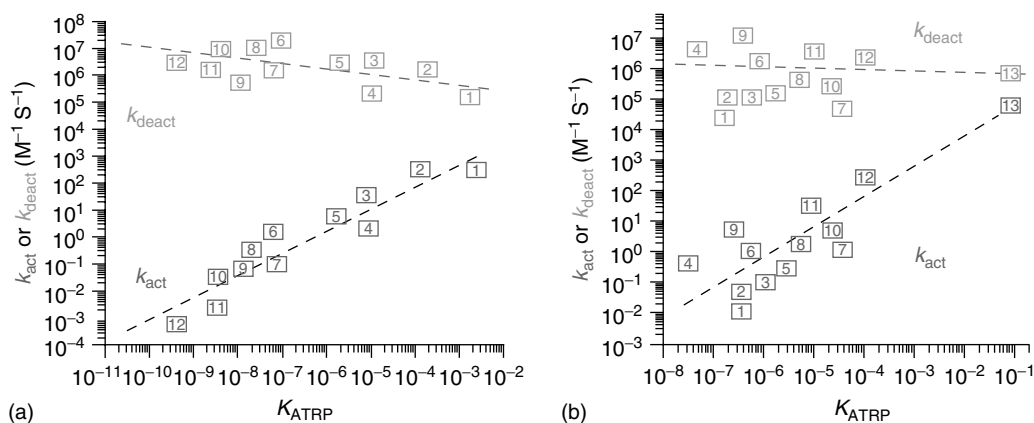


Figure 6 Correlation of activation (k_a) and deactivation (k_d) rate constants with equilibrium constant (K_{ATRP}) for various Cu(I)Br/L complexes with (a) EBrIB as initiator and (b) various initiators with Cu(I)TPMA complex. (a) Ligands 1: Cyclam-B, 2: Me6TREN, 3: TPMA, 4: BPED, 5: TPEDA, 6: PMDETA, 7: BPMPA, 8: dNbpy, 9: HMTETA, 10: bpy, 11: N4[3,2,3], 12: N4[2,3,2]. (b) Initiators 1: McAc, 2: BzCl, 3: PECl, 4: MCIP, 5: EtClIB, 6: BzBr, 7: CIAN, 8: PEBr, 9: MBrP, 10: CIPN, 11: EtBrIB, 12: BrPN, 13: EBPA.

relatively stable 1:1 copper complexes, the redox potential can be calculated using the following equation^{206–210}:

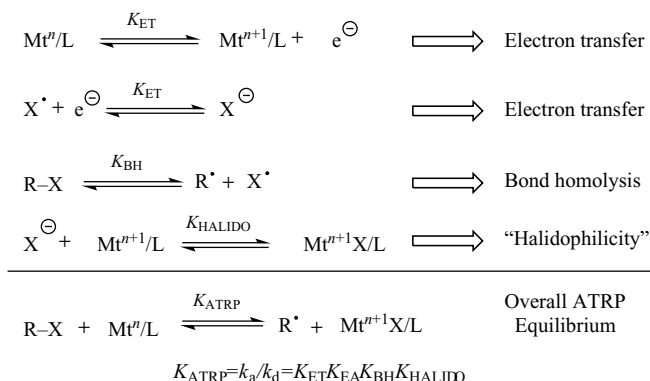
$$\beta_k^m = \frac{[\text{Cu}^m \text{L}_k]}{[\text{Cu}^m][\text{L}]^k}; m = \text{I or II}$$

$$E \approx E^0 + \frac{RT}{F} \ln \frac{[\text{Cu(II)}]_{\text{total}}}{[\text{Cu(I)}]_{\text{total}}} - \frac{RT}{F} \ln \frac{\beta(\text{II})}{\beta(\text{I})} \quad (4)$$

The redox potential of the Cu(II)L/Cu(I)L couple is related to the equilibrium constant for electron transfer (K_{ET}) according to the equation

$$E = -\frac{RT}{F} \ln K_{ET} \quad (5)$$

As indicated in Scheme 12, for a given alkyl halide R–X, the activity of the catalyst in ATRP does not only depend on the redox potential but also on the “halidophilicity” of the metal complex



$$\frac{K_{\text{ATRP}}}{K_{\text{EA}}K_{\text{BH}}} = K_{\text{ET}}K_{\text{HALIDO}}$$

Scheme 12 Reactions formally contributing to the overall ATRP equilibrium.

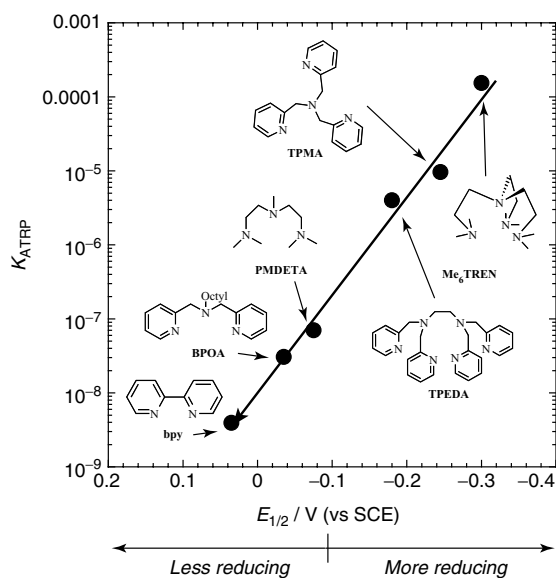


Figure 7 A plot of K_{ATRP} versus $E_{1/2}$. K_{ATRP} values are reported for Cu(I)Br/L complexes and ethyl 2-bromoisobutyrate, and $E_{1/2}$ was measured relative to standard calomel electrode (SCE) (solvent = CH_3CN , $T = 22^\circ\text{C}$).^{183,211,212}

(K_X). Both parameters are affected by the nature of transition metal and complexing ligand (including binding constants, basicity, back bonding, etc). For complexes that have similar “halidophilicities,” the redox potential can be used as a measure of catalyst activity in ATRP. This was demonstrated in the linear correlation between K_{ATRP} and $E_{1/2}$ values for

a series of copper(I) complexes with nitrogen-based ligands (Figure 7).^{183,211,212}

4.5 Radical Nature of Propagating Species

On the basis of several experimental evidences and observations, TMC ATRP is a radical process. Chemoselectivity,²¹³ cross-propagation kinetics,²¹⁴ kinetic isotope effects,²¹⁵ the reactivity ratios,^{214,216–220} and regio- and stereoselectivity^{65,217,221,222} are similar to those of free-radical polymerizations. ATRP is initially retarded in the presence of small amounts of oxygen or free-radical inhibitors, such as galvinoxyl or TEMPO, which directly react with a growing radical and inhibit chain growth by terminating the polymerization.²²³ Furthermore, ATRP can be conducted in the presence of water or other protic solvents, and is tolerant to a wide variety of functionalities present in the (co)monomers.^{224,225} Cross-exchange between different halogens²²⁶ and different polymerization systems (thermal and ATRP or nitroxide-mediated polymerization and ATRP) demonstrates that these reactions have the same intermediates and supports a common radical mechanism.²²⁷ ATRP can be converted to a system that displays conventional radical polymerization by the addition of octanethiol as a chain transfer reagent.²²⁸ Chain transfer in *n*-butyl acrylate polymerization also resembles the conventional radical

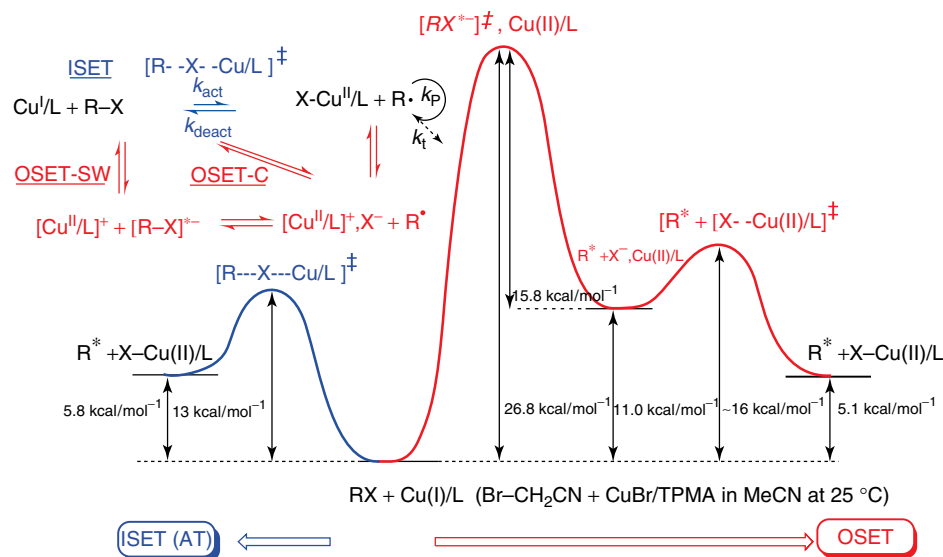


Figure 8 Comparison of free energies during an ISET and concerted OSET process for the reaction of bromoacetonitrile with Cu(I)/TPMA complex in CH₃CN at 25 °C. [Reproduced with permission from Ref. 237. Copyright 2008 American Chemical Society.]

process.²²⁹ Lastly, racemization studies using optically active alkyl halides,²²³ direct observation of deactivator species (transition metal complexes in the higher oxidation state, i.e., Cu(II))^{230–235} and propagating free radicals in the polymerization of dimethylacrylates²³⁶ by EPR also supports radical mechanism.

Mechanistically, atom transfer radical process could occur either via the outer-sphere electron transfer (OSET) or via inner-sphere electron transfer (ISET), that is, atom transfer passing through a Cu–X–C transition state, which is formally also a single-electron transfer process. OSET can proceed in a stepwise manner with radical anion intermediates or in a concerted process with simultaneous dissociation of alkyl halide to a radical and anion. According to the Marcus analysis of electron transfer processes, OSET should have an energy barrier approximately 15 kcal mol^{−1} higher than what was experimentally measured.²³⁷ In other words, OSET should be approximately 10¹⁰ times slower than experimentally measured values. The results clearly indicate that the differences between energy barriers for ISET and OSET are much greater than any computational or experimental errors, and it can therefore be concluded that the mechanism of ATRP occurs via a copper-catalyzed concerted homolytic dissociation of an alkyl halide. Additionally, the one-step dissociative electron

transfer to form a radical and an anion is energetically more favorable than the two-step process via the radical anion intermediates. The free-energy profiles of computational analysis of the reaction of Cu(I)/TPMA complex with bromoacetonitrile in CH₃CN at 25 °C are shown in Figure 8.

5 CONTROL OF POLYMER COMPOSITION

As mentioned previously, ATRP is particularly suited for the synthesis of well-defined (co)polymers. The spectrum of (co)polymers that can be prepared by a well-controlled ATRP includes polymers with virtually any desired distribution of monomer units along the polymer backbone, or within any specific segment in a copolymer. This includes homopolymers as well as random, alternating, gradient, block, graft, brush, and star copolymers (Figure 9).⁶³ Each type is discussed in detail in the following sections.

5.1 Well-Defined Homopolymers

Copper-catalyzed ATRP is particularly suitable for homopolymerization of a wide variety of monomers (Scheme 7) that contain an α -stabilizing substituent

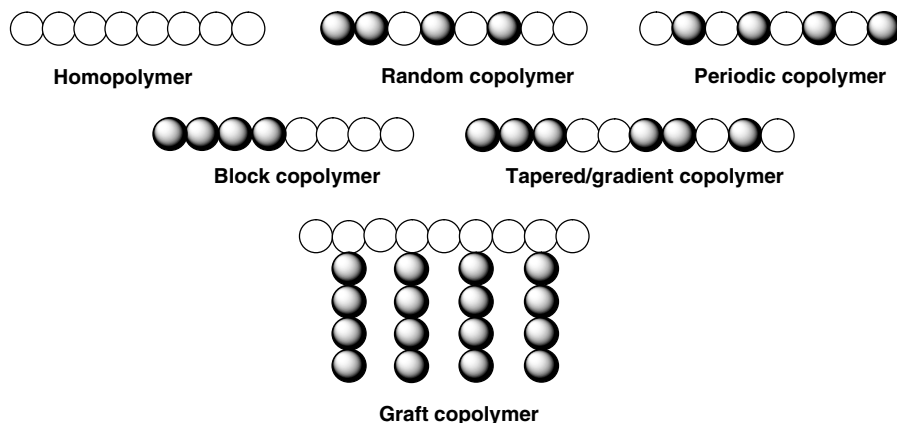


Figure 9 Composition of (co)polymers synthesized using ATRP.

adjacent to the transferable atom or group in order that the dormant chain end can be reactivated. Therefore, simple α -olefins cannot be easily homopolymerized. However, they can be copolymerized with highly active monomers such as acrylates. With acidic monomers, carefully chosen reaction conditions are needed in order to minimize protonation of nitrogen-based complexing ligands, which leads to diminished catalytic activity. Potential solutions are to utilize protected groups (acetal, *t*-butyl ester) or anionic forms (sodium salt or protonated tertiary amines).

Monomers/polymers that can complex copper species (amides, polyamines, or some proteins) can displace ligands and deactivate catalysts unless the stability constants are large enough (e.g., for TPMA). Finally, monomers containing groups that easily participate in radical transfer, such as thiols, cannot be used directly in ATRP and should be protected. The major difference between the polymers prepared by ATRP and prior art polymers prepared by free-radical polymerization are the additional degrees of control over architecture, molecular weight, molecular weight distribution, and telechelic functionality.⁴⁷

5.2 Well-Defined Copolymers

5.2.1 Copolymers with Controlled Molecular Weight

One of the main advantages of TMC ATRP is the ability to control molecular weight and molecular

weight distribution of copolymers containing functional monomers. Control over molecular weight requires efficient initiation and preservation of activity in the majority of the polymeric chains. However, termination and other side reactions are also present in ATRP, and they usually become more prominent as higher molecular weight polymers are targeted. For example, in copper-mediated ATRP of styrene, a slow termination process was observed, mainly arising from the interaction of the copper(II) species with both the growing radical and the macromolecular alkyl halide.²³⁸ The catalytic species can participate in the OSET reactions by either oxidation of the polystyryl radicals to carbocations or reduction of radicals to carbanions via reactions with copper(II) and copper(I) species. Studies with model compounds and macromolecular polystyrene species have demonstrated that the elimination reaction was accelerated in the presence of the copper(II) complex. This process limited the molecular weight of the resulting homopolymers.^{238,239} However, these prior limitations on the maximum molecular weight of the (co)polymers that can be prepared by ATRP have been surmounted by the development of ARGET ATRP which minimizes OSET catalyst-based oxidation or reduction reactions,^{240,241} allowing the synthesis of high molecular weight polymers such as styrene acrylonitrile (SAN)²⁴² copolymers and polyacrylonitrile (PAN) with less apparent tailing ($M_n \sim 200\,000 \text{ g mol}^{-1}$ and $M_w/M_n \sim 1.2$).²⁴³ A recent extension of ARGET ATRP was also demonstrated in preparation of poly(methyl methacrylate)

with molecular weight as high as $1\,000\,000\text{ g mol}^{-1}$ using a dithioester initiator.^{244,245}

Another approach to high molecular weight polymers is conducting ATRP under elevated pressure. At high pressures, the propagation rate constant is enhanced and that of the termination suppressed, thereby resulting in a higher ratio of k_p/k_t . For example, at 6 kbar pressure, polystyrene with $M_n = 1\,000\,000\text{ g mol}^{-1}$ and $M_w/M_n = 1.24$ and PMMA with $M_n = 1\,200\,000\text{ g mol}^{-1}$ and $M_w/M_n = 1.17$ were synthesized at room temperature within a few hours with targeted molecular weight.^{246,247}

5.2.2 Statistical and Gradient Linear Copolymers

Reactivity ratios in ATRP are the same as in radical polymerization, although small differences exist that have been ascribed to nonequilibrated systems.^{248,249} In contrast to conventional free-radical copolymerization, where differences in comonomer reactivity ratios result in a variation in copolymer composition, in CRP this variation in instantaneous incorporation of the monomers into the copolymer results in a tapering in composition along the main chain of the copolymer.^{250,251} Gradient copolymers can be prepared by either simultaneous copolymerization of monomers with different reactivity ratios (spontaneous gradient) or by continuous feeding of one monomer (forced gradient).^{218,252} The shape of the gradient depends on the concentration of comonomers, their reactivity ratios, and the feeding process. In a mini-emulsion, it also depends on the comonomer's solubility.^{253,254} Gradients can be linear, V-shaped, or curved. Gradient may reflect not only the density of grafting or composition but also the stereostructure.²⁵⁵

5.2.3 Alternating Copolymers

Alternating copolymers are the simplest periodic copolymers. There are several comonomer pairs that copolymerize in alternating fashion by ATRP. They include strong electron donors and strong electron acceptors, for example, styrene-maleimides.²⁵⁶ It is also possible to use one kinetically reactive but thermodynamically non-homopolymerizable monomer.

Another possibility is to use a less reactive monomer in large excess. In such a way, nearly alternating copolymers of acrylates with olefins have been prepared.^{89,257} The reactivity ratios of the monomers can also be affected by complexation. For example, in the presence of strong Lewis acids, methyl methacrylate tends to form alternating copolymers with styrene.²⁵⁸ For some imers with a reactive alkyl halide but unreactive alkene, a polyaddition is possible that generates a new polymer structure with a heteroatom in the main chain.^{259,260}

5.2.4 Linear Segmented Copolymers (Block and Multisegmented)

The area of segmented copolymers is perhaps the most prolific in ATRP. The end groups of polymers prepared by other techniques, including cationic, anionic, coordination, and step-growth polymerization, were converted to ATRP-initiating sites and used directly as macroinitiators for ATRP.

Efficient block copolymerization requires an appropriate sequence of blocks. This order generally follows radical stabilities and can be correlated with the proportion of the active species. This order may be specific for a particular polymerization. In ATRP, the order is as follows: acrylonitrile > methacrylates > styrene ~ acrylates > acrylamides. In ATRP, the block order can be altered by using halogen exchange. This way, thermoplastic elastomers of PMMA-PBA-PMMA were successfully obtained by starting from Br-PBA-Br and using CuCl/L to extend the chain with MMA.^{110,261–263} ABC, ABCD, and ABCBA blocks were also prepared by ATRP.²⁶⁴

ATRP macroinitiators were successfully converted to reverse addition-fragmentation chain transfer (RAFT) (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications** and NMP see **Nitroxide-Mediated Polymerization and its Applications**) initiators. After site transformation, these macroinitiators served as a starting point for RAFT- and NMP-mediated block copolymerization.²⁵¹ Dual initiators could also be used for a successive ATRP and RAFT polymerization,²⁶⁵ and other techniques.^{266,267}

The dormant species in styrene cationic polymerizations and ATRP systems have identical

structure. Therefore, Cl-terminated polystyrenes from cationic polymerization could be efficiently extended via ATRP with polystyrene and also with poly(meth)acrylates.¹⁰⁸ ATRP was initiated by acetal end-functionalized alkyl halides which were subsequently used to grow vinyl ethers by living cationic polymerization. The reverse process was also successful owing to the high tolerance of cationic polymerization of vinyl ethers to impurities.²⁶⁸ Living carbanions were quenched by species serving as initiators for ATRP, and subsequently chain-extended.²⁶⁹ Cationic polymerization of tetrahydrofuran (THF) was initiated by 2-bromoisobutryl bromide and silver triflate. The subsequent addition of ATRP catalyst allowed the controlled polymerization of MMA, n-butyl acrylate (BA), and styrene from the residual bromoester moiety.²³² Bromo-end groups in ATRP of styrene were used to directly initiate ring-opening polymerization of oxazolines.²⁷⁰ Hydroxy end groups in polymers from anionic ring-opening polymerization (AROP) of ethylene oxide or lactones were directly esterified to bromoesters and used as ATRP initiators. 2-Hydroxyethyl 2'-bromoisobutyrate is a simple dual initiator capable of initiating both AROP and ATRP.²⁷¹ Depending on the initiating/catalytic systems, the rates of both processes can be comparable, allowing the simultaneous presence of two noninterfering processes.^{272,273}

Unsaturated chain ends in polyethylene and polypropylene were transformed to bromoesters to initiate ATRP of styrene and (meth)acrylates. Hydroxy functional polyethylene obtained in degenerative transfer polymerization of ethylene was used in a similar way for block copolymerization via ATRP.^{274–277} A similar approach was used to create graft copolymers. Copolymerization of ethylene and 10-undecen-1-ol in the presence of a trialkylaluminum protecting group can be conducted with a metallocene catalyst. The hydroxyl functionality was converted into an α -bromoisobutyrate functionality, and the resulting polyethylene multifunctional macroinitiator was used for a “grafting-from” ATRP procedure. In this way, copolymers such as polyethylene-*g*-poly(methyl methacrylate) have been produced which act as compatibilizers for otherwise immiscible polymers.^{276,278,279}

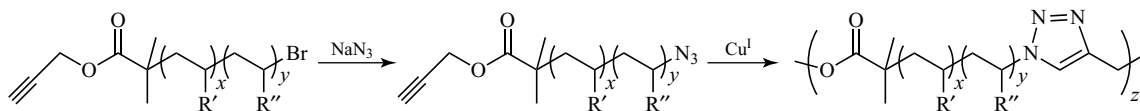
Several methods combine CRP with ROMP. Molybdenum alkylidene chain ends are destroyed by aldehydes. Thus, aldehydes with activated alkyl

bromides were used to terminate ROMP of norbornene and subsequently form block copolymers with styrene and (meth)acrylates.²⁸⁰ Another interesting possibility is the simultaneous growth of polymer chains via ROMP on ruthenium alkylidenes which also serve as ATRP catalysts. Interestingly, an excess of phosphines reduces the rate of ROMP, but does not affect the rate of ATRP.^{150,281}

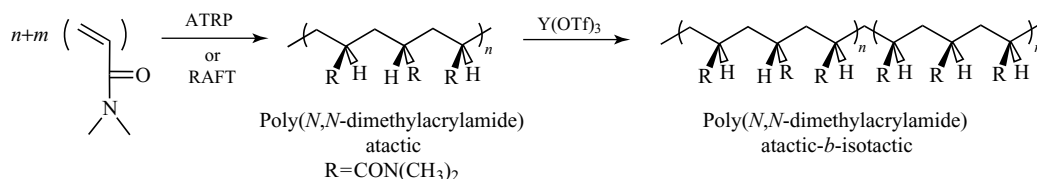
End groups from many step-growth polymers are easily transformed to ATRP macroinitiators. Thus, terminal hydroxy groups from polyesters, polycarbonates, or polysulfones were esterified to bromoesters and subsequently chain-extended with styrene or (meth)acrylates.^{109,282,283} Polythiophenes are formed by polycondensation, but the mechanism follows a chain-growth rather than a step-growth process. It is therefore possible to prepare polythiophenes with low polydispersity. End groups are well controlled and can be converted to ATRP initiators. Block copolymerizations with this technique have been very efficient, and well-defined nanostructured materials have been prepared.^{284–287}

CRP was also combined with polymers prepared by conventional radical polymerization. For example, telechelic polymers prepared by radical polymerization can either contain ATRP-active sites or can be converted to the corresponding macroinitiators and used for controlled ATRP. In such a way, poly(vinyl acetate) was block copolymerized with styrene and acrylates. Conversely, well-defined blocks were used to initiate uncontrolled radical polymerization of vinyl acetate to afford another type of block copolymer.²⁸⁸

Multisegmented block copolymers are typically prepared by polycondensation processes. ATRP can be used to make ABC or ABCBA segments by sequential polymerization. However, chain coupling can afford multisegmented copolymers in a much simpler way. Such coupling can be done with termination by radical coupling; however, yields in these reactions are rather low. Another approach involves click chemistry. An ATRP initiator with an acetylene functionality (such as propargyl 2-bromoisobutyrate) was used to synthesize an α -alkyne- ω -bromo-terminated block copolymer which was further reacted with NaN_3 to generate the corresponding α -alkyne- ω -azido-terminated block copolymer. This functional diblock was then click-coupled in a step-growth process at room temperature in the presence of Cu(I) to generate segmented block copolymers (Scheme 13).^{289,290}



Scheme 13 Segmented block copolymers synthesized using a combination of ATRP and “click” chemistry.



Scheme 14 Stereoblock poly(atactic-dimethylacrylamide)-*b*-poly(isotactic-dimethylacrylamide).

5.2.5 Stereoblock Copolymers

Radical polymerization is not stereoselective (see **Stereoselective Radical Reactions**). However, in the presence of some complexing agents that strongly interact with the pendent groups of the polymer chain end and/or the monomer, the proportion of syndiotactic or isotactic triads can be significantly increased. This has been demonstrated for the polymerization of acrylamides in the presence of catalytic amounts of $\text{Yb}(\text{OTf})_3$ or $\text{Y}(\text{OTf})_3$ ²⁹¹ and also in the polymerization of vinyl esters in fluoroalcohols.²⁹² ATRP offers the special advantage that atactic segments formed without complexing agent can be extended with regular blocks formed in the presence of such agents. In such a way, stereoblock poly(atactic-dimethylacrylamide)-*b*-poly(isotactic-dimethylacrylamide) was formed (Scheme 14).^{293–295} An interesting extension of this approach was applied to prepare stereo-gradient copolymers.²⁵⁵

conditions. There are many initiators and macroinitiators that contain functional group(s) and therefore add value to the obtained products.^{47,250} Several difunctional activated alkyl halides are commercially available. Many others can be prepared by simple esterification of diols and functional alcohols with, for example, 2-bromoisobutyryl bromide.

6.2 Star Polymers

Star polymers can generally be prepared using four different approaches.²⁹⁶ Multifunctional initiators can be used to simultaneously grow several arms via a core-first approach (left part of Scheme 15). Polyols were converted to the ATRP initiating core with 3, 4, 6, 12, or more initiating sites.^{297–299} Core was also prepared by cross-linking the divinyl compound under high dilution.³⁰⁰ The synthesis of star-like structures by CRP using a core-first method faces the danger of potential cross-linking and gelation because of radical coupling. Thus, a relatively low concentration of radicals and low conversions are often used to minimize star–star coupling.

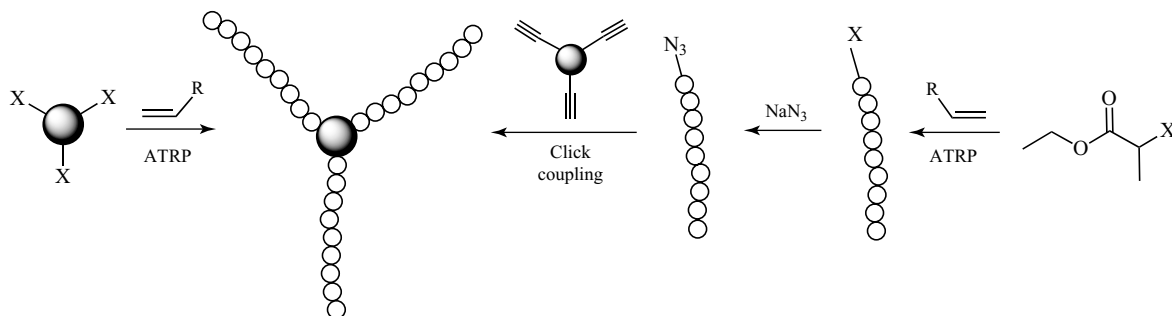
An arm-first approach involves attachment of chains to a functional core (right part of Scheme 15). Linear monofunctional Br-terminated chains formed by ATRP were converted to azides and subsequently “clicked” to a core with several acetylene groups.³⁰¹

Another approach utilizes arms that are cross-linked in the presence of divinyl compounds (Scheme 16). In this case, the number of arms in the resulting stars is not precisely controlled. Also, star–star coupling between the

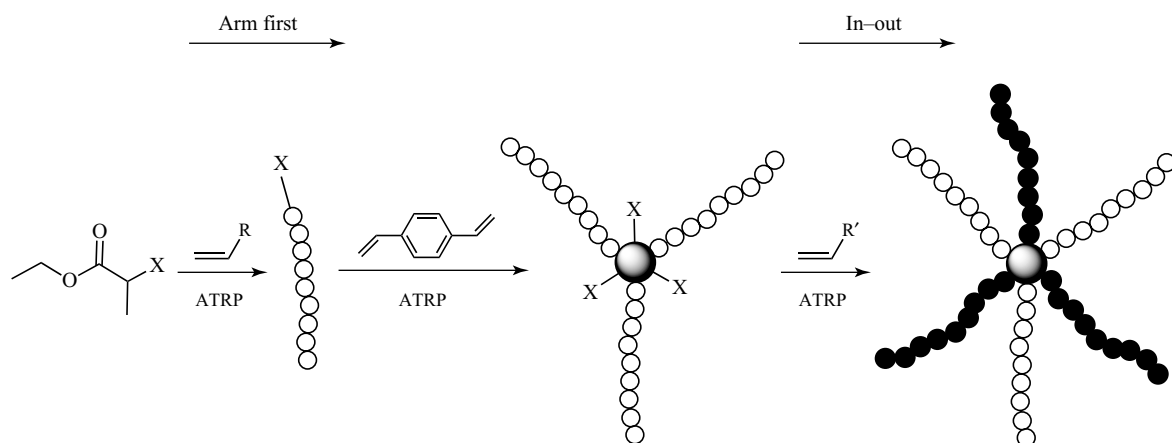
6 POLYMER TOPOLOGY BY ATRP

6.1 Linear Chains

ATRP was successfully used in the synthesis of linear chains in the range $M_n > 1$ million. The use of difunctional initiators allowed, for the first time in a radical process, simultaneous two-directional chain growth. This gives access to functional telechelic polymers and polymers with molecular weights twice larger than otherwise attainable under similar



Scheme 15 Approaches used for the synthesis of star copolymers.



Scheme 16 Synthesis of stars by crosslinking of arms in the presence of divinyl compounds.

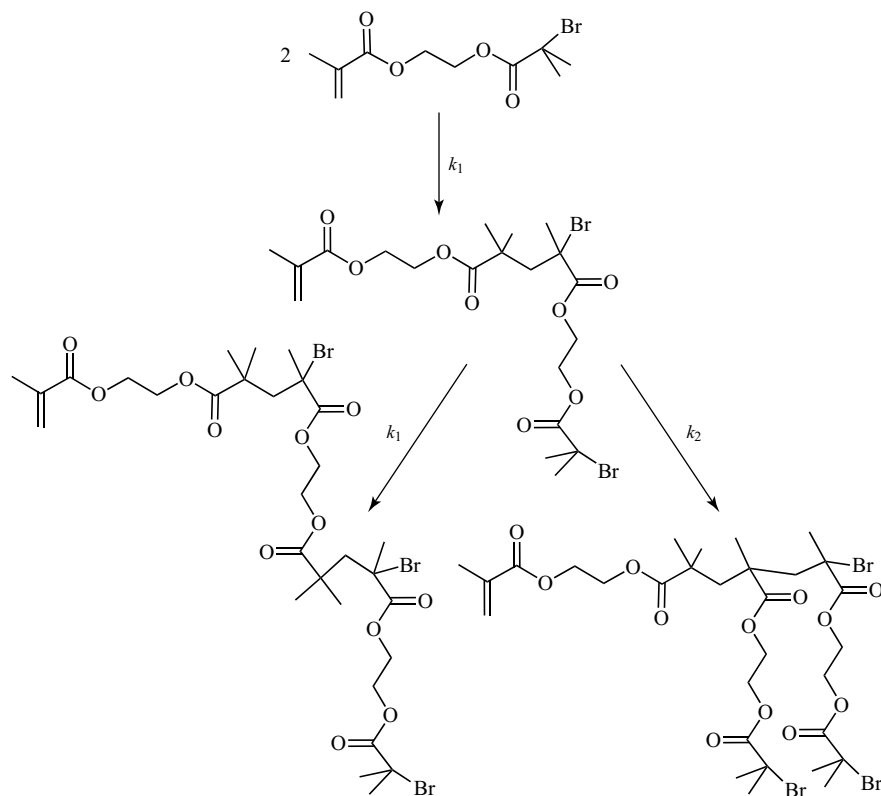
cores may occur. This synthetic procedure requires precise manipulation of arm length, the amount of divinyl compound, and the reaction time.^{302–304} A cross-linker can be added to isolated arms or at a certain moment during the arm synthesis, allowing for control of the core density. All of these parameters affect the resulting star structure. As an example, the synthesis of stars with ~50 arms in >90% yield will require ~10-fold molar excess of crosslinker (vs. arm end groups) for precursors with DP ~100. Stars in even higher yield (>98%) and with lower PDI (<1.2) can be prepared by replacing macroinitiators with macromonomers. In that case, R in the monomer is a macromolecular substituent and the initiator is used under substoichiometric conditions (Scheme 16).³⁰⁵

Stars prepared via the arm-first process still contain active/dormant species at the core. Thus, they can be used to grow a second generation of arms by the so-called in-out approach. Such

mikto-arm stars can contain the same monomeric units but can be of different lengths; they can also contain hetero-arms. The efficiency of reinitiation is often low owing to the poor accessibility of the monomer/catalyst to the sterically congested core, but may also result from enhanced termination inside the core. By using a degradable cross-linker with an S–S linking unit, it was determined that efficiency of reinitiation is usually ~30%.^{304,306} The vinyl and/or halide residual functionalities were used for further core functionalization.³⁰⁷

6.3 Comb and Graft Copolymers

Comb-like polymers can be prepared using techniques similar to those described for stars.^{250,308} However, instead of a compact core, a long, linear backbone was employed. These three techniques correspond to grafting-from, -onto, and -through.



Scheme 17 Synthesis of branched polymers using ATRP.

Interesting brush topologies³⁰⁹ with unique properties were prepared using different macro-monomers in heterografted brush copolymers³¹⁰ or block brush copolymers prepared by a combination of grafting-from and grafting-through.³¹¹ When macro-monomers are polymerized by grafting from a macroinitiator, double-grafted brush copolymers can be synthesized where each graft is a brush.³¹²

the concentration of deactivator. Copolymerization of inimers with regular monomers reduces the degree of branching and increases the branch length.³¹⁶

Hyperbranched structures can also be obtained when divinyl monomers are copolymerized in small amounts or in the presence of chain transfer compounds (thiols)³¹⁷ or ATRP initiators that favor the formation of branched products.^{318,319}

6.4 Branched and Hyperbranched Polymers

ATRP was used to prepare hyperbranched polymers.^{313–315} Monomers that also serve as initiators (so-called inimers) were successfully used to make such materials (Scheme 17). The ratio of reactivities of the initiating site and the active species resulting from the alkene moiety define the degree of branching (which can approach 50%). It is possible to additionally affect this ratio by varying

6.5 Dendritic Structures

While hyperbranched systems are irregular, branching is well controlled in dendritic structures. Dendritic structures have been prepared by ATRP alone or by combinations with other controlled living polymerization techniques.^{320–322} Polymer chains were grafted from dendrimers or attached to dendrimers. Single chains were combined with

dendrimer structures, and dendrons were also functionalized with methacrylate groups and copolymerized to form stiff polymer chains.^{323–326}

6.6 Polymer Networks and Microgels

Most polymer networks have irregular structures. However, ATRP can significantly improve network uniformity. When a divinyl compound is copolymerized with a monovinyl compound, the gel point in ATRP occurs much later than in radical polymerization. This is due to the fact that, in ATRP, only short chains are formed at the early stages and the number of pendant double bonds in each chain is much lower than in conventional radical polymerization.³²⁷ The gel point depends on the ratio of cross-linker to initiator and generally requires the ratio to exceed unity for moderate intramolecular cyclization. However, gel point depends also on the moment of cross-linker addition, initiation efficiency, monomer reactivity, chain polydispersity, and other parameters.^{319,328} Gels prepared by ATRP have generally a much higher swelling ratio than those made by conventional radical polymerization.^{318,327,329} Degradable gels were prepared by the copolymerization of styrene or methyl methacrylate and a disulfide-containing difunctional methacrylate.^{330,331} It is also possible to use cross-linkers that can be reversibly cleaved, which leads to the formation of reversible gels.^{168,304}

6.7 Cyclic Polymers

CRP has no special advantage in forming cyclic polymers. Rather, anionic and/or cationic polymerizations are better suited to make cyclics by using complementary reagents at very low concentrations. However, cyclization has been reported when click chemistry was used in a reaction of azido- and acetylene-terminated chains.^{289,332}

6.8 Molecular Hybrids

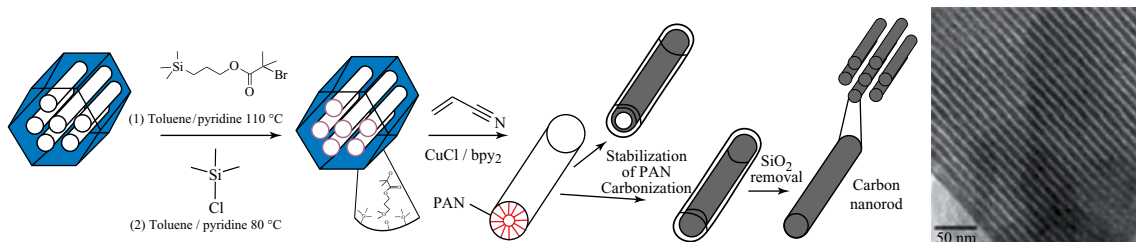
Molecular hybrids comprise synthetic polymers attached covalently to inorganic materials

and to natural products.^{333,334} The well-defined organic–inorganic hybrids can be formed by grafting from flat, convex, concave, or irregular surfaces.^{114,335} Surfaces of gold, silicon, silica, iron, and other inorganic substrates were functionalized with bromoesters to initiate the growth of polystyrene, poly(meth)acrylates, polyacrylonitrile, or polyacrylamide chains via ATRP.³³⁶ It is possible to vary the grafting density and prepare very densely grafted films, with density approaching ~ 0.5 to 1 chain per square nanometer.^{337,338} Grafting density could be continuously varied along the substrate to prepare surfaces with a macroscopic gradient.³³⁹ Very dense grafting is not possible via grafting onto, since the attached polymer chains collapse on the surface and prevent other chains from the solution from reaching the surface. Nonuniform growth cannot provide a high grafting density. Only when polymer chains grow by adding “a few monomer units at a time” is high grafting density possible. The resulting hybrids have many new and unusual properties related to their unique compressibility, lubrication, swelling, or interpenetration.³³⁸ Grafting can be performed by normal ATRP and also by ARGET.¹⁷³

It is also possible to graft polymers and block copolymers onto inorganic surfaces. For example, poly(methacrylic acid)-*b*-poly(methyl methacrylate)-*b*-poly(sodium styrenesulfonate) prepared by ATRP was grafted onto ~ 200 -nm diameter iron particles to destroy residual chlorinated pollutants.³⁴⁰

Slower chain growth in ATRP facilitates better control in templated systems. Mesoporous silica was functionalized with bromoesters and used to grow polyacrylonitrile, polystyrene, or poly(meth)acrylates. Growth of polymer chains was followed by thermogravimetric analysis (TGA), porosity measurements, and analysis of detached polymers. Highly uniform growth was achieved on the molecular level (as evidenced by low polydispersity of detached polymers analyzed by gel permeation chromatography (GPC) but also macroscopically (overall porosity measurements). The resulting polyacrylonitrile was converted to very regular nanosize carbon filaments ($D \sim 10$ nm, $L > 1 \mu\text{m}$, $S = 840 \text{ m}^2 \text{ g}^{-1}$; Scheme 18).^{114,341,342}

Functional groups in natural products have been converted to ATRP initiators (NH_2 or OH groups converted to bromoamides and bromoesters).^{113,334,343} During polymerization, the



Scheme 18 Synthesis of nanosize carbon filaments.

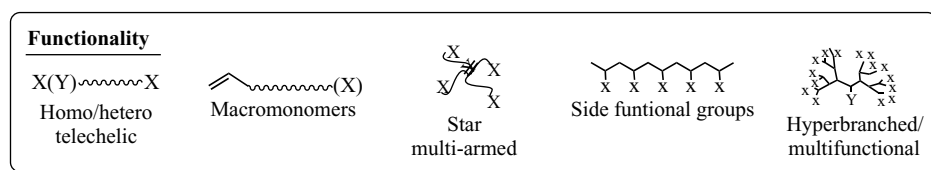


Figure 10 Multifunctional polymers prepared using ATRP/CRP techniques.

original substrate should not interfere with the ATRP process and the functionality and properties of the natural products should not be destroyed by ATRP. Alternatively, chains prepared by CRP-containing functionalities (NH_2 or OH) were used to grow polypeptides or DNA. It is also possible to fuse functionalized natural products and organic polymers together with click reactions, by biotin–avidin chemistry, or from genetically modified peptides.^{334, 344–357}

7 FUNCTIONAL POLYMERS

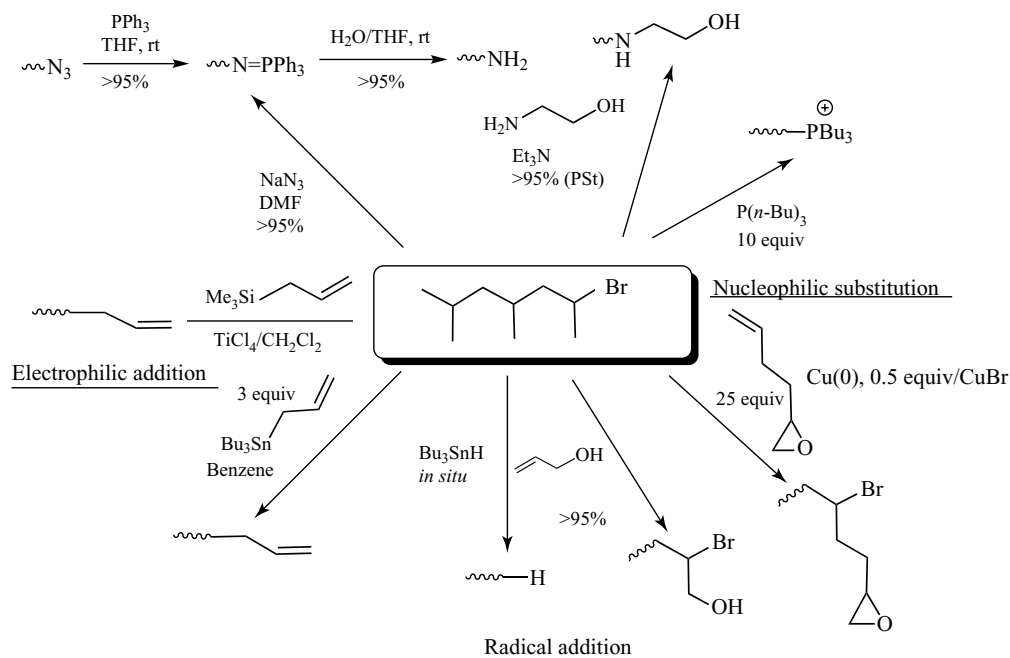
Radical polymerization is tolerant to many polar groups such as $-\text{OH}$, $-\text{NH}_2$, or $-\text{COOH}$ and can be carried out in water. In CRP, functionalities can be incorporated into specific parts of polymer chains, as shown in Figure 10.⁴⁷

Functional monomers were directly incorporated into polymer backbones, as well as in a protected form. For example, 2-hydroxyethyl (meth)acrylate was homopolymerized and copolymerized by ATRP.^{77,79} Also, trimethylsilyl (TMS) derivatives were polymerized and subsequently deprotected. The hydroxy groups were then functionalized with 2-bromopropionate groups and extended to form densely grafted molecular brushes.^{79,110}

End groups can be incorporated either by using functional initiators or by converting the growing chain ends to another functional group.⁴⁷

Functional initiators allow the introduction of functionality to only one chain end. Various functionalized ATRP initiators were used to prepare hetero-telechelic polymers.⁴⁷ Additionally, atom transfer radical coupling enables the efficient coupling of chains and provides a route to telechelic polystyrenes.³⁵⁸ Atom transfer radical coupling is less efficient for methacrylates (the growing radicals predominantly disproportionate rather than couple) and for acrylates (too low an equilibrium constant). However, it is sufficient to add a few styrene units at the acrylate chain end to successfully form polyacrylate telechelics. Multifunctional star polymers were prepared from functional macroinitiators.

The dormant chain end in all CRP processes can be further converted to other functional groups by radical or nonradical processes. For example, dithioesters in RAFT (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**) were converted to thiols, the alkoxyamines in NMP (see **Nitroxide-Mediated Polymerization and its Applications**) to alkyl chlorides, and the alkyl halides in ATRP to allyl, hydroxy, amino, azido, and ammonium or phosphonium groups in excellent yields. It is also possible to incorporate one functional monomer at the chain end if the monomer is much less reactive and forms an unreactive dormant species.



Scheme 19 Post-polymerization functionalization of ω -telechelic transferable atoms.

Scheme 19 presents three types of reactions employed for end-functionalization of ATRP polymers: nucleophilic substitution, electrophilic substitution, and in stars to multifunctional polymers. A similar approach was applied to hyper-branched polymers prepared by (co)polymerization of inimers.

8 APPLICATIONS

8.1 Applications of Materials Prepared by ATRP

Block copolymers based on acrylates and other polar monomers find applications as polar thermoplastic elastomers²⁶² in automotive applications, as they do not swell in hydrocarbons. However, they can also be used for much more sophisticated applications such as controlled drug release in cardiovascular stents.³⁵⁹ Amphiphilic block copolymers with water-soluble segments have been successfully used as very efficient surfactants³⁶⁰ and

were also used for higher end applications including pigment dispersants,^{361,362} various additives, and components of health and beauty products. Segmented copolymers with nanostructured morphologies are promising as microelectronic devices.^{285,363}

Graft copolymers have been used as compatibilizers for polymer blends and may be used in many applications described for block copolymers.²⁷⁶ Gradient copolymers hold great promise in applications ranging from surfactants to noise and vibration dampening materials.^{218,364,365}

Designed branching allows precise control over melt viscosity and polymer processing. Such polymers (as well as comb and star polymers) can be used as viscosity modifiers and lubricants.³⁶⁶

An ultimate example of controlled topology might be a macromolecular bottle-brush.³⁰⁹ Such polymers, when lightly cross-linked, result in super-soft elastomers.³⁶⁷ Materials were synthesized with moduli ~ 1 kPa, which is in the range attainable by hydrogels. However, hydrogels must be swollen 100 times by water to reach such low moduli. Molecular brushes are swollen by their own short side chains that never leach. Thus, applications are foreseen ranging from intraocular lenses and other

biomedical applications requiring a soft material that does not leach to the surrounding tissue to electronic applications requiring the protection of delicate components by a soft solid. These materials also show very high ionic conductivities reaching 1 ms cm^{-1} for Li cations at room temperature.³⁶⁸ Brushes can be also used as core-shell cylindrical templates to prepare various nanostructured materials.^{369,370}

ATRP offers unprecedented control over chain end functionality. End functional polyacrylates are excellent components of sealants for out-door and automotive applications.^{53,371} Multifunctional low molecular weight polymers are desirable components in coatings with a low organic solvent content important for volatile organic compound (VOC) reduction.³⁷² It is also possible to design systems with two types of functionalities, curable by two independent mechanisms. Incorporation of degradable units into the backbone of vinyl polymers allows controlled cleavage and degradation/recycling of such polymers.

Molecular hybrids with a covalent attachment of well-defined functional polymer to either an inorganic component or a natural product are currently being extensively investigated and should lead to numerous materials with previously unattainable properties. Such hybrids allow better dispersability of inorganic components (pigments, carbon black, carbon nanotubes, nanoparticles), they dramatically enhance the stability of such dispersions, and they allow the formation of molecular nanocomposites. Also, dense polymer layers improve lubrication, prevent corrosion, and facilitate surface patterning. Precise grafting from chromatographic packing enables enhanced chromatographic resolution of oligopeptides and synthetic prions.³⁷³

Other potential applications include microelectronics, microfluidics, and optoelectronics, as well as biomedical applications such as components of tissue and bone engineering, controlled drug release and drug targeting, antimicrobial surfaces,³⁷⁴ steering enzyme activity,^{334,356,375–377} and many others.

However, it is very interesting to note that most recent developments in ATRP that allowed significantly diminish concentration of transition-metal catalysts have been adopted to ATRA and ATRC processes. Thus, although originally ATRA provided guidelines for ATRP, the cycle closed by passing the most recent developments in ATRP to ATRA.

The last section covers the most recent progress in transition-metal-mediated (TMC) ATRA and ATRP processes inspired by ARGET and ICAR ATRP systems.

8.2 ATRA and ATRC via ICAR and ARGET Processes

TMC ATRA and ATRC reactions are very versatile tools for the synthesis of small organic molecules starting from alkyl halides and alkenes.^{4,16,17,37,39,120,179,378} However, these methods for carbon-carbon bond formation are still not fully utilized in free-radical synthesis, and are by far much less represented in the literature than standard tin hydride-mediated radical addition to alkenes (see **Tin Hydrides and Functional Group Transformations**)³⁷⁹ and iodine atom transfer (see **Synthetic Radical Photochemistry**) radical reactions.³⁸⁰ The principal reason for small participation of TMC ATRA and ATRC reactions in organic synthesis until recently was the large amount of metal catalyst needed to achieve high selectivity of the desired monoadduct (typically between 5 and 30 mol% relative to substrate). Such large amounts of catalyst were required in these transformations in order to compensate for the accumulation of the deactivator or transition-metal complex in the higher oxidation state, as a result of unavoidable and often diffusion controlled radical-radical termination reactions ($k_t \approx 2.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$).

Until recently, the relatively high amount of transition-metal catalysts in ATRA made this methodology rather unsuitable for fine-chemicals synthesis because of the lengthy procedures needed to remove the catalyst from the reaction mixture. Also, on the other hand, the process was generally considered non-atom-economic because it required a relatively large excess of alkyl halide, was environmentally unfriendly, and was expensive. From the early stages, researchers have recognized these limitations of TMC ATRA, and various methodologies have been developed to overcome these problems. In particular, catalyst removal in TMC ATRA was addressed through the design of solid-supported catalysts,^{17,381,382} as well as the use of biphasic systems containing fluorosolvents.^{383–386}

Additionally, particularly in the case of copper, various highly active nitrogen-based complexing ligands have been developed that enable homogeneous ATRA reactions to be conducted using much smaller amounts of metal.^{59,387}

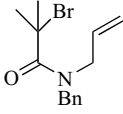
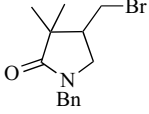
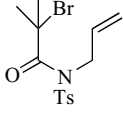
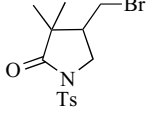
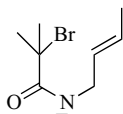
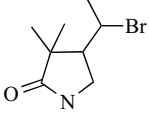
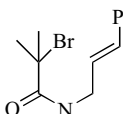
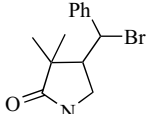
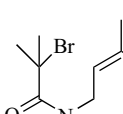
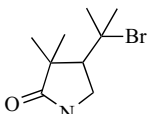
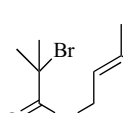
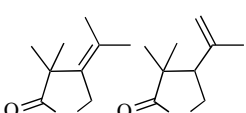
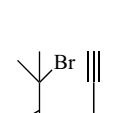
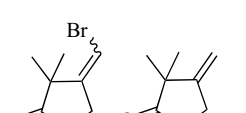
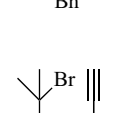
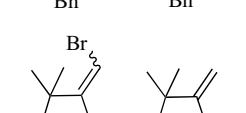
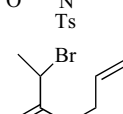
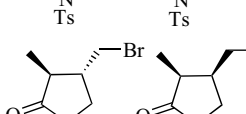
However, by far the most attractive method that solves the above issues in TMC ATRA reactions involves catalyst regeneration in the presence of environmentally benign reducing agents.^{120,165,170,171,174,178,388} This methodology was originally developed for mechanistically similar ATRP in processes termed ICAR and ARGET ATRP.^{44,120,165,167,170–174} Both processes were already illustrated in Scheme 10 (see below). Subsequently, this methodology was first applied to ATRA reactions catalyzed by ruthenium³⁸⁸ and then copper.¹⁷⁸ In all of these processes, the activator (transition-metal complex in the lower oxidation state) is continuously regenerated from deactivator (transition-metal complex in the higher oxidation state) in the presence of reducing agents such as phenols, glucose, ascorbic acid, hydrazine, tin(II) 2-ethylhexanoate, magnesium, and free-radical initiators. Such regeneration compensates for unavoidable radical termination reactions, enabling a significant reduction in the amount of metal catalyst. When applied to ATRA of CCl_4 to alkenes catalyzed by $\text{Cp}^*\text{Ru(III)Cl}_2(\text{PPh}_3)$ complex in the presence of AIBN, turn-over numbers (TONs) as high as 44 500 were obtained.³⁸⁸ Even more impressive TONs were achieved with CBr_4 and $[\text{Cu(II)(TPMA)Br}][\text{Br}]$ (TPMA = tris(2-pyridylmethyl)amine) complex (as high as 160 000), enabling efficient ATRA reactions in the presence of as low as 5 ppm of copper.¹⁷⁷ Previous TONs for copper-catalyzed ATRA ranged between 0.1 and 10.^{17,120} Since the initial reports by our group¹⁷⁸ and the research group of Severin,³⁸⁸ this method of catalyst regeneration in ATRA has been utilized in a series of organic transformations, with particular emphasis on detailed structural and mechanistic understanding of this process.^{39,40,120,175,180,181,377,389–411} This, in turn, could be a clear indicator that this methodology is on a potential trajectory to become a “greener” alternative to currently available synthetic processes for such organic transformations.^{39,120,179} The following sections describe recent synthetic applications of this novel catalytic system.

8.2.1 Highly Efficient TMC ATRC Reactions in the Presence of Reducing Agents

The methodology used to regenerate activator in ATRA originally developed for Ru^{388} and $\text{Cu}^{177,178}$ catalysts has been successfully utilized in a range of 5-exo-trig and 5-exo-dig ATRC reactions of bromoacetamides using 0.1–1 mol% of Cu(I)(TPMA)Br or $[\text{Cu(II)(TPMA)Br}][\text{Br}]$ complexes (Table 3).³⁹⁷ The presence of AIBN as a reducing agent enabled a 30–300-fold reduction in the amount of catalyst previously reported for such cyclizations.^{17,382,412–415} In a related study, $[\text{Cp}^*\text{Ru(III)Cl}_2(\text{PPh}_3)]$ complex, in conjunction with magnesium as a reducing agent, was also shown to be effective in ATRC reactions, producing lactones, lactams, and furans in excellent yields (Table 4).³⁹⁵ *N*-Allyldichloroacetamides are generally considered less reactive substrates for ATRC and, when standard catalysts such as Cu(I)Cl/bpy^{416} ($\text{bpy} = 2,2'$ -bipyridine) or $[\text{RuCl}_2(\text{PPh}_3)_3]^{417}$ are used, high catalyst loadings and/or elevated reaction temperatures are required. Although some ruthenium catalysts have been reported to catalyze ATRC reactions with these substrates at ambient temperatures and relatively low catalyst loadings, the main drawback of these complexes is their high air and moisture sensitivity.^{416,418} As indicated in Table 4, *N*-allyl-*N*-tosyldichloroacetamide successfully undergoes ATRC using as low as 5 mol% of air-stable $[\text{Cp}^*\text{Ru(III)Cl}_2(\text{PPh}_3)]$ complex, in combination with Mg, yielding 94% of the corresponding γ -butyrolactam after 4 hours at room temperature. The 5-endo cyclization reaction of α -bromo enamides has been investigated by Clark *et al.*^{17,381,413,414} Tertiary bromo enamides can be cyclized at room temperature using 30 mol% of $\text{Cu(I)Br/Me}_6\text{TREN}$ complex ($\text{Me}_6\text{TREN} = \text{tris}[2-(N,N\text{-dimethylamino})\text{ethyl}]\text{amine}$) in a reaction that proceeds through a radical–polar crossover mechanism with elimination of HBr .⁴¹³ Using the same ruthenium complex and Mg, instead of $\text{Cu(I)Br/Me}_6\text{TREN}$, the catalyst concentration can be reduced to 0.05 mol% without compromising the yield of the reaction (Table 4).

The last two examples in Table 4 indicate that Mg is also an effective reducing agent in ruthenium-catalyzed ATRC reactions of ethers and dichloroesters. The ATRC of 2,2,2-trichloroethyl ethers has been previously studied by Ram and

Table 3 ATRC of bromoacetamides catalyzed by copper complexes with TPMA ligand in the presence of AIBN.³⁹⁷

Substrate ^a	Product	Solvent	T (°C)	Yield (%)
		CH ₂ Cl ₂	50	84
		CH ₂ Cl ₂	50	97 ^b
		Toluene	110	87
		CH ₂ Cl ₂	50	95
		CH ₂ Cl ₂	50	100
		CH ₂ Cl ₂	50	99
		CH ₂ Cl ₂	50	99
		CH ₂ Cl ₂	50	13 ^b
		Toluene	110	88(1 : 2) ^b
		CH ₂ Cl ₂	50	30(3 : 2)
		Toluene	110	51(1 : 1)
		CH ₂ Cl ₂	50	33(1 : 2)
		Toluene	110	67(1 : 1)
		Toluene	110	80(1 : 1) ^b
		Toluene	110	90(4 : 1)

^a Reactions were performed with [substrate]₀: [Cu(I) or Cu(II)]₀: [AIBN]₀ = 1: 0.01 : 0.10 for 24 h.

^b CuBr₂/TPMA complex was used instead.

Table 4 ATRC reactions catalyzed by $[\text{Cp}^*\text{Ru(III) Cl}_2(\text{PPh}_3)]$ in the presence of Mg.³⁹⁵

Substrate ^a	Product(s)	$[\text{Ru}]_0$ (mol%)	T (°C)	t (h)	Yield (%) ^b
	 (87:13)	5	rt	4	94
	 (37:63)	0.05	rt	9	94
	 (92:8)	0.5	rt	9	89
	 (86:14)	1	60	48	67

^aThe reactions were performed in the presence of activated Mg powder with $[\text{substrate}]_0 = 0.14 \text{ M}$.^bIsolated yield.

Charles.⁴¹⁹ However, efficient cyclizations were achieved at 80 °C using as much as 30 mol% of Cu(I)Cl/bpy complex. Similar catalyst loadings were also required for ATRC of dichloroesters to yield medium-sized lactones.^{384,385,420}

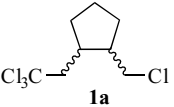
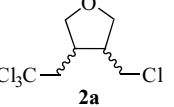
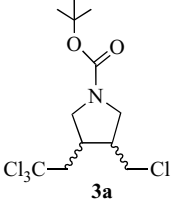
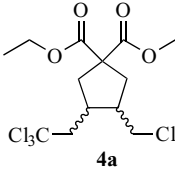
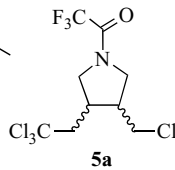
8.2.2 Atom Transfer Sequential Radical Addition/Cyclization Processes

The principal advantages of the methodology for catalyst regeneration in atom transfer sequential radical addition/cyclization reactions are twofold. On one hand, the presence of reducing agents enables a significant reduction in the amount of metal catalyst. Such reduction is very beneficial because it increases the radical annulation efficiency by decreasing the rate of radical trapping by the deactivator (transition-metal complex in the higher oxidation state), compared to the rate of radical ring closure. On the other hand, the rate

constant of deactivation can be further controlled through the choice of complexing metal or ligand design.

The results for ATRA followed by sequential ATRC of CCl_4 to various 1,6-dienes (Scheme 20) catalyzed by $[\text{Cu(II)(TPMA)Cl}][\text{Cl}]$ ¹⁸¹ and $\text{Cu(I)Tp}^{\text{X}398}$ ($\text{X} = 3\text{-}t\text{-Bu,5-Me}$ or 3-Cy,4-Br) complexes in the presence of free-radical diazo initiators (AIBN or V-70) and Mg as reducing agents are summarized in Table 5. AIBN or V-70 initiated the ATRA of carbon tetrachloride to 1,6-heptadiene in the absence of a catalyst resulted in approximately 20% yield of the 5-*exo*-trig product, which formed as a result of simple Kharasch addition. For all other dienes investigated, no cyclic products were observed. However, when the $[\text{Cu(II)(TPMA)Cl}][\text{Cl}]$ complex was used in combination with the free-radical diazo initiator, truly remarkable results were obtained. In the presence of AIBN at 60 °C, cyclic products derived from the^{39,40,410,411} addition of CCl_4 to 1,6-heptadiene, diallyl ether

Table 5 ATRA of CCl_4 to 1,6-dienes followed by sequential ATRC catalyzed by copper(I) homoscorpionate ($\text{Cu(I)(Tp}^X\text{)}$) and $[\text{Cu(II)(TPMA)Cl}][\text{Cl}]$ complexes in the presence of free-radical diazo initiators and Mg .^{181,398}

Products						
						
Product	Ligand ^a	<i>T</i> (°C)	Reducing agent	[Cat.] ₀ (mol%)	Yield (%)	cis : trans
1a	$\text{Tp}^{t\text{-Bu,Me}}$	30	—	1.0 ^b	59	87 : 13
	$\text{Tp}^{\text{Cy,4Br}}$	30	—	1.0	62	84 : 16
	TPMA	60	AIBN	0.02	95(83) ^c	84 : 16
		30	V-70	0.04	92	85 : 15
		rt ^d	V-70	0.04	87	86 : 14
2a	$\text{Tp}^{t\text{-Bu,Me}}$	30	Mg	1.0	>99	86 : 14
	$\text{Tp}^{\text{Cy,4Br}}$	30	Mg	1.0	>99	82 : 18
	TPMA	60	AIBN	0.05	89(70) ^c	80 : 20
		30	V-70	0.1	91	79 : 21
		rt	V-70	0.1	80	82 : 18
3a	$\text{Tp}^{t\text{-Bu,Me}}$	30	Mg	1.0	95	87 : 13
	$\text{Tp}^{\text{Cy,4Br}}$	30	Mg	1.0	90	83 : 17
	TPMA	60	AIBN	0.02	96	74 : 26
		60	AIBN	0.01	91(75) ^c	66 : 34
		30	V-70	0.02	87	64 : 36
4a		rt	V-70	0.02	77	56 : 44
	$\text{Tp}^{t\text{-Bu,Me}}$	30	Mg	1.0	>99	93 : 7
	$\text{Tp}^{\text{Cy,4Br}}$	30	Mg	1.0	>99	90 : 10
	TPMA	60	AIBN	0.02	>99	86 : 14
		60	AIBN	0.01	89(80) ^c	84 : 16
5a		30	V-70	0.02	90	91 : 9
		rt	V-70	0.02	81	86 : 14
	TPMA	60	AIBN	0.02	90(77) ^c	81 : 19
		60	AIBN	0.01	73	84 : 16
		30	V-70	0.1	95	73 : 27
		rt	V-70	0.1	87	73 : 27

^aReactions with $[\text{Cu(II)(TPMA)Cl}][\text{Cl}]$ were performed in CH_3OH for 24 h with $[\text{CCl}_4]_0 : [\text{diene}]_0 : [\text{AIBN or V-70}]_0 = 1.25 : 1 : 0.05$, $[\text{diene}]_0 = 1.0 \text{ M}$. Reactions with Cu(I)Tp^X were performed in benzene- d_6 for 24 h with $[\text{diene}]_0 : [\text{CCl}_4]_0 = 100 : 400$. The yield is based on the formation of 5-*exo*-trig product (cis and trans) and was determined by ^1H NMR using toluene or 1,4-dimethoxybenzene as internal standard (relative errors are $\pm 15\%$).

^bMol percent of catalyst relative to diene.

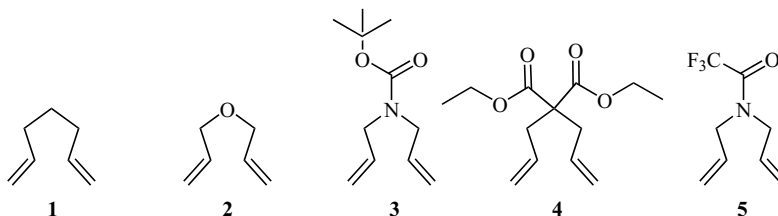
^cIsolated yield after column chromatography for the large-scale reaction.

^drt = $22 \pm 2^\circ\text{C}$.

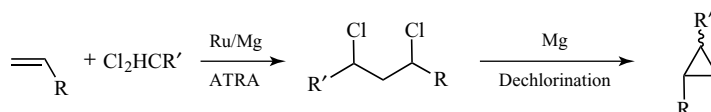
and *N,N*-diallyl-2,2,2-trifluoroacetamide were synthesized in nearly quantitative yields using as low as 0.02 mol% of the catalyst (relative to diene). On the other hand, excellent results with *tert*-butyl-*N,N*-diallylcarbamate and diethyl diallylmalonate were also achieved using even smaller amounts of the catalyst (0.01 mol%). Cyclizations were also very efficient at ambient temperature using V-70 as a reducing agent, although slightly higher catalyst loadings were required (0.04–0.1 mol%). Similarly,

neutral copper(I) homoscorpionate complexes also required higher catalyst loadings at 30°C (1 mol%).³⁹⁸

The data presented in Table 5 also indicate that, regardless of the choice of diene, catalyst, reaction temperature, or reducing agent, 1,2-disubstituted cyclopentanes showed a strong preference for the formation of the cis product, which was also observed in similar free-radical cyclizations that do not utilize transition-metal complexes as halogen atom transfer agents.^{421–423}



Scheme 20 1,6-Dienes used for sequential ATRA followed by ATRC.



Scheme 21 Synthesis of cyclopropanes via sequential ATRA/dechlorination reactions catalyzed by Ru in the presence of Mg.⁴⁰⁵

8.2.3 Sequential Organic Transformations Involving ATRA/ATRC

Apart from being successful for a variety of ATRA/ATRC reactions discussed above,^{39,120,175,177–181,388,395,398,404,405,424,425} the new methodology for catalyst regeneration in the presence of reducing agents was also successfully applied to one-pot synthesis of cyclopropanes via sequential ATRA–dechlorination reactions in the presence of $[\text{Cp}^*\text{Ru(III)Cl}_2(\text{PPh}_3)]$ complex and magnesium.⁴⁰⁵ In this organic transformation, magnesium not only regenerates the active Ru(II) species needed for ATRA and ATRC but also acts as a dechlorination reagent. The reaction sequence is depicted in Scheme 21. Alkenes are first reacted with 1,1'-dichlorides in ruthenium-catalyzed ATRA process. The resulting 1,3-dichlorides are then directly converted into cyclopropanes by reductive coupling with magnesium. Shown in Table 6 are some representative examples for this transformation.

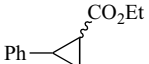
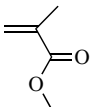
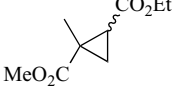
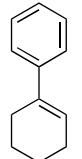
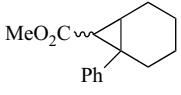
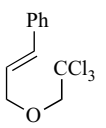
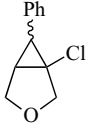
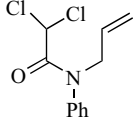
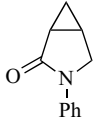
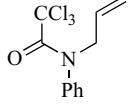
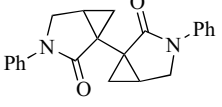
As evident from Table 6, sequential ATRA/dechlorination reactions are applicable to a variety of alkenes (styrene, methyl methacrylate, and cyclohexenylbenzene) as well as alkyl halides (dichloroacetate, chloroform, and dichloroacetonitrile). The corresponding yields of the cyclopropanes are relatively high, with the trans isomer being slightly preferred. Also, the reactions can be conducted in an intramolecular fashion to yield the corresponding

bicyclic cyclopropanes. This has been demonstrated in the case of trichlorinated allylethers and di- and trichlorinated *N*-allylacetamides (Table 6). Cyclopropanes were isolated in yields between 57 and 67% using 1–2 mol% of the $[\text{Cp}^*\text{Ru(III)Cl}_2(\text{PPh}_3)]$ complex in conjunction with 40 equiv of Mg (relative to substrate). It is interesting to note that ATRA/dechlorination of *N*-allyl-2,2-dichloroacetamides yielded the corresponding 3-azabicyclo-[3.1.0]hexan-2-one derivatives, which are precursors of *cis*-2-amino-methylcyclopropanecarboxylic acid (CAMP), a pharmacologically active analog of γ -amino butyric acid (GABA).

Furthermore, in some cases trichloroacetamides yielded a complete dechlorination product in which two 3-azabicyclo-[3.1.0]hexan-2-one fragments were bridged through a carbon–carbon bond. It is quite remarkable that such a complex molecule can be obtained with high diastereoselectivity in a simple one-pot reaction.

Additionally, one-pot sequential reactions involving azide-alkyne $[3 + 2]$ cycloaddition^{426–429} and ATRA catalyzed by $[\text{Cu(II)(TPMA)X}][\text{X}]$ ($\text{X} = \text{Br}^-$ or Cl^- , TPMA = tris(2-pyridylmethyl)amine) in the presence of ascorbic acid as a reducing agent have been reported.⁴³⁰ Reactions with azidopropyl methacrylate and 1-(azidomethyl)-4-vinylbenzene in the presence of a variety of alkynes (phenylacetylene, 3,4-difluorophenylacetylene, propargyl alcohol, 2-methyl-3-butyn-2-ol, methyl propiolate and

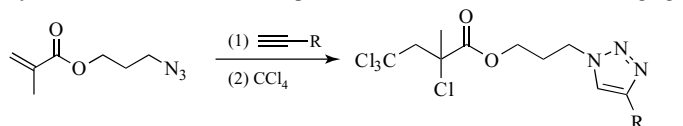
Table 6 Sequential ATRA(ATRC)/dechlorination reactions catalyzed by the $[\text{Cp}^*\text{Ru}(\text{III})\text{Cl}_2(\text{PPh}_3)]$ complex in the presence of Mg .⁴⁰⁵

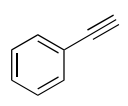
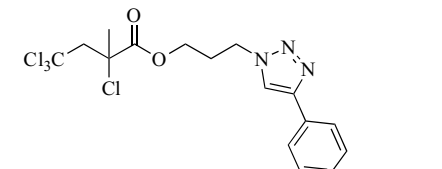
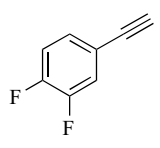
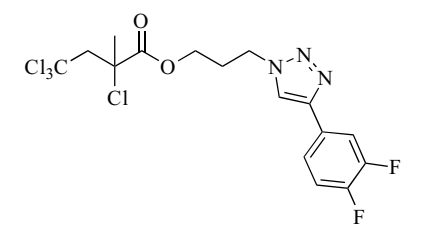
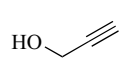
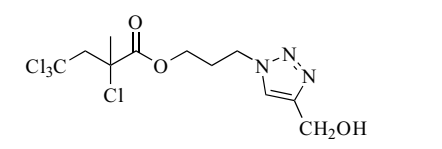
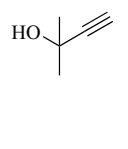
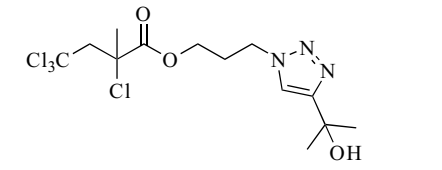
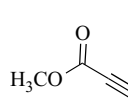
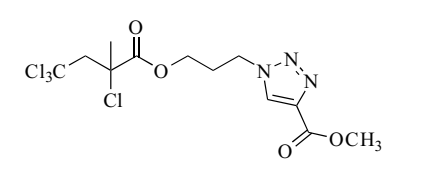
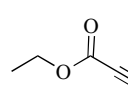
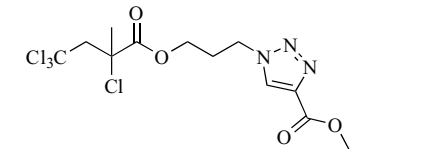
Substrate(s) ^a	Product	t_1 (h)	t_2 (h)	Yield ^b	cis:trans ^c
ATRA					
 $\text{Cl}_2\text{HCCO}_2\text{Et}$		6	1	74	1 : 3.0
 Cl_2HCCN		24	2	70	1 : 2.8
 CHCl_3		24	2	71	1 : 2.3
 $\text{Cl}_2\text{HCCO}_2\text{Et}$		8	3	60	1 : 2.9
 $\text{Cl}_2\text{HCCO}_2\text{Et}$		48	0.5	51	1 : 12.6
ATRC					
		3	1	67	1 : 11.7
		4	0.5	65	—
		2	24	61	—

^a ATRA reactions were performed in toluene with $[\text{alkene}]_0 = 0.33$ M, $[\text{Cl}_2\text{HR}]_0 = 0.33$ M, and $[\text{alkene}]_0/[\text{Mg}]_0 = 1 : 40$ with 1 mol% of Ru catalyst. ATRC reactions were performed in toluene with $[\text{alkene}]_0 = 0.16$ M and $[\text{alkene}]_0/[\text{Mg}]_0 = 1 : 40$ with 1 or 2 mol% of Ru catalyst. After the time t_1 at 60 °C, the reaction mixture was diluted with 2.5 times the volume of THF and then stirred for time t_2 at either 0 °C or 25 °C.

^b Isolated yield.

^c cis/trans ratio was determined by ^1H NMR analysis.

Table 7 Sequential azide–alkyne [3 + 2] cycloaddition and atom transfer radical addition (ATRA) of carbon tetrachloride catalyzed by [Cu(II)(TPMA)Cl][Cl] in the presence of ascorbic acid^a as a reducing agent.⁴³⁰


Alkyne	Product	[Cu(II)] ^b	t (h) ^c	Yield (%) ^d
		1.0 0.50 0.25 0.20	2 3 3 3	~100(91) ^e 90 78 70
		1.0 0.50 0.25	3 4 6	96 90 83
		1.0 0.50 0.25 0.20	3 3 3 3	95(86) ^e 86 83 73
		1.0 0.50 0.25 0.20	3 3 3 3	~100 86 74 72
		1.0 0.50 0.25 0.20	1 1 1 1	98 91 86 72
		1.0 0.50 0.25 0.20	3 3 3 3	~100(89) ^e ~100 85 65

^a All reactions were performed in CH₃OH at 60 °C using [AzPM]₀: [Alkyne]₀ = 1 : 1, [AzPM]₀ = 0.50 M. The amount of ascorbic acid in each system ranged between 20 and 25 equiv relative to copper(II) complex.

^b Mole percent relative to alkyne.

^c Reaction time for azide–alkyne cycloaddition (time for ATRA reaction was 8 h for all substrates with [AzPM]₀: [CCl₄]₀ = 1 : 1.25).

^d The yield is based on the formation of the product and was determined by ¹H NMR spectroscopy using *p*-dimethoxybenzene as internal standard (relative errors are ±15%).

^e Isolated yield for the large scale reaction.

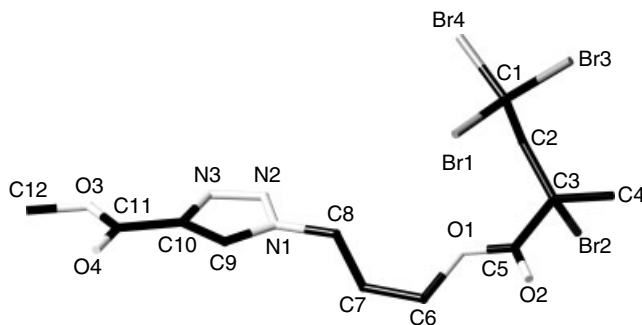


Figure 11 Molecular structure of (*S*)-monoadduct formed by the sequential azide–alkyne [3 + 2] cycloaddition between azidopropyl methacrylate and methyl propiolate followed by ATRA of CBr_4 .

ethyl propiolate), and alkyl halides (carbon tetrachloride, carbon tetrabromide, ethyl trichloroacetate, methyl trichloroacetate, ethyl dichloroacetate, methyl dichloroacetate, dichloroacetonitrile, and 2-bromopropionitrile) proceeded efficiently to yield highly functionalized (poly)halogenated esters and aryls containing triazolyl group in the presence of as low as 0.5 mol% of the catalyst. Some representative examples in the case of CCl_4 are shown in Table 7. The molecular structure of the product isolated from the reaction between azidopropyl methacrylate and methyl propiolate, followed by ATRA of CBr_4 is depicted in Figure 11. It is envisioned that the presented methodology involving a combination of azide–alkyne [3 + 2] cycloaddition and ATRA could have further implications in organic synthesis of functionalized triazoles, which have recently been identified as the lead targets for the screening of potential pharmaceutical drugs.

9 CONCLUSIONS AND FUTURE OUTLOOK

This article focused on TMC ATRP and mechanistically similar ATRA. Both processes utilize TMCs as halogen atom transfer agents. ATRP enables the synthesis of polymeric materials with well-controlled molecular weight, molecular weight distribution, composition, molecular architecture, and chain end functionality. ATRA, on the other hand, is particularly suitable for the synthesis of small and highly functional organic molecules. Basic phenomenology, components (alkyl halide, monomer, solvent and catalyst), as well as current and forthcoming applications are reviewed.

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Sb, Bi, Te, and I-Transfer Polymerization and Applications

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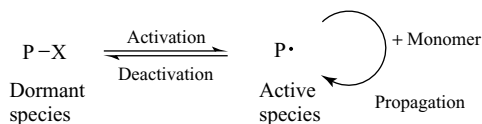
1 INTRODUCTION

Radical polymerization is one of the most successful industrial utilizations of radical chemistry, and nearly 50% of all synthetic polymers are estimated to be produced by this method (see **Radical Polymerization in Industry**). This is primarily because of the robustness of radical polymerization, which originates from the characteristic features of radicals. Owing to soft, neutral, and highly reactive characters of radicals, the polymerization is compatible with a variety of polar functional groups and solvents and usually proceeds under mild conditions.^{1–4} The conditions are strikingly different from other vinyl polymerization methods, namely anion, cation, and coordination polymerizations, which usually require stringent reaction conditions to avoid the occurrence of undesirable side-reactions involving protic solvents, oxygen, and/or polar functional groups. The disadvantage of the conventional radical polymerization is, however, insufficient control of the macromolecular structure of the resulting polymers and gives macromolecules that are polydisperse with a broad molecular weight distribution (MWD). While living anionic^{5,6} cationic,^{7,8} and coordination polymerization^{9–11} have already been developed to control molecular weights, MWDs, and monomer sequences through block copolymer synthesis, the living version of radical polymerization has become possible only recently.

The living or controlled radical polymerization (LRP) has been becoming an indispensable method for creating well-controlled but highly complex macromolecules with the hope that they will lay the essential foundation for new polymeric materials with improved and/or new properties and functions.

The difference between LRP and conventional radical polymerization is that the activity of polymer-end species is preserved throughout the polymerization period by reversible generation of the radical from a so-called dormant species, which possesses appropriate functional groups at the polymer end for radical generation (Scheme 1).^{12,13} This “pseudo” deactivation of the polymer-end radical to the dormant species decreases the concentration of radical species in solution and minimizes undesirable side reactions leading to dead polymers. Furthermore, the rapid deactivation makes it possible to elongate all the polymer chains with similar chain lengths. The faster deactivation leads to higher control of MWD under an ideal condition without any termination reactions.

LRPs that have been widely used include nitroxide-mediated radical polymerization (NMP, see **Nitroxide-Mediated Polymerization and its Applications**),¹⁴ atom-transfer radical polymerization (ATRP, see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**),^{13,15–17} and reversible addition–fragmentation chain-transfer



Scheme 1 General mechanism of LRP. P and X denote polymer-end and capping species, respectively.

radical polymerization (RAFT, see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).^{18–20} Organostibine-,^{21–24} organobismuthine-,^{25,26} and organotellurium-mediated^{27–34} LRP (SBRP, BIRP, and TERP, respectively)^{35,36} are relatively new methods developed by the author's research group. New variants of LRP have also emerged, such as cobalt-mediated polymerization,³⁷ single-electron transfer LRP,^{38–40} and titanium-catalyzed polymerization.⁴¹ Organoiodine-mediated LRP (IRP), which is one of the oldest LRP,⁴² has also been used in many instances. Each method utilizes unique chemical structures and activation/deactivation mechanisms of the dormant species, and these differences make each LRP method unique both mechanistically and synthetically.

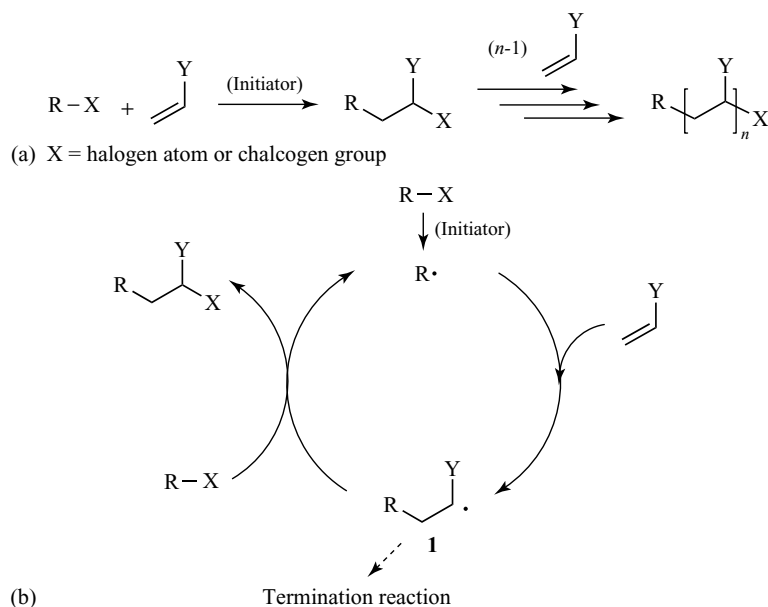
This review surveys the synthetic and mechanistic aspects of SBRP, BIRP, TERP, and IRP, all of which proceed through similar activation/deactivation mechanism of dormant and radical species. One of the theoretical criteria of the livingness in LRP is low MWD ($M_w/M_n < 1.5$, where M_w and M_n refer to weight and number average molecular weights, respectively), which is inaccessible by the conventional radical polymerization (see **Fundamentals of Controlled/Living Radical Polymerization**). Therefore, examples that meet the criteria are only included in this review. In addition, while organoiodine compounds are sometimes used as initiators for ATRP in the presence of a metal catalyst, such examples are also excluded in this article. Recent developments in LRP under different methods (see **Nitroxide-Mediated Polymerization and its Applications, Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications and Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**) and background and kinetics of the LRP (see **Fundamentals of Controlled/Living Radical**

Polymerization and Kinetics of Polymerizations) are also included in this article.

2 BACKGROUND: EARLY DEVELOPMENTS IN ORGANOHETEROATOM-MEDIATED LRP

Radical-mediated atom-transfer addition reactions of haloalkanes to alkenes in the presence of a radical initiator were first reported by Kharasch in 1945 (Scheme 2a).^{43,44} This type of reaction has caught attentions from organic chemists since the rediscovery of the iodine group transfer radical addition reaction by Curran in 1986.^{45–47} Phenylselenyl group transfer and phenyltellanyl group transfer radical addition reactions of organoselenides and organotellurides, respectively, were subsequently reported by several groups.^{48–57} The reaction proceeds by a radical chain reaction, and carbon-centered radical R generated from an organoheteroatom compound, R–X, reacts with an alkene or alkyne to generate a new carbon-centered radical (1), which reacts with R–X to give the addition product with the regeneration of R radical (Scheme 2b).

Repetition of atom or group transfer addition reactions to alkenes leads to the formation of living polymers possessing heteroatom functionality X at the ω -polymer end (Scheme 2a). The effect of heteroatom compounds on the control of MWD was recognized for the first time by Tatemoto and coworkers, who observed the living character of radical polymerization of fluorinated monomers by the addition of organoiodine compounds, $(CF_3)_2CFI$, and obtained polymers with low MWDs.⁵⁸ They also observed the linear increase in the molecular weight versus the conversion and also successfully synthesized block copolymers. The drawback of IRP is, however, its low versatility, and other conventional monomers, such as styrene and (meth)acrylate derivatives, have been used with only limited success.^{59–66} Several new conditions have been recently reported to increase the control in IRP. For example, Kamigaito and coworkers reported that fluoroalcohols are effective solvents to increase the control of tacticity and MWDs in the polymerization of vinyl acetate.⁶⁷ They also found that manganese-mediated photo-induced polymerization considerably increased the polymerization of conventional monomers.^{68–70} Goto and coworkers



Scheme 2 (a) Atom and group transfer radical addition reaction and (b) its mechanism.

have recently developed a modified version of IRP, in which several inorganic and organic halides, phenols, and hydrocarbons in the presence of conventional organoiodine chain-transfer agents (CTAs) increase the control of MWD in IRP.^{71–76} They call this method as *reversible chain transfer-catalyzed polymerization* (RTCP), because inorganic or organic radicals generated from the additives reversibly activate organoiodine CTAs. Since various monomers gave structurally well-controlled polymers with MWD of below the theoretical limit by RTCP, synthetic and mechanistic aspects of these results are discussed in this article.

Kwon *et al.*^{77–79} have utilized diaryldiselenides as a photoiniferter or radical trapping agent,⁸⁰ which generate organoselenium dormant species *in situ* by the reaction of the monomers. They also employed phenylselenenyl-substituted CTAs for the polymerization of styrene (St) under photo irradiation.⁸¹ The polymerization showed living character as judged from a linear increase in M_n on monomer conversion and successful synthesis of block copolymers. However, the control of MWD was insufficient, and polymers with considerably high MWDs were obtained ($M_w/M_n > 1.5$). The same group also reported the effect of diphenylditelluride on the conventional 2,2-azobisisobutyronitrile (AIBN)-initiated radical polymerization of St.⁸²

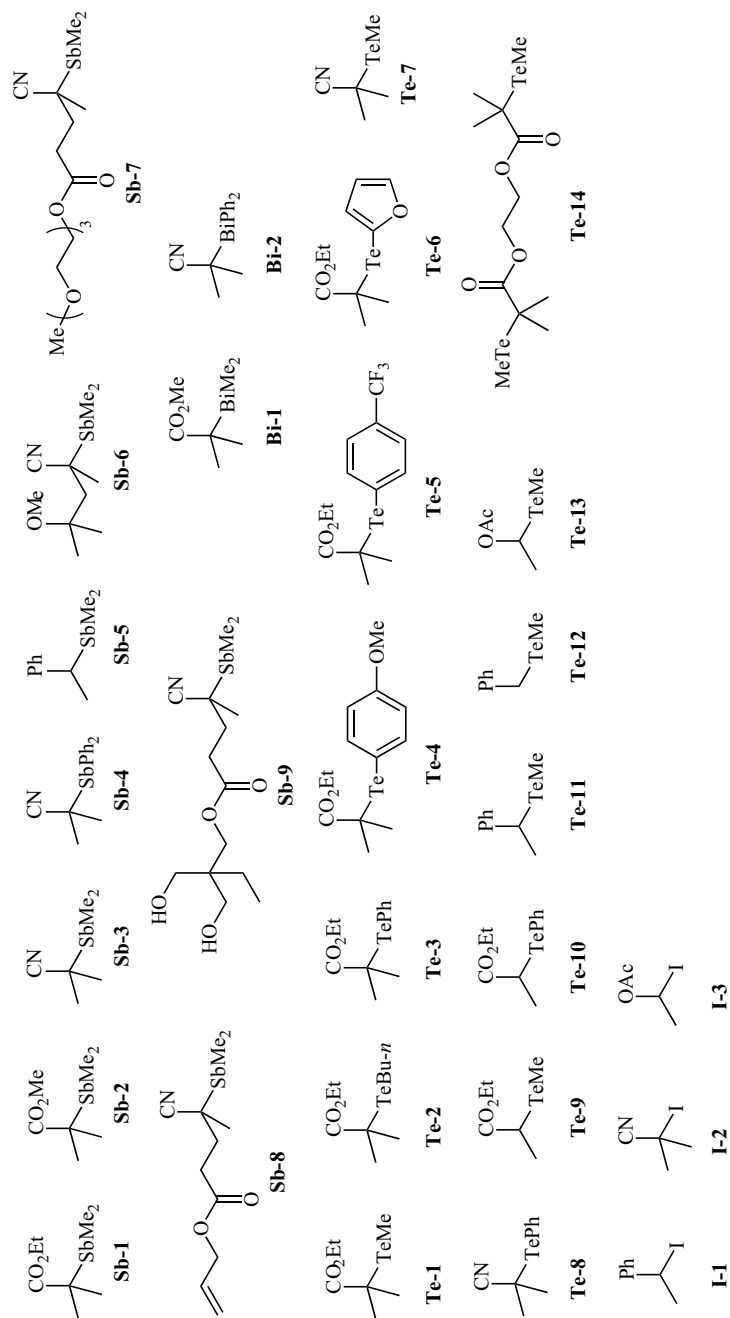
They found that MWD becomes narrow ($M_w/M_n = 1.26–1.18$) with the addition of more than 0.5–2.0 equiv of diphenylditelluride to AIBN, whereas the addition of more ditelluride led to the formation of polystyrene (PS) with lower M_n . They also propose the existence of a phenyltellanyl-substituted ω -polymer-end group, but there was no direct evidence to support the end group structure.

On the basis of the findings of reversible radical generation from organotellurium compounds via carbon–tellurium bond thermolysis and photolysis^{83,84} and its applications to organic synthesis,^{85–92} Yamago and coworkers developed TERP, SBRP, and BIRP.^{35,36,93} The details of these methods are discussed below.

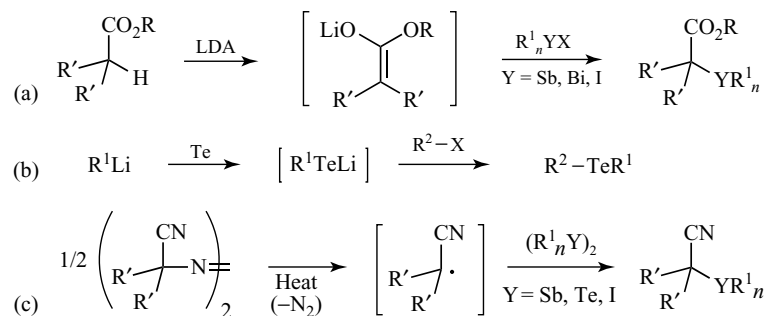
3 ORGANOHETEROATOM-MEDIATED LRP

3.1 Chain Transfer Agents

CTAs applied to the controlled polymerization under SBRP, BIRP, TERP, and IRP are summarized in Scheme 3. Although organostibine, organobismuthine, and organotellurium CTAs are moderately air (oxygen) sensitive, they can be stored for long periods under a nitrogen atmosphere and are handled using standard syringe techniques. Organoiodine



Scheme 3 Structures of organoheteroatom CTAs.



Scheme 4 Synthetic route to organoheteroatom CTAs.

CTAs are stable to air, but they easily decompose by heat and light with elimination of HI. Therefore, organoiodine CTAs cannot be stored for a long period. This is probably because C–I bond is more ionic than C–Sb, C–Bi, and C–Te bonds.

The availability of CTAs is a key issue with respect to practical applications of LRPs. Many of the organoheteroatom CTAs shown in Scheme 3 are prepared on large scales and easily purified. Most scalable synthetic route to these CTAs are ionic reaction, such as an enolate route for the preparation of organostibine and bismuthine CTAs (Scheme 4a) and halogen (usually bromine)-heteroatom exchange reaction for organotellurium and organoiodine CTAs (Scheme 4b). Radical chemistry also plays important role in the preparation of CTAs, especially those possessing polar functional groups.

As the heteroatom functional groups in the CTAs are moderately sensitive to oxygen and also reactive under various conditions, postmodifications to introduce functional groups starting from the existing CTAs are limited. In addition, as the synthesis of CTAs requires basic conditions, many polar functional groups are not compatible. The method shown in Scheme 4c, which relies on the reaction of a radical generated from an azo-initiator with distibines,²³ ditellurides,³⁰ and molecular iodine^{61,62,65,66,72,74} proceeds under neutral conditions and is applicable to the synthesis of functional CTAs.

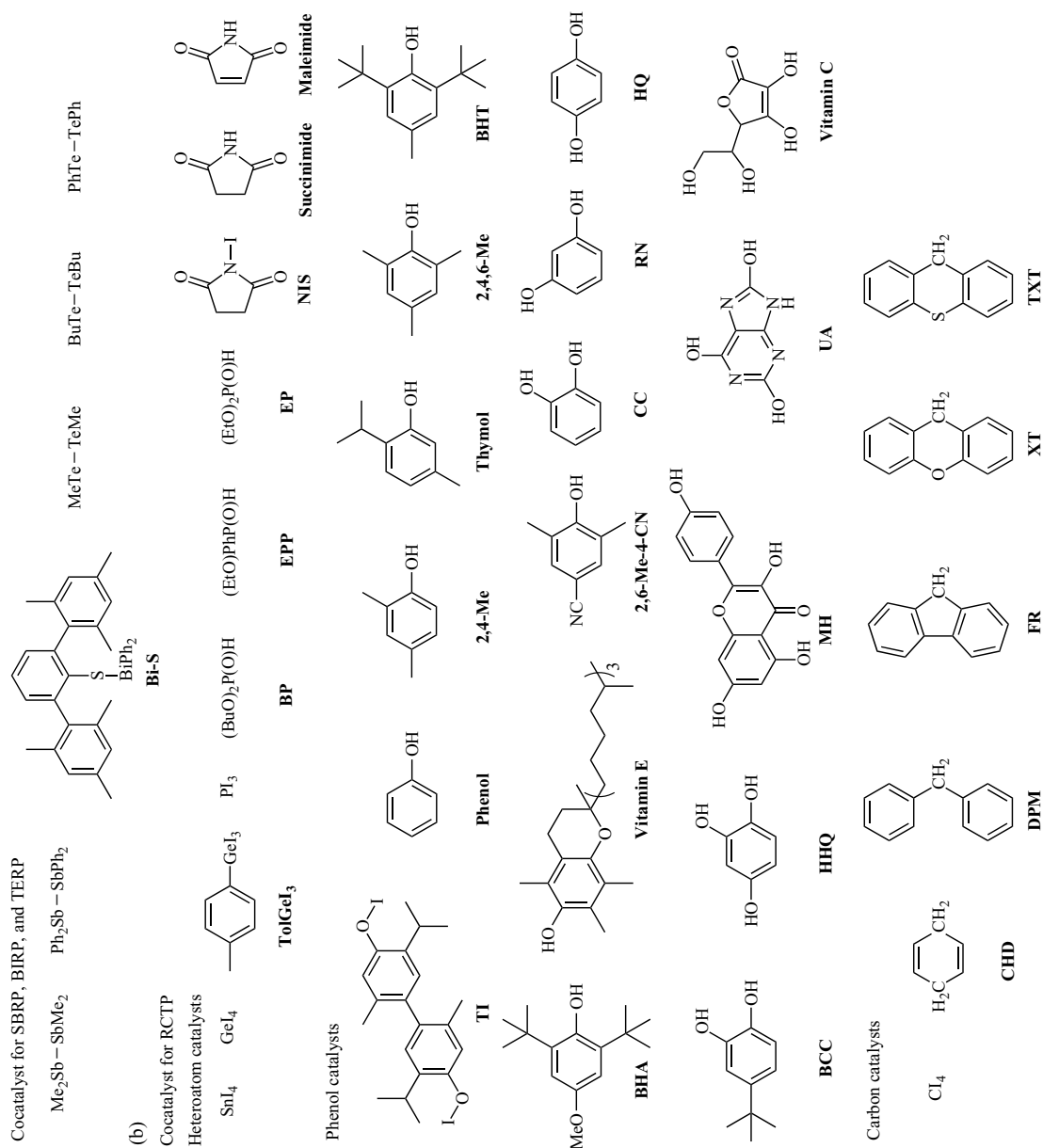
The reaction of azo-initiators with tetramethyl-distibine and molecular iodine took place with high coupling efficiencies. Yields of the CTAs were about 60% when a 1:1 mixture of an azo-initiator and the distibine molecular iodine was employed. Since about 40% of the radicals generated from the azo-initiators dimerize within a solvent cage,⁹⁴ the result indicates that almost all the radicals

that diffused from the cage were captured by the distibine and iodine. Organostibine CTAs **Sb-3**, **Sb-6**, **Sb-7**, **Sb-8**, and **Sb-9** were prepared via this route starting from the corresponding azo-initiators. Ester, ether, terminal alkene, and alcohol groups were incorporated into the CTAs. α -Functional polymers were synthesized starting from these functional CTAs (see below). On the contrary, trapping of radicals by ditellurides was insufficient and gave the desired CTAs in low yields (8–18%).

Goto and Tsujii recently reported that benzyl alcohol and its derivatives can be used as an initiator for the polymerization of methyl methacrylate (MMA) in the presence of *N*-iodosuccinimide (NIS) and AIBN under RTCP conditions.⁷⁵ Hydroxyl radical generated from an alcohol and NIS reacts with a monomer followed by trapping with iodine source generating an organoiodine dormant species. Among primary, secondary, and tertiary alcohols, the primary alcohol exhibited the highest initiation efficiency, but the efficiency was at most 55%.

3.2 Additives (Cocatalysts)

Several diheteroatom compounds, such as tetra-methyl distibine, tetraphenyl distibine, 2,6-dimesitylphenylthiodiphenylbismuthine (**Bi-S**), dimethyl ditelluride, dibutyl ditelluride, and diphenyl ditelluride, were used as an additive to SBRP, BIRP, and TERP (Scheme 5a). These compounds considerably increase the MWD control by affecting the activation/deactivation reactions of the dormant/radical species (see mechanistic section in detail). However, they do not directly generate initiating radicals and, thus, new polymer chains. Therefore, these compounds can be regarded as a



cocatalyst in controlling the MWD. A binary system consisting of an organoheteroatom CTA and a cocatalyst and a ternary system consisting of a CTA, a cocatalyst, and a conventional radical initiator were employed for the LRP (see Section 3.4).

Vast array of compounds having X–I and X–H bonds, in which X refers to carbon and heteroatom, are reported to be effective cocatalysts to increase the MWD control in the presence of organoiodine CTAs under RTCP condition (Scheme 5b). These compounds include inorganic and organic heteroatom compounds, such as SnI_4 , GeI_4 , *p*-tolyl- GeI_3 (TolGeI₃), PI_3 , butyl phosphite, ethyl phenylphosphinate, ethyl phosphite, NIS, succinimide, and maleimide, phenol derivatives, such as thymol diiodide, phenol, 2,4-dimethylphenol (2,4-Me), thymol, 2,4,6-trimethylphenol, dibutylhydroxytoluene, dibutylhydroxyanisole, vitamin E, 4-cyano-2,6-dimethylphenol (2,6-Me-4-CN), catechol, resorcinol, hydroquinone, 4-*t*-butyl catechol, hydroxyl hydroquinone (HHQ), morin hydrate (MH), uric acid (UA), and vitamin C, and carbon compounds, such as Cl_4 , 1,4-cyclohexadiene, diphenylmethane, fluorene, xanthene (XT), and thioxanthene (TXT). Synthetic scope and the role of the diheteroatom compounds are discussed in the following section.

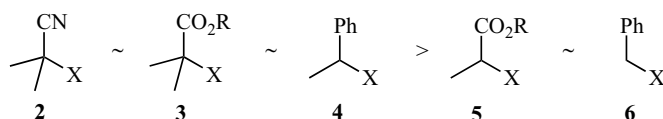
3.3 Structural Effect of CTAs on the Control of LRP

Besides the requirement of the efficient activation/deactivation reaction in LRP for the control of MWD, the general requirement for the control of MWD in living polymerization is the efficient initiation reaction. This step must be faster than or at least similar to the propagation step. To ensure the fast activation reaction, CTAs mimicking the polymer-end structure have been used for all methods.

Structures of organoheteroatom CTAs on the control of MWDs are generalized in Scheme 6. Specific examples using organotellurium CTAs are summarized in Table 1. These CTAs mimic the polymer-end structure of polymethacrylate, polymethacrylonitrile, polyacrylate, and PS. Ester and nitrile groups stabilize carbon-centered radicals about 40 kJ mol^{-1} and phenyl group about 70 kJ mol^{-1} by conjugation when hydrogen is replaced by these groups.⁹⁵ Alkyl group also stabilizes its α -radical via hyperconjugation by about $15\text{--}20 \text{ kJ mol}^{-1}$. Therefore, the radical species generated from **2**, **3**, and **4** are about 20 kJ mol^{-1} more stable than those from **5** and **6**, as indicated by the bond dissociation energies (BDEs) of methyltellanyl derivatives ($\text{X} = \text{TeMe}$, Table 1). In addition, the reactivities of the radicals generated from these CTAs to monomers are similar when the radical possesses same stabilizing group. Therefore, CTAs having polymethacrylate and polymethacrylonitrile structures show higher control than polyacrylate structures, and phenylethyl-substituted CTAs mimicking PS polymer end are better CTAs than benzyl derivatives. The same structural effects on the control of MWD have also been observed in NMP,^{96,97} ATRP,⁹⁸ and RAFT.⁹⁹ It should be noted that control of the MWD does not always correlate to the BDEs of CTAs as well as those of dormant species because bond homolysis is not the main mechanism of the activation of dormant species in SBRP, BIRP, TERP, and IRP as discussed in the mechanistic section.

3.4 Polymerization Conditions

Three conditions have been developed for conducting SBRP, BIRP, TERP, and IRP. These conditions are defined by the method for generating initiating radical species as discussed in the mechanistic section. The first condition (A in Table 2) is a purely thermal condition, in which a CTA and



Scheme 6 Structural effect of CTA on the control of LRP.

Table 1 Structural effect of organostibine,²¹ organobismuthine,²⁵ and organotellurium^{27,29,33} chain-transfer agents (CTAs) on the polymerization of styrene (100 equiv) under thermal conditions.

CTA	BDE (kJ mol ⁻¹) ^a	Yield (%)	M_n (g mol ⁻¹)	M_w/M_n
Sb-1	121	99	8700	1.14
Sb-3	—	95	9000	1.17
Sb-5	—	99	9300	1.22
Bi-1	113	99	10 500	1.07
Te-1	114	88	11 500	1.18
Te-2	—	99	10 300	1.25
Te-3	—	88	12 200	1.08
Te-4	—	90	9400	1.09
Te-5	—	81	9100	1.06
Te-6	—	88	7800	1.23
Te-7	120	98	9400	1.15
Te-9^b	142	70	3100	1.33
Te-11	123	91	9100	1.18
Te-12	142	86	8300	1.34

^aBond dissociation energy calculated by the B3LYP/6-31G*(H,C,N,O)+LANL2DZ(Sb,Bi,Sb).^bPolymerization was carried out with 30 equiv of styrene.**Table 2** Polymerization of styrene (St), *n*-butyl acrylate (BA), and methyl methacrylate (MMA) under different conditions.

Monomer	Condition ^a	Temperature (°C)	Time (h)	Yield (%)	M_n (g mol ⁻¹)	M_w/M_n
BA	A	100	24	69	8300	1.12
	B	60	0.5	92	10 700	1.17
	C	0	4	86	10 500	1.16
St	A	100	98	98	9400	1.15
	B	60	11	94	11 300	1.17
	B ^b	40	23	82	7400	1.21
MMA ^c	A	80	13	81	8300	1.12
	B	60	2	98	9600	1.15

^aConditions: (A) A mixture of chain-transfer agent (**Te-1**) and monomer (1 : 100) was heated.²⁷ (B) A mixture of AIBN, chain-transfer agent (**Te-1** or **Te-7**), and monomer in a ratio of 1 : 1 : 100 was heated.²⁹ (C) A mixture of chain-transfer agent (**Te-3**) and monomer was irradiated with a 500-W high-pressure Hg lamp through a cutoff filter.³⁴^b2,2'-Azobis(4-methoxyvaleronitrile) was used instead of AIBN.^cOne equiv of dimethyl ditelluride was added.

a monomer are typically heated between 80 and 110 °C.^{27,28} BIRP and TERP proceed under this condition. The second condition (B) is a ternary system consisting of a radical initiator, a CTA, and a monomer,²⁹ and all methods proceed under this condition. Azo-initiators are typically employed under thermal conditions, but photo-initiators are also utilized. The polymerization conditions depend on the decomposition temperature of the initiator used, and it usually proceeds at lower temperature than that of the condition A. The third condition (C) proceeds under photo irradiation of a mixture of an organotellurium CTA and a monomer,³⁴ and the

polymerization proceeds under much milder conditions, such as temperatures in the range of 0 °C to room temperature. The cocatalysts can be added to the above-mentioned conditions to improve the MWD control.

Effects of the conditions on the polymerization of *n*-butyl acrylate (BA), St, and MMA in the presence of organotellurium CTAs **Te-1**, **Te-3**, and **Te-7** are summarized in Table 2. Polymerization of BA (100 equiv) under the condition A was sluggish and monomer conversion reached 70% after being heated at 100 °C at 24 hours. Despite long reaction time required to achieve high monomer

conversion, poly(butyl acrylate) (PBA) with narrow MWD ($M_w/M_n = 1.12$) was obtained. Polymerization under the condition B, on the other hand, completed within 0.5 hours at 60 °C by the addition of AIBN and gave well-controlled polymers ($M_w/M_n = 1.17$). Uncontrolled free radical polymerization did not compete with LRP even in the presence of azo-initiators. Polymerization proceeded even at 0 °C under condition C, and PBA with a narrow MWD ($M_w/M_n = 1.16$) was also obtained with high monomer conversion.

Polymerization of St and MMA under the conditions A and B has been reported. Polymerization of St and MMA under condition A proceeded in the temperature range of 80–100 °C and that under condition B with AIBN as an initiator proceeded at 60 °C. Polymerization of St using condition B took place at 40 °C with 2,2'-azobis(4-methoxyvaleronitrile) as an initiator, which decomposes at a lower temperature than AIBN does. High level of control of MWD ($M_w/M_n = 1.12$ – 1.21) was observed regardless of the method used.

Since polymerization takes place at lower temperatures and with shorter reaction times under conditions B and C than those under condition A, these methods should be suitable for monomers that undergo unwanted side reactions at high temperatures. The high energy efficiencies of conditions B and C are also useful for industrial applications.

Since thermolysis of the dormant species is the rate determining step in condition A (see mechanistic section in detail), the rate of polymerization is strongly affected by the strength of the carbon–heteroatom bond of the dormant species. The PBA dormant species has a higher BDE than the PS- and poly(methyl methacrylate) (PMMA) dormant species do by an analogy from the BDEs of structurally related CTAs (Table 1). Therefore, the polymerization of BA required a higher temperature and a longer reaction time than those of St and MMA. Conversely, the rate control step is usually the propagation reaction in condition B because the initiating radicals are provided from azo-initiators. Therefore, the rate of polymerization is similar to the propagation rate; BA is the fastest followed by MMA and then St.

SBRP, BIRP, TERP, and IRP are routinely carried out without solvent (bulk polymerization), but several solvents have also been used. Polar solvents, such as *N,N*-dimethylformamide (DMF)

and tetrahydrofuran, were used for the polymerization of *N*-isopropylacrylamide (NIPAM), acrylonitrile (AN), *N*-vinylcarbazole (NVC), and acrylic acid (AA).^{21,25,28,34} TERP of NIPAM was also carried out in a DMF/water mixture at 20 °C under condition C.³⁴ RTCP of polar monomers, such as glycidyl methacrylate (GMA), hydroxyethyl methacrylate (HEMA), phenyl methacrylate (PHMA), and AN were carried out in anisole, ethanol, 1-propanol, methyl ethyl ketone, ethylene carbonate, and dipropylene glycol monomethyl ether.^{71,73,76}

Owing to the high compatibility of water, TERP³¹ and RTCP¹⁰⁰ were applied to a mini-emulsion condition by Okubo *et al.* also reported that TERP of BA and St could be carried out under emulsifier-free emulsion polymerization conditions by employing a water soluble macro-CTA, PMMA₃₀-TeMe, and a water soluble azo-initiator.^{101–103} These results demonstrate the applicability of TERP and RTCP in aqueous heterogeneous systems.

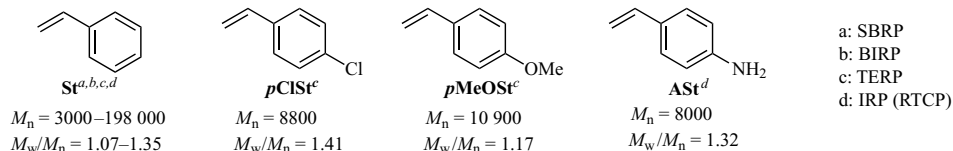
3.5 Synthetic Scope: Homopolymerization

A synthetic advantage of SBRP, BIRP, TERP, and IRP (RTCP) is their high versatility in polymerizing a variety of monomer families using the same CTAs. Selected monomers polymerized in a controlled manner using these methods are summarized in Scheme 7. M_n and MWD data were taken from the polymerization using CTAs with general structures **2**, **3**, and **4**. The monomer conversions are usually high (>90%), and polymers with narrow MWDs were obtained in all cases.

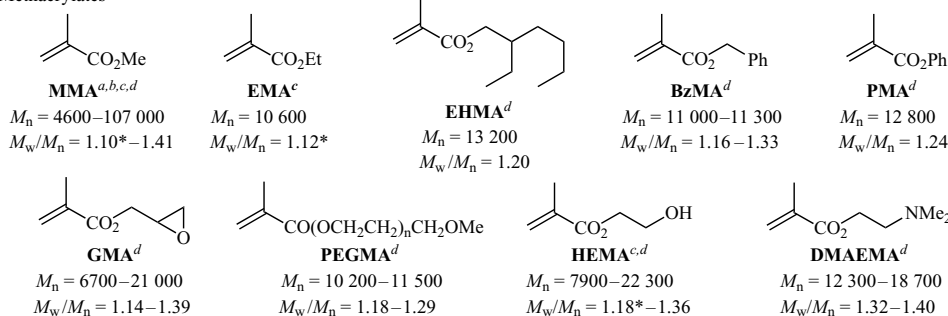
3.5.1 Styrenes

St was polymerized under conditions A and B by SBRP, BIRP, and TERP with and without a cocatalyst, and structurally well-defined PS with M_n close to the theoretical values and low MWDs was formed.^{25,27,29,30,33} M_n increased linearly with an increase in the St/CTA ratio, and PSs with M_n in the range of 3000–87 000 and narrow MWDs ($M_w/M_n < 1.3$) were prepared in the absence of a cocatalyst. *p*-Chlorostyrene (*p*ClSt) and *p*-methoxystyrene (*p*MeOSt) were also successfully polymerized.²⁷ Although the MWD control in

Styrenes

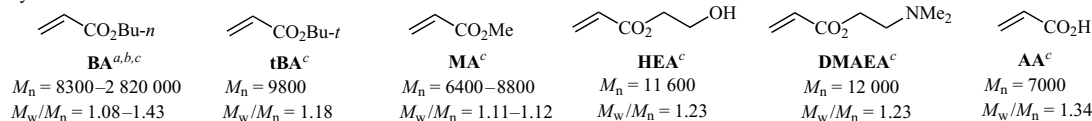


Methacrylates

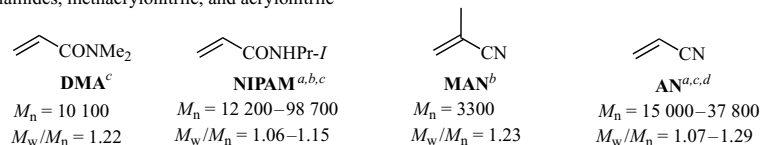


*Ditelluride was added for TERP

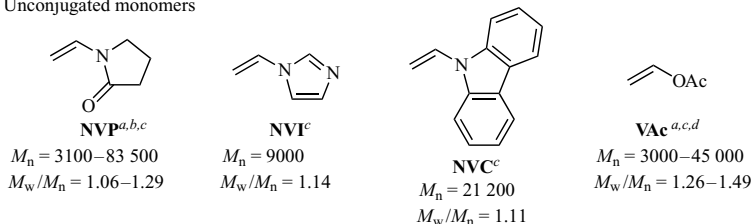
Acrylates



Acrylamides, methacrylonitrile, and acrylonitrile



Unconjugated monomers



Scheme 7 Selected monomers polymerized using (a) SBRP, (b) BIRP, (c) TERP, and (d) IRP (RTCP). Polymerization data (M_n and M_w/M_n values) were taken from the data obtained using CTAs having general structures **2**, **3**, and **4** (M_n was given in g mol^{-1}).

*p*ClSt polymerization was less efficient than those in St and *p*MeOSt polymerizations, presumably due to the higher propagation rate of the former than the latter, the level of control was still below the theoretical limit.

A binary system consisting of a distibine and organostibine CTA^{23,104} and a ditelluride and

organotellurium CTA¹⁰⁵ was effective to increase the MWD control of St polymerization, but the effect was less pronounced than that in methacrylate polymerization as discussed below. Both low and high molecular weight PSs with M_n s in the range of $1.0 \times 10^4\text{--}2.0 \times 10^5 \text{ g mol}^{-1}$ and narrow MWDs ($M_w/M_n = 1.07\text{--}1.15$) were synthesized with high

monomer conversion (>90%) by adding a catalytic amount of thiobismuthine cocatalyst **Bi-S** to organobismuthine CTA **Bi-1**.²⁶

IRP of St was less successful than SBRP, BIRP, and TERP, and PS with considerable broad MWD was obtained even when the targeted molecular weight was low ($M_n \sim 6500 \text{ g mol}^{-1}$, $M_w/M_n \sim 1.4$) using **I-1** as a CTA.⁶⁰ This is primarily due to the low exchange constant C_{ex} in IRC than that in other methods as discussed in the mechanistic section. Polymerization under RTCP conditions, on the other hand, significantly increases the MWD control.^{71–73, 76} Polymerization of St in the presence of an organoiodine CTA and a cocatalyst listed in Scheme 5b gave PS with narrow MWDs ($M_n = 2500\text{--}27\,000 \text{ g mol}^{-1}$, $M_w/M_n = 1.16\text{--}1.48$). Phenol derivatives were especially effective among the cocatalysts, and PSs with $M_n \sim 7000 \text{ g mol}^{-1}$ and $M_w/M_n < 1.2$ were obtained by the addition of 2,4,6-Me, vitamin E, HHQ, UA, and MH.⁷⁶

3.5.2 Methacrylates

SBRP and BIRP exhibited higher MWD control than TERP in methacrylate polymerization, and PMMAs with narrow MWDs ($M_w/M_n = 1.10\text{--}1.25$) and M_n in the range of $10\,000\text{--}100\,000 \text{ g mol}^{-1}$ were obtained. The MWD control further increased on addition of distibine cocatalysts in SBRP. For example, SBRP of MMA using **Sb-1** proceeded with reasonable MDW control ($M_w/M_n = 1.24$) and that in the presence of 0.1 equiv of tetramethyldistibine afforded PMMA with highly controlled structures ($M_w/M_n = 1.05$).²³ The addition of further distibine, on the other hand, had virtually no effect on the MWD control, and significant rate retardation of the polymerization was observed. PMMAs of higher molecular weights ($M_n = 34\,700\text{--}122\,900 \text{ g mol}^{-1}$) and very narrow MWDs ($M_w/M_n = 1.05\text{--}1.15$) were prepared by increasing the ratio of MMA to **Sb-1** in the presence of 0.1 equiv of tetramethyldistibine. Methacrylonitrile was also polymerized in a controlled manner by BIRP.¹⁰⁶

The control of MWD in the polymerization of methacrylate was not always sufficient via TERP. Polymerization of MMA using organotellurium CTAs resulted in the formation of PMMAs with

considerably broad MWDs ($M_w/M_n > 1.37$). However, the control increased with the addition of ditellurides as a cocatalyst, such as dimethyl, dibutyl, and diphenylditelluride, and PMMAs with narrow MWDs ($M_w/M_n = 1.12\text{--}1.16$) and M_n in the range of $8600\text{--}79\,400 \text{ g mol}^{-1}$ were obtained depending on the monomer/CTA ratio.^{28,30} A catalytic amount of ditelluride was effective when the targeted molecular weight was small, but substoichiometric to excess amounts of ditelluride were used when the targeted molecular weight was large.

IRC of MMA afforded PMMAs with broad MWDs ($M_w/M_n > 1.5$),^{60,62} but RTCP of MMA gave PMMAs with narrow MWDs ($M_n = 6300\text{--}13\,000 \text{ g mol}^{-1}$, $M_w/M_n = 1.22\text{--}1.38$).^{71,73,76} Among the cocatalysts, Tol-GeI₃, XT, and TXT exhibited superior cocatalyst for the increased control. Ethylhexyl methacrylate, benzyl methacrylate (BzMA), and PHMA with $M_n \sim 10\,000 \text{ g mol}^{-1}$ were also polymerized in a controlled manner under RTCP conditions ($M_w/M_n = 1.16\text{--}1.33$).

3.5.3 Acrylates

Acrylates, acrylamides, and AN were polymerized in a controlled manner under conditions A, B, and C by SBRP, BIRP, and TERP. However, IRC of acrylates resulted in low control with broad MWDs ($M_w/M_n > 1.6$).^{60,61} Polymerization of acrylates under RTCP condition has not been reported so far.

High temperature and long reaction times were required to reach high monomer conversion under condition A due to inefficient generation of the initiating radicals from the dormant species.²⁸ The high temperatures were also unsuitable because a considerable amount of branching occurred due to a back-biting reaction.^{107–109} Therefore, conditions B²⁴ and C³⁴ at low to ambient temperature are more suitable for the polymerization of these monomers. PBAs with narrow MWDs ($M_w/M_n = 1.10\text{--}1.20$) and M_n in the range of $11\,000\text{--}122\,000 \text{ g mol}^{-1}$ were successfully synthesized at 60°C using BIRP under condition B with AIBN as the initiator. Polymerization of BA proceeded in the temperature range of $0\text{--}50^\circ\text{C}$ using TERP under UV-vis irradiation (condition C), and PBAs with narrow MWDs ($M_w/M_n = 1.08\text{--}1.19$) and M_n in the range of $13\,000\text{--}223\,000 \text{ g mol}^{-1}$ were synthesized.

Addition of thiobismuthine cocatalyst **Bi-S** was especially suitable for the synthesis of ultrahigh molecular weight polyacrylates. PBAs with M_n s in the range of 1.2×10^4 – 2.8×10^6 g mol⁻¹ and narrow MWDs ($M_w/M_n = 1.06$ – 1.43) were prepared under mild thermal conditions under a ternary system consisting of **Bi-1**, **Bi-S**, and AIBN. The Gel Permeation Chromatography (GPC) traces of all of the PBAs were unimodal, and the peak maxima shifted to higher molecular weights as the targeted molecular weight increased (Figure 1). A PBA with an M_n of 1.4×10^6 g mol⁻¹ and a narrow MWD ($M_w/M_n = 1.22$) was obtained at 47% monomer

conversion when 20 000 equiv of BA was employed. Moreover, a PBA with an M_n of 2.8×10^6 g mol⁻¹ was obtained at 41% monomer conversion when 50 000 equiv of BA was employed. Although the MWD was slightly large ($M_w/M_n = 1.43$), it is still below the theoretical limit.

A significant drawback of LRP is the synthesis of high molecular weight polymers because the polymer-end radicals are always subject to irreversible termination reactions.¹¹⁰ Only a few examples have been reported for the synthesis of ultrahigh molecular weight polyacrylates and polymethacrylates with M_n s exceeding

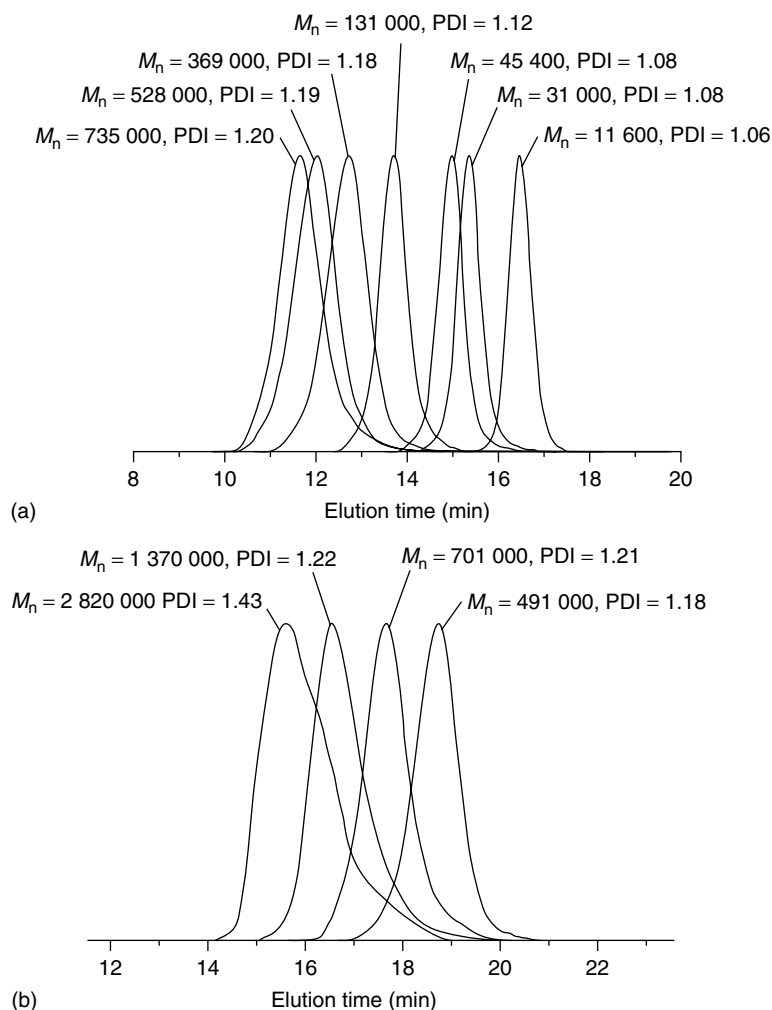


Figure 1 GPC traces of PBA samples prepared by varying the BA/**Bi-1** ratio in the presence of **Bi-S** measured by GPC columns with exclusion limits of (a) 2×10^6 and (b) 2×10^7 (M_n was given in g mol⁻¹). [Reprinted from Ref. 26. © American Chemical Society, 2009.]

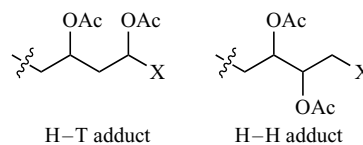
$1 \times 10^6 \text{ g mol}^{-1}$ and with narrow MWDs: RAFT¹¹¹ and ATRP^{112,113} under high pressure conditions, Single-electron transfer LRP using a copper catalyst,¹¹⁴ and ATRP under mini-emulsion conditions.¹¹⁵ Therefore, BIRP in the presence of **Bi-S** provides a new route to structurally well-defined ultrahigh molecular weight polymers.

3.5.4 Functional Monomers

Since SBRP, BIRP, TERP, and IRC (RTCP) are performed under thermal or photochemical conditions without catalysts that are incompatible with the functionalities of the monomers, controlled polymerization of various monomers possessing functional groups was achieved.^{28,34,71–73,76} For example, methacrylates and acrylates with a free hydroxyl group, such as HEMA and hydroxyethyl acrylate, a carboxylic acid group, such as AA, and an amine group, such as *p*-aminostyrene, *N,N*-dimethylaminoethyl methacrylate (DMAEMA), *N,N*-dimethylaminoethyl acrylate, were polymerized using TERP and RTCP in a controlled manner. Acryl amides, such as *N,N*-dimethylacrylamide and NIPAM also gave the corresponding controlled polymers by SBRP, BIRP, and TERP. Monomers possessing epoxide and ethers, such as GMA and poly(ethylene glycol)methacrylate (PEGMA), were also polymerized under RTCP conditions. Protection of the acidic proton in the hydroxyl, carboxylic acid, and amide groups was not necessary because polymerization proceeded under neutral conditions and carbon–heteroatom bonds in the dormant species are resistant to polar functional groups.

3.5.5 Unconjugated Monomers

The most notable feature of these LRP methods is that they can control the polymerization of both conjugated and unconjugated monomers using the same CTAs.^{21,25,32,34} Since polymer-end radicals generated from unconjugated monomers are less stable than those from conjugated monomers, the dormant species of unconjugated monomers possess stronger carbon–heteroatom bond than those of conjugated monomers. Therefore, conditions B and C are effective for the polymerization of unconjugated monomers.



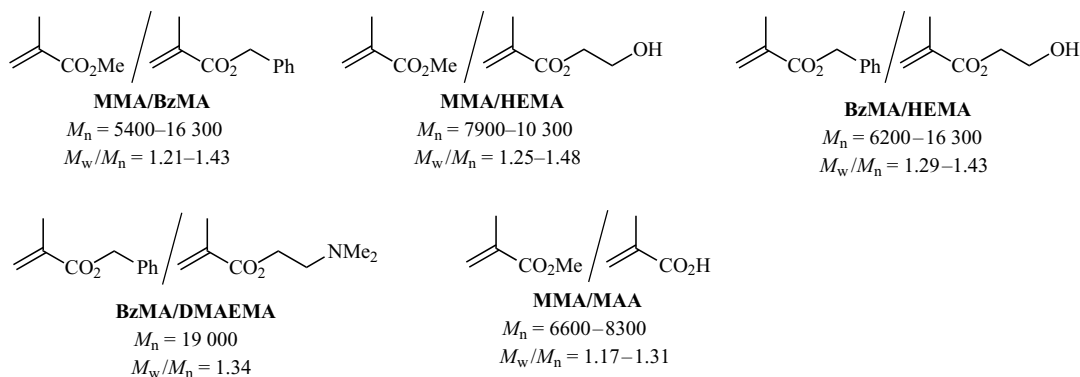
Scheme 8 Structure of head-to-tail (H-T) and head-to-head (H-H) addition adducts at ω -polymer-end group in PVAc.

SBRP, BIRP, and TERP of *N*-vinylpyrrolidone (NVP) afforded poly(*N*-vinylpyrrolidone)s (PNVPs) with M_n in the range of 3100–83 500 g mol^{-1} and narrow MWDs ($M_w/M_n = 1.06–1.29$). *N*-Vinylimidazole and NVC were also polymerized in a controlled manner using TERP under photo irradiation.^{21,22,25,32,34}

Polymerization of vinyl acetate (VAc) using SBRP²¹ and TERP¹¹⁶ gave the controlled poly(vinyl acetate)s (PVAc)s, but the control was limited to low molecular weight polymers ($M_n < 5000 \text{ g mol}^{-1}$) due to the formation of dormant species by head-to-head (H–H) addition reaction.¹¹⁶ IRC showed better control than TERP and SBRP, and PVAc of M_n ranging from 4000 to 34 000 g mol^{-1} were synthesized under controlled manner ($M_w/M_n < 1.5$).¹¹⁷ Kamigaito and coworkers have recently shown that PVAc with considerable high molecular weights were synthesized with narrow MWD ($M_n \sim 45\,000 \text{ g mol}^{-1}$, $M_w/M_n < 1.5$) by IRP carrying out the polymerization in a fluoroalcohol solvent.⁶⁷ While fluoroalcohols were used to control the tacticity by coordination to VAc, its effect on the tacticity was marginal. Instead, the solvents perturb the monomer reactivity and decrease the formation of the H–H adduct (Scheme 8). Since the H–H adduct serves as a dead polymer, its reduction leads to the increased control of VAc polymerization (see Section 4.1).

3.6 Random and Alternating Copolymerization

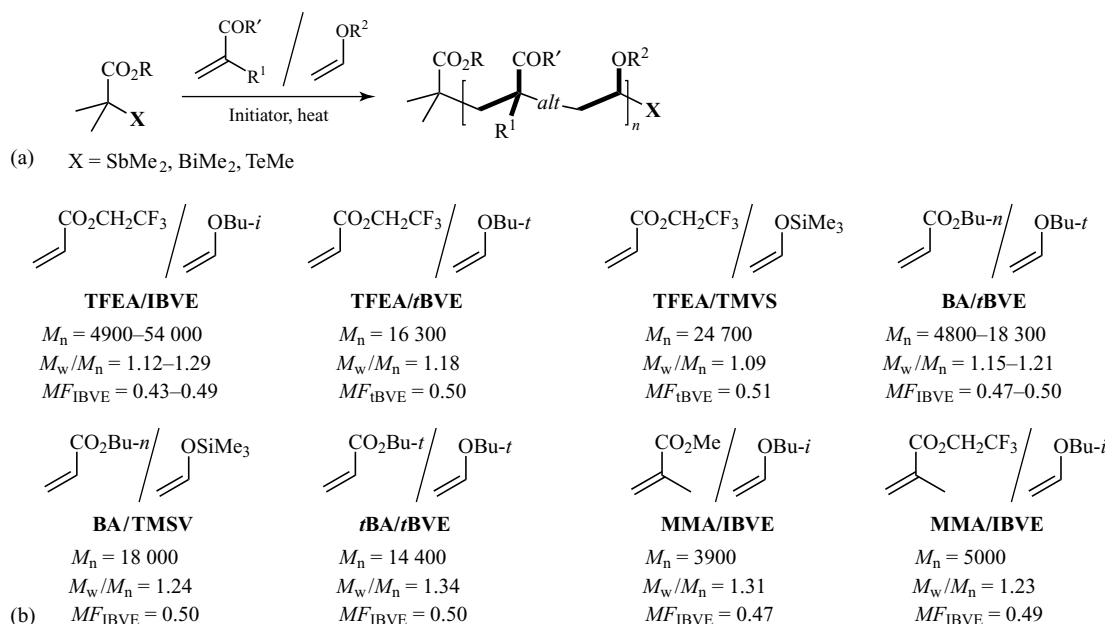
Copolymerization, in which a mixture of two or more monomers is polymerized, is a powerful synthetic technique to modulate the properties of polymer materials. Therefore, the controlled copolymerization would provide a diverse range of polymeric materials. Goto and coworkers reported random copolymerization of methacrylate derivatives under RTCP conditions (Scheme 9). A



Scheme 9 Combination of methacrylate monomers used for copolymerization under RTCP condition (M_n was given in g mol^{-1}).

various combination of methacrylate derivatives, such as MMA and BzMA, MMA and HEMA, BzMA and HEMA, BzMA and DMAEMA, and MMA and methacrylic acid (MAA), with M_n ranging from 5400 to 19 000 g mol^{-1} , gave the desired copolymer with controlled structure ($M_w/M_n < 1.5$). While there are no reports on random copolymerization of conjugated monomers by SBRP, BIRP, and TERP, it is reasonable to assume that the copolymerization will proceed in a controlled manner.

Mishima and Yamago¹¹⁸ reported that copolymerization of (meth)acrylate monomers, conjugated monomers, and vinyl ethers, unconjugated monomers, took place with high MWD control. Furthermore, high alternating monomer sequence was achieved by employing an excess amount of vinyl ethers (5–10 times) over methacrylates (Scheme 10a). For example, when a 1:1 mixture of 2,2,2-trifluoroethyl acrylate (TFFA) and isobutyl vinyl ether (IBVE) was polymerized in the presence of organotellurium CTA **Te-1**, the resulting



Scheme 10 (a) Controlled alternating copolymerization of (meth)acrylates and vinyl ethers and (b) combination of (meth)acrylate/vinyl ether monomers in random and alternating copolymerization by TERP, SBRP, and BIRP (M_n was given in g mol^{-1}).

copolymer possessed low MWD ($M_w/M_n = 1.12$) with mole fraction of IBVE ($MF_{IBVE} = 0.43$). The polymerization did not proceed further after all the TFEA was consumed, and IBVE remained under the polymerization conditions. This is because vinyl ethers do not homopolymerize under radical conditions. A polymer-end radical formed from TFEA reacts with TFEA and IBVE, but that formed from IBVE only reacts with TFEA. Therefore, more TFEA than IBVE was incorporated.

When the amount of IBVE was increased (IBVE/TFEA = 5), nearly complete alternating copolymer with $MF_{IBVE} = 0.49$ and controlled MWD ($M_w/M_n = 1.18$) was formed. The alternating structure was confirmed by two-dimensional NMR and mass spectroscopy analyses. This alternating copolymerization took place for the combination of various (meth)acrylates and vinyl ethers: TFEA and *t*-butyl vinyl ether (*t*BVE), TFEA and trimethyl(vinyloxy)silane (TMVS), BA and IBVE, BA and TMSV, *t*BA and *t*BVE, MMA and IBVE, and MMA and IBVE (Scheme 10b). Highly controlled alternating copolymers with respect to MWD and monomer sequence were formed in all cases under TERP, SBRP, and BIRP conditions.

3.7 Block Copolymerization

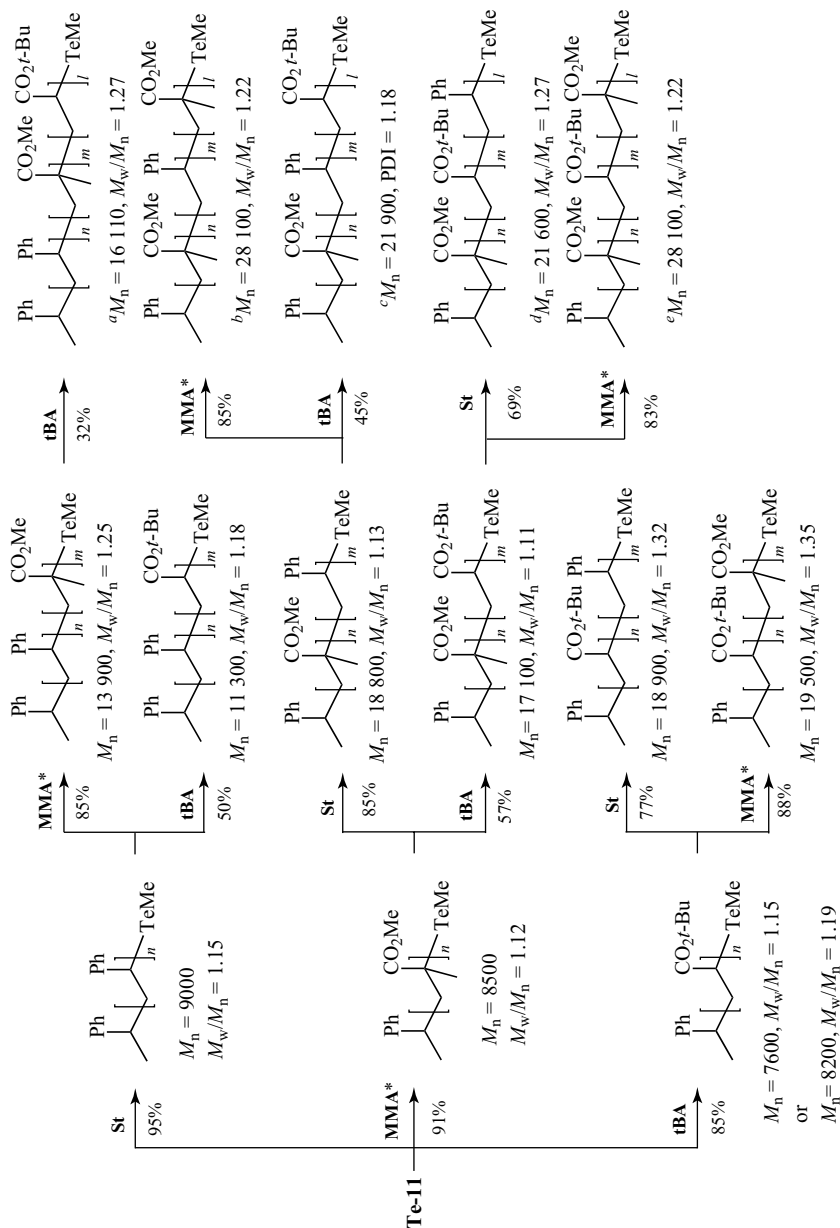
Block copolymers comprise two or more homopolymer subunits linked by covalent bond and are regarded as next-generation functional materials for a variety of applications, such as photonic, magnetic, and electronic materials, thermoplastic elastomers, adhesives, and dispersants. In addition, the morphology of the phase separated structure of block copolymers have been utilized for fabrication of structurally well-controlled nano-structure based on the bottom-up approach.^{119–121} Therefore, the controlled synthesis of new block copolymer represents a challenge in nano-sciences and technologies.

A notable feature of SBRP, BIRP, and TERP is their versatility in the synthesis of block copolymers. Although the success of block copolymer synthesis is, in general, highly dependent on the order of monomer addition, especially when different families of monomers are used, these methods are more tolerant toward the order of addition than other LRP methods.^{122–125} For example, blocking of the PS macro-CTA was successfully carried out

for MMA and *t*BA, and the desired AB-diblock copolymers with narrow MWDs were obtained in both cases (Scheme 11).²⁸ The essentially complete disappearance of the starting macro-CTAs and the formation of the desired diblock copolymers were observed. The addition of ditelluride is necessary when MMA is used as a monomer. The controlled syntheses of AB-diblock copolymers starting from a PMMA macro-CTA with St and *t*BA, or from a poly(*t*-butyl acrylate) (*Pt*BA) macro-CTA with St and MMA, were also examined. Desired diblock copolymers with narrow MWDs ($M_w/M_n < 1.35$) were synthesized in all cases regardless of the order of monomer addition.

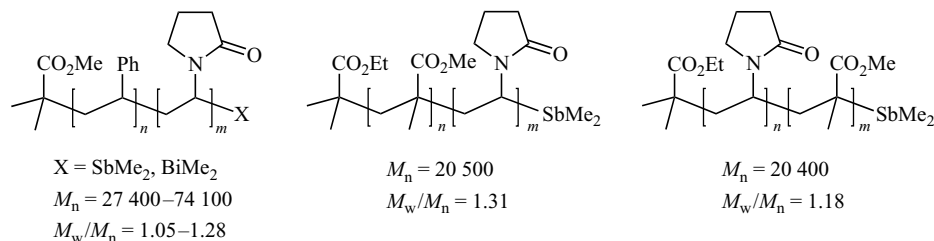
As the order of monomer addition is less important in TERP compared to that in other LRP methods, it was possible to prepare ABA and ABC triblock copolymers starting from diblock macro-CTAs (Scheme 11). Treatment of PMMA-*block*-PS and PMMA-*block*-*Pt*BA macro-CTAs with MMA gave the desired ABA triblock copolymers with narrow MWDs. ABC-triblock copolymers with different monomer sequences of St, MMA, and *t*BA, namely PS-*block*-PMMA-*block*-*Pt*BA, PMMA-*block*-PS-*block*-*Pt*BA, and PMMA-*block*-*Pt*BA-*block*-PS, were also synthesized in a controlled manner by the sequential addition of each monomer.

Block copolymers comprising conjugated and unconjugated monomers were also synthesized in a controlled manner using SBRP, BIRP, and TERP.^{21,22,25,32} Synthesis of these block copolymers is more difficult than that from both conjugated monomers because stabilities and reactivities of the dormant species and polymer-end radicals derived from conjugated and unconjugated monomers are quite different. Polymerization of organostibine and organobismuthine PS macro-CTAs with NVP in the presence of AIBN in DMF at 60 °C resulted in the complete consumption of the CTAs and the formation of desired PS-*block*-PNVP in high monomer conversion (Scheme 12). The diblock copolymers composed of different compositions of PS and PNVP segments were successfully synthesized in a controlled manner ($M_w/M_n = 1.05–1.28$) by altering the molecular weight of PS macro-CTAs and the amount of NVP. PMMA-*block*-PNVP was also synthesized in a controlled manner ($M_n = 20500 \text{ g mol}^{-1}$, $M_w/M_n = 1.31$) by treating an organostibine-PMMA macro-CTA with NVP in the presence of AIBN. Although the block polymer synthesis starting from PNVP macro-CTA



*[MeTe]₂ [1 equiv] was added.

Scheme 11 Syntheses of AB-block, ABA-triblock, and ABC-triblock copolymers using St, MMA, and tBA. In total, 100 equiv of each monomer was used to synthesize diblock copolymer. M_n and MWD of the diblock macro-CTAs for the synthesis of triblock copolymers were as follows: (a) $M_n = 12\,600$, $M_w/M_n = 1.30$; (b) $M_n = 18\,700$, $M_w/M_n = 1.18$; (c) $M_n = 19\,000$, $M_w/M_n = 1.13$; (d) $M_n = 11\,500$, $M_w/M_n = 1.09$; and (e) $M_n = 11\,000$, $M_w/M_n = 1.11$ (M_n was given in g mol^{-1}).



Scheme 12 Chemical structures of diblock copolymers containing a PNVP segment prepared by SBRP and BIRP (M_n was given in g mol^{-1}).

with St was inefficient, that to MMA proceeded smoothly in the presence of AIBN to give highly controlled PNVP-*block*-PMMA with a narrow MWD ($M_w/M_n = 1.18$). Since these block copolymers comprise hydrophobic PS or PMMA and hydrophilic PNVP blocks, their physical properties will be of great interest.

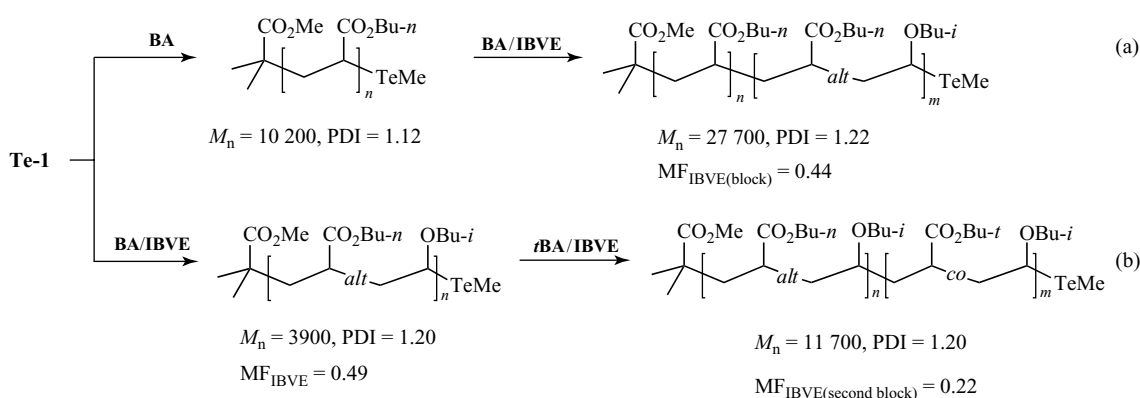
New block copolymers comprising an alternative copolymer consisted of acrylates and vinyl ethers as a block segment were also synthesized.¹¹⁸ For example, polymerization of organotellurium-PBA macro-CTA prepared from **Te-1** with a mixture of BA and IBVE afforded a block copolymer poly[BA-*block*-(BA-*alt*-IBVE)] with controlled MWD ($M_n = 27700 \text{ g mol}^{-1}$, $M_w/M_n = 1.22$) (Scheme 13a). The MF of IBVE in the second block was 0.44, suggesting that highly alternating copolymerization occurred during the formation of the second block.

An alternating copolymer was also used as a macro-CTA. Organotellurium-poly(BA-*alt*-IBVE) macro-CTA ($M_n = 3900 \text{ g mol}^{-1}$, $M_w/M_n = 1.20$,

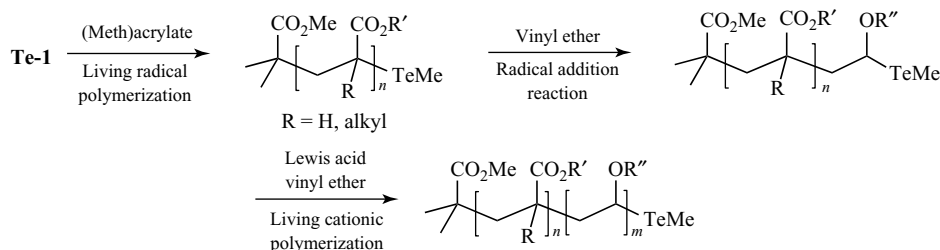
$\text{MF}_{\text{IBVE}} = 0.49$) was prepared by copolymerizing BA (20 equiv) and IBVE (100 equiv) in the presence of **Te-1**. Since about 80 equiv of unreacted IBVE remained in the reaction mixture, addition of *t*BA (50 equiv) reinitiated the copolymerization, affording poly[(BA-*alt*-IBVE)-*block*-(*t*BA-*co*-IBVE)] with a narrow MWD ($M_n = 11700 \text{ g mol}^{-1}$, $M_w/M_n = 1.20$) (Scheme 13b).

As vinyl ethers do not homopolymerize, the group transfer radical addition reaction of poly(meth)acrylate prepared by LRP to vinyl ethers can be used for selective end-group transformation reaction (Scheme 14). The resulting adduct was used for a macro-CTA for living cationic polymerization of vinyl ethers in the presence of Lewis acid giving poly[(meth)acrylate-*block*-(vinyl ether)].¹²⁶

This one-pot, three-step reaction was applied to the combination of BA and IBVE, BA and *n*-butyl vinyl ether, BA and *n*-octyl vinyl ether, and MMA and IBVE. Desired block copolymers with M_n ranging from 8000 to 20 000 g mol^{-1} with



Scheme 13 Synthesis of block copolymers containing a poly(BA-*alt*-IBVE) segment (M_n was given in g mol^{-1}).

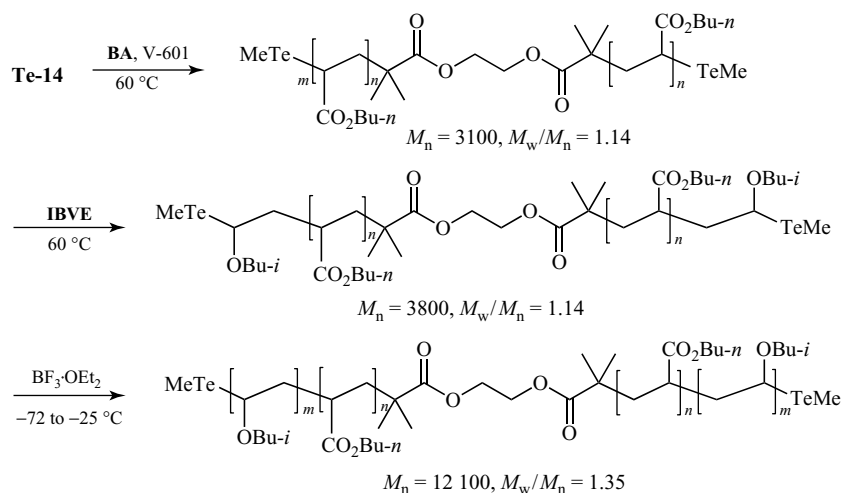


Scheme 14 Synthesis of “hybrid” block copolymer by successive living radical and living cationic polymerization reactions.

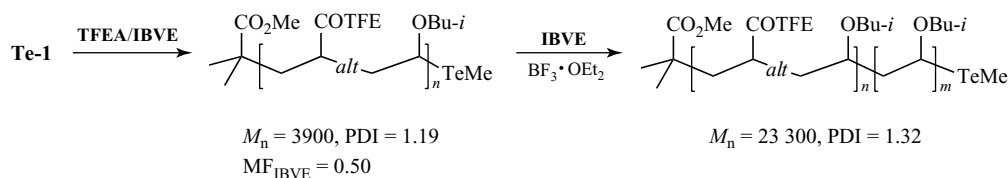
controlled MWD ($M_w/M_n = 1.21\text{--}1.46$) were successfully synthesized. Starting from a bifunctional CTA **Te-14**, a symmetrical ABA-triblock copolymer, poly(IBVE-*block*-BA-*block*-IBVE), was successfully synthesized by TERP of BA, the radical addition reaction to IBVE, and living cationic polymerization of IBVE by employing $\text{BF}_3\cdot\text{OEt}_2$ as a Lewis acid (Scheme 15).

(Meth)acrylates and vinyl ethers are orthogonal monomer families under radical and cationic polymerization conditions, and they cannot be polymerized under cationic and radical conditions, respectively. However, a selective chain end transformation via a radical-mediated tellurium-group transfer addition reaction of poly(meth)acrylate macro-CTA to vinyl ethers alternates the reactivity of ω -polymer-end group and enables the synthesis of “hybrid” block copolymer by successive living radical and living cationic polymerizations.

Moreover, macro-CTAs prepared by alternating copolymerization of (meth)acrylates and vinyl ethers were used as initiators for living cationic polymerization (Scheme 16).¹²⁶ Since excess amount of vinyl ethers was employed over (meth)acrylates to achieve highly alternating monomer sequence, polymer-end unit is derived from vinyl ethers. Therefore, the copolymer formed by LRP was directly used as a macro-CTA for the cationic polymerization. For example, an alternating copolymer-macro-CTA ($M_n = 3900 \text{ g mol}^{-1}$, $M_w/M_n = 1.19$, $\text{MF}_{\text{IBVE}} = 0.50$) was prepared by TERP of TFEA (20 equiv) and IBVE (200 equiv) in the presence of **Te-1**. After the reaction mixture was diluted with CH_2Cl_2 , the addition of $\text{BF}_3\cdot\text{OEt}_2$ triggered the living cationic polymerization of IBVE. Desired block copolymer poly[(TFEA-*alt*-IBVE)-*block*-IBVE] was



Scheme 15 Synthesis of a ABA-triblock copolymer by successive living radical and living cationic polymerization reaction starting from a bifunctional CTA **Te-14** (M_n was given in g mol^{-1}).



Scheme 16 Cationic polymerization starting from a macro-CTA prepared by alternating copolymerization of TFEA and IBVE by TERP (M_n was given in g mol^{-1}).

formed with a controlled macromolecular structure ($M_n = 23300 \text{ g mol}^{-1}$, $M_w/M_n = 1.32$).

3.8 End Group Transformation

A characteristic feature of the SBRP, BIRP, and TERP is the versatility of the transformations that can be carried out on the polymer-end groups. Since polymer-end radicals are easily generated from the organoheteroatom dormant species, several polymer-end group transformations mediated by radical species have been developed. While organoiodine polymer-end group in IRP including RTCP is expected to have similar reactivities to those in SBRP, BIRP, and TERP, its utilization has not been well studied yet.

Radical-mediated reduction of organoheteroatom ω -end groups is the simplest route to ω -protonated and deuterated polymers.^{21,25,27,30} For example, treatment of PMMA **7** bearing dimethylstibanyl group with tributyltin hydride and deuteride gave end protonated deuterated PMMA **8** and **8-d**, respectively, in quantitative conversion through the polymer-end radical species (Scheme 17a).¹⁰⁶ Structures of **8** and **8-d** were unambiguously determined by Matrix Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) mass (Figure 2) and ^2H NMR spectroscopy. Not only tin hydrides, which pose environmental concerns, but arylthiols can also be used as reducing agents.¹²⁷

When **7** was treated with ethyl [(tributylstannyl)methyl]acrylate (**9**)¹²⁸ in the presence of AIBN, ω -vinylidene functionalized PMMA **10** was formed (Scheme 17b).^{27,106} Structurally related ω -vinylidene functionalized PMMA **11** was also formed when PMMAs prepared using SBRP, BIRP, and TERP were treated with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) under thermal or photochemical conditions (Scheme 17c).¹⁰⁶

The formation of **11** is due to the abstraction of a β -hydrogen adjacent to the radical center by TEMPO. The same protocol could be used for the synthesis of ω -vinylidene functionalized polymethacrylonitrile. The complete end group transformation must be due to the high efficiency of radical generation by direct carbon–heteroatom homolysis.

The selective ω -end group transformation combined with the use of functional CTAs, such as **Sb-8** and **Sb-9**, have led to the synthesis of structurally well-controlled telechelic polymers,¹²⁹ which possess reactive functional group(s) at both polymer ends.²³ For example, PS **12**, which possesses an alkene functionality at the α -polymer-end prepared from **Sb-8** and St, was heated with allylstannane **9** in the presence of AIBN at 80°C , giving telechelic polymer **13** as the sole product (Scheme 18a). Aerobic oxidation of an organostibanyl group to a hydroxyl group has been reported,¹³⁰ and application of this procedure to **12** resulted in the selective formation of ω -hydroxylated PS **14** (Scheme 18b). The different functional groups at the α -polymer and ω -polymer ends of these PSs should be useful for further selective synthetic transformations.

The reaction of living polymers prepared using RAFT with an excess amount of AIBN has recently been reported to form the bis-functionalized polymers by Perrier *et al.*,¹³¹ and this method has been applied to organostibine-substituted living polymers (Scheme 19).²³ For example, the reaction of azo-initiator **15** with tetramethyldistibine gave CTA **Sb-9** (Scheme 19). Then, organostibine-PS **16**, which was prepared using SBRP of St with **Sb-9**, was treated with 40 equiv of **15** to give α,ω -bisfunctionalized PS **17**. These results indicate that not only homotelechelic polymers but also heterotelechelic polymers, which possess different functional groups at their α -polymer and ω -polymer ends, can be synthesized by

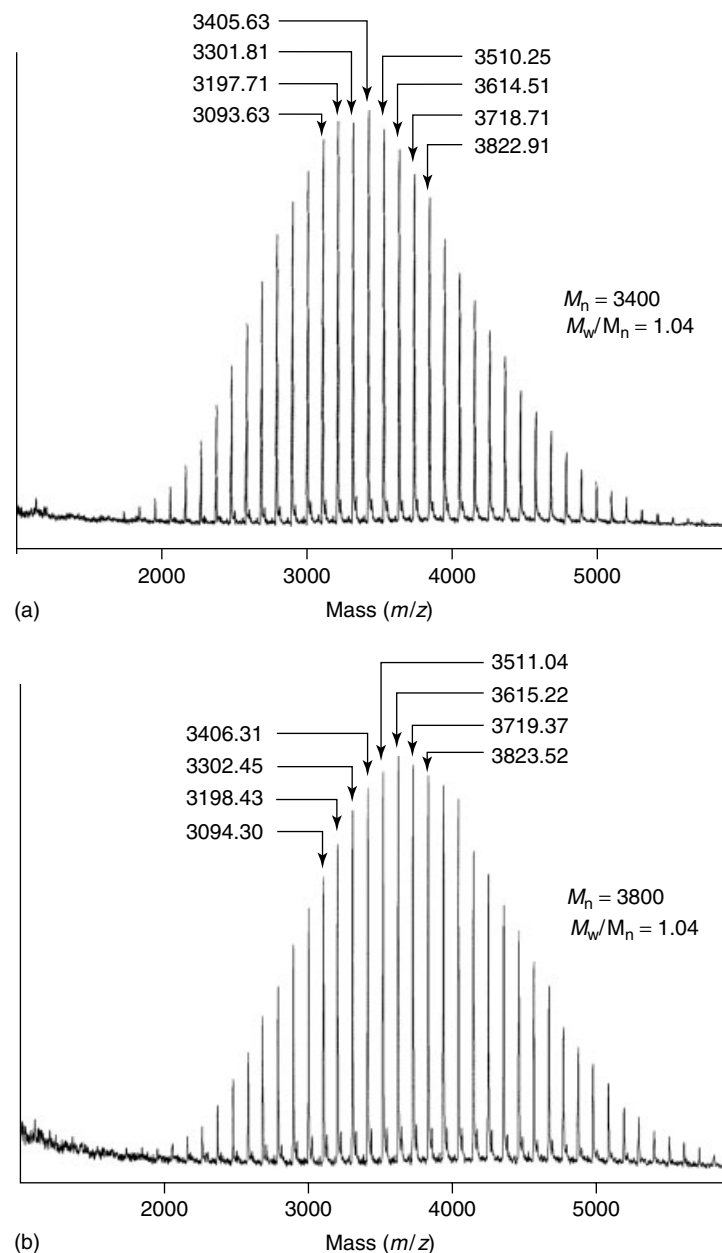
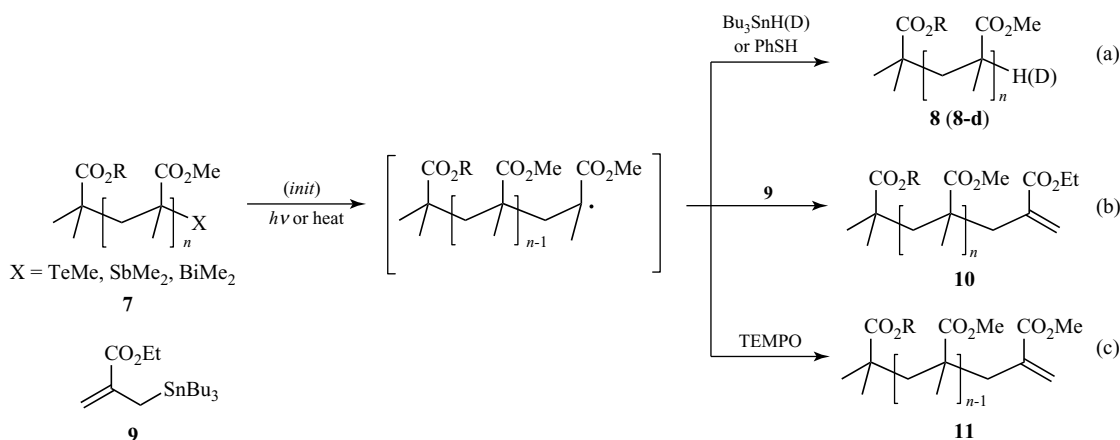


Figure 2 MALDI-TOF mass spectra of (a) end-protonated polystyrene **8** and (b) end-deuterated polystyrene **8-d**. The molecular ions were observed as silver ion adducts ($m/z = (M + Ag)^+$). [Reprinted from Ref. 30. © American Chemical Society, 2003.]

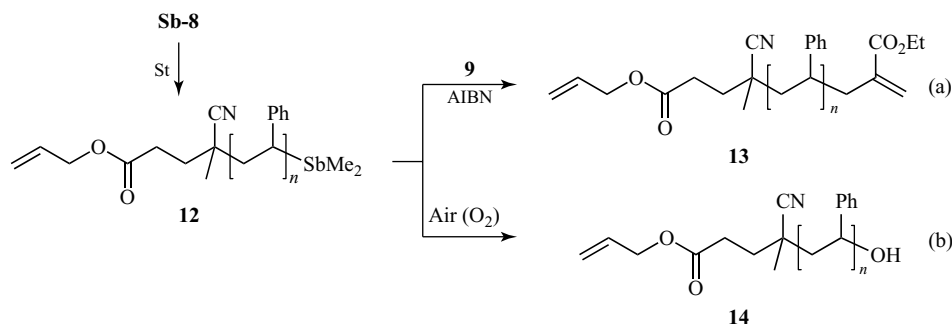
arbitrary choice of the azo-initiator for preparation of the CTA and the subsequent ω -polymer-end transformation.

Organotellurium compounds are excellent precursors not only for carbon-centered radicals but also for carbanions and carbocations.^{132–134} Once

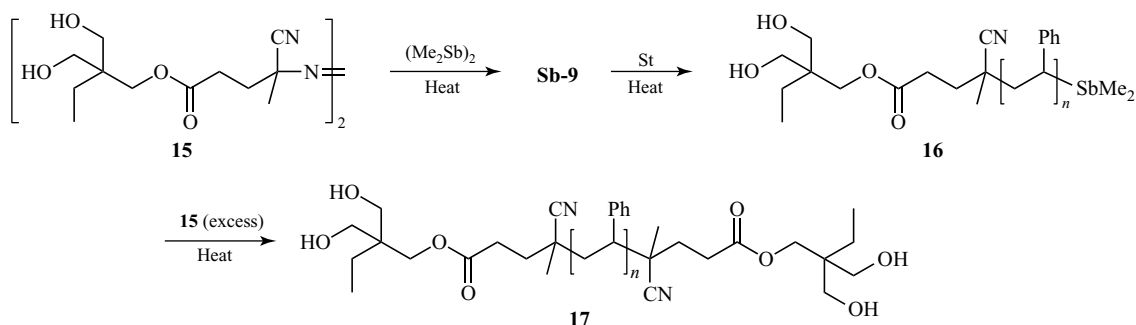
such ionic species are selectively generated from the polymer-end organotellurium compounds, they are highly effective intermediates for the end functionalization (Scheme 20). Tellurium–lithium transmetalation^{135,136} was achieved by the treatment of organotellurium-PS **18** possessing



Scheme 17 Radical-mediated transformations of heteroatom-substituted PMMA polymer-end.



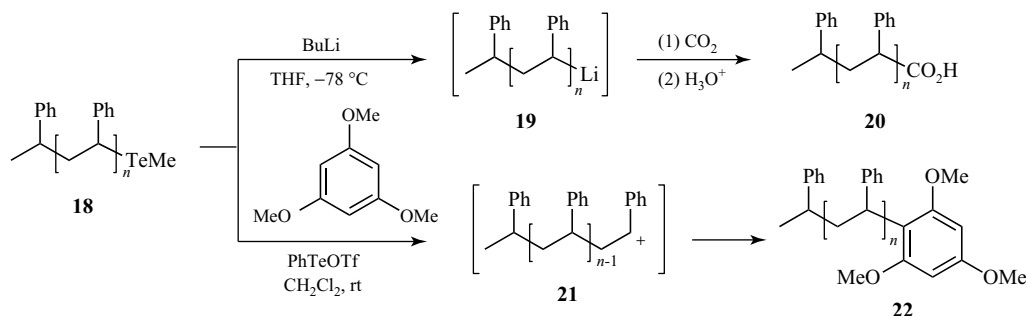
Scheme 18 Synthesis of telechelic polymer starting from functional CTA **Sb-8** and ω -end functionalization.



Scheme 19 Synthesis of diol-functionalized telechelic polymer through radical coupling reaction.

methyltellanyl group at the polymer end with butyllithium to give benzyl lithium **19**, which was trapped with an electrophile, such as carbon dioxide, giving carboxylic acid functionalized PS **20**.²⁷ The carboxylic acid was further transformed

to different functional groups using standard techniques, such as esterification. Treatment of **18** with phenyltellanyl triflate in the presence of 1,3,5-trimethoxybenzene afforded Friedel–Crafts product **22** through benzilic cation **21**.¹³⁷

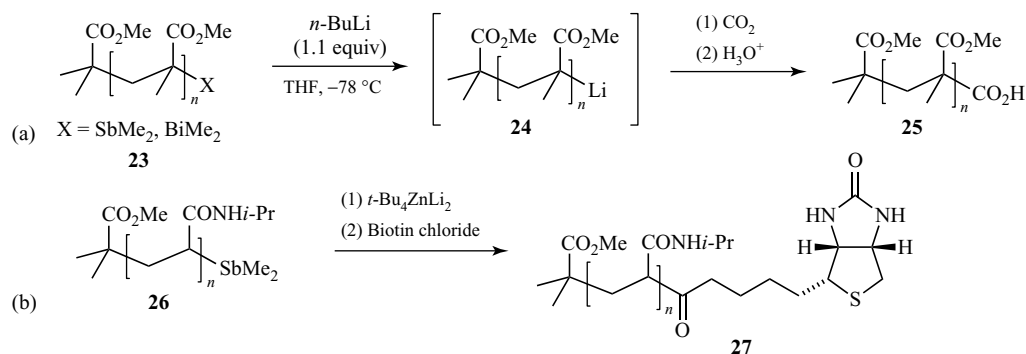


Scheme 20 Carbanion- and carbocation-mediated transformation of PS-TeMe.

Since carbanions occupy a central position in organic synthesis,^{138,139} the end-group modification via a polymer-end anionic species, for example, **19**, is an attractive method. However, carbanions are usually incompatible with polar functional groups that are often present in polymers prepared by LRP. Kayahara *et al.* recently reported that organostibines and organobismuthines are highly reactive to stibine–metal and bis-muthine–metal exchange reaction, respectively, and that the exchange reaction proceeds much faster than the reaction of organometallic species reacting to polar functional groups. The method was applied to the end group modification of living polymers prepared by SBRP and BIRP.¹⁰⁴ For example, the exchange reaction between organostibine- and organobismuthine-PMMA **23** prepared by SBRP and BIRP, respectively, and *n*BuLi selectively occurred to give polymer-end anion **24**. Treatment of **24** with various electrophiles, for example, carbon dioxide selectively gave ω -carboxylated PMMA **25** in quantitative conversion (Scheme 21a). While

PMMA **25** ($M_n \sim 3000 \text{ g mol}^{-1}$) contains about 30 ester groups, the exchange reaction exclusively occurs at the polymer-end group. The exchange reaction with tetraalkylzincates, Me_4ZnLi_2 ^{140–142} and $t\text{Bu}_4\text{ZnLi}_2$,^{143–145} and $i\text{PrMgCl}\cdot\text{LiCl}$ ^{146,147} also took place chemoselectively leaving ester groups intact.

The exchange reaction can also be applicable for polyacrylates and polyacrylamides possessing acidic hydrogen in the main chain as well as the side chain by employing $t\text{BuZnLi}_2$. For example, polymer-end dimethylstibanyl group in PNIPAM **26** was successfully transformed to the corresponding anionic species by $t\text{BuZnLi}_2$ in DMF without protection of the amide protons. Subsequent addition of biotin chloride exclusively afforded ω -biotinylated PNIPAM **27**. The structure of **27** was unambiguously confirmed using ^1H NMR and MALDI-TOF mass spectroscopy analyses. PNIPAM is a thermoresponsive polymer and possesses lower critical solution temperature (LCST) in water. On the other hand, biotin is a good ligand for proteins, such



Scheme 21 Synthesis of ω -functionalized PMMA through chemoselective heteroatom–lithium exchange reaction.

as avidin and streptavidin. Therefore, this polymer and its analogs would make it possible to thermally modulate the properties of biomaterials for biological applications.¹⁴⁸

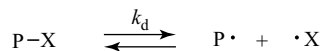
As the reactivity of organotellurium and organoiodine compounds toward the exchange reaction is very similar to organostibine and organobismuthine compounds,¹⁰⁴ the same type of anion-mediated transformations of organotellurium polymer-end group would also be possible for the living polymers prepared by TERP and IRP.

4 MECHANISM

4.1 Activation/Deactivation Mechanism of Dormant/Radical Species

Studies on the kinetics involved in the activation and deactivation of dormant species have revealed the existence of two mechanisms: reversible termination (RT, Scheme 22a) and degenerative chain transfer (DT, Scheme 22b).^{24,29,116} Although NMP and ATRP proceed exclusively via the RT mechanism and RAFT via the DT mechanism, TERP, SBRP, and BIRP proceed through the two mechanisms. Involvement of the two mechanisms makes these LRP methods unique, and it is the origin of three

(a) Reversible termination (RT) mechanism



(b) Degenerative transfer (DT) mechanism



Scheme 22 Activation/deactivation mechanisms involved in SBRP, BIRP, TERP, and IRP.

polymerization conditions described in the previous section.

The first-order rate constant for the activation of the dormant species via RT (k_d) and the second-order rate constant for the activation via DT (k_{ex}) in SBRP,^{21,24} BIRP,²⁵ TERP,^{29,33,116} and IRP¹⁴⁹ are summarized in Table 3. The rate constants of NMP¹⁵⁰ and RAFT¹⁵¹ are also listed as a reference. For example, the k_d and k_{ex} for TERP using the methyltellanyl derivative ($X = \text{TeMe}$) at 60 °C in St polymerization are $1.2 \times 10^{-5} \text{ s}^{-1}$ and $5.7 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. The activation energy of DT was also determined to be 30 kJ mol^{-1} , whereas that for RT of PS-TeMe is estimated to be around 120 kJ mol^{-1} from the BDE of polymer-end mimetic CTA **Te-11**. Therefore, DT is the predominant mechanism in TERP. Although the rate constants

Table 3 Kinetic parameters for the activation of stibine-,^{21,24,152} bismuthine-,²⁵ tellurium-,^{29,33,116} iodine-,¹⁴⁹ dithiocarbonyl,¹⁵¹ and TEMPO-capped¹⁵⁰ dormant species at 60 °C in homopolymerization.^a

P-X	$k_d \text{ (s}^{-1}\text{)}$	$k_{ex} \text{ (M}^{-1} \text{ s}^{-1}\text{)}$	$k_p \text{ (M}^{-1} \text{ s}^{-1}\text{)}$	C_{ex}
PS-SbMe ₂	~0	1.1×10^4	3.4×10^2	32
PS-SbPh ₂	~0	4.0×10^4	—	118
PS-BiMe ₂	$(3 \times 10^{-4})^b$	1.8×10^4	—	53
PS-TeMe	1×10^{-5}	5.7×10^3	—	17
	$(2 \times 10^{-4})^b$	—	—	—
PS-I	~0	1.2×10^3	—	3.5
PS-TeBu- <i>n</i>	1×10^{-5}	3.4×10^3	—	10
PS-TePh	1×10^{-5}	9.6×10^3	—	28
PS-TeC ₆ H ₄ OMe- <i>p</i>	4×10^{-5}	1.2×10^4	—	35
PS-TeC ₆ H ₄ CH ₃ - <i>p</i>	5×10^{-5}	1.4×10^4	—	41
PS-SC(=S)Me	~0	6.1×10^{14}	—	180
PS-TEMPO	1×10^{-5}	0	—	—
PMMA-TeMe	5×10^{-6}	3.0×10^3	8.3×10^2	3.6
PMA-TeMe	$\leq 1 \times 10^{-3}$	4.6×10^5	2.4×10^4	19
PVAc-TeMe (H-T) ^b	~0	$1.0 (\pm 0.3) \times 10^6$	9.5×10^3	110 ± 30
PVAc-TeMe (H-H) ^b	~0	1.1×10^4	—	1.2

^aThe k_d , k_{ex} , and k_p are the rate constants for reversible termination (Scheme 22a), degenerative transfer (Scheme 22b), and propagation, respectively. C_{ex} is the degenerative chain-transfer constant ($= k_{ex}/k_p$).

^bData obtained at 100 °C.

are affected by the heteroatom species and the substituents on the heteroatom, the contribution of the RT mechanism is always considerably smaller than that of the DT mechanism in SBRP, BIRP, TERP, and IRP. Therefore, once the initiating radical species have formed, they predominantly undergo the DT-mediated polymerization reaction in all cases.

Under condition A (Section 3.4), the initiating radicals are provided via the thermolysis of the heteroatom CTA. The high temperatures and long reaction times required for the polymerization are due to the high activation energy required for the thermolysis. The initiating radicals are generated from azo-initiators under mild thermal conditions under condition B, and the polymerization proceeds exclusively via the DT mechanism. Under condition C, direct carbon–tellurium bond photolysis occurs to afford the initiating radicals from the dormant species. Since photochemical reactions do not require heat, polymerization also proceeds at low temperatures exclusively via DT. It is worth noting that, as the rate of polymerization becomes slower at lower temperatures, heating is sometimes necessary to complete the polymerization within a reasonable timescale when monomers with low propagation rates are employed under conditions B and C.

When LRP proceeds by DT mechanism, MWD of polymers can be estimated using (1) under steady-state conditions without any side reactions leading to dead polymers, where DP_n , c , C_{ex} ($= k_{ex}/k_p$), k_{ex} , and k_p are the number-average degree of polymerization, monomer conversion, a DT constant, a rate constant for DT, and a rate constant for the propagation reaction, respectively¹:

$$M_w/M_n = 1 + 1/DP_n + (2/c - 1)/C_{ex} \quad (1)$$

Since k_p and DP_n are constant when the same monomer with the same targeted M_n are considered, a faster k_{ex} and thus a higher C_{ex} leads to higher MWD control of the resulting polymer.

High values of k_{ex} and C_{ex} were observed for dimethylstibanyl, diphenylstibanyl, dimethylbismuthanyl, and methyltellanyl polymer-end group in SBRP ($C_{ex} = 32$ –118), BIRP ($C_{ex} = 53$), and TERP ($C_{ex} = 17$) in St polymerization. These values are sufficiently high to achieve high MWD control. Although C_{ex} ($= 10$) of the butyltellanyl group is slightly smaller than that of the methyltellanyl group, it is still faster than that

of the iodine atom ($C_{ex} = 3.5$).¹⁴⁹ The DT of the phenyltellanyl, *p*-methoxyphenyltellanyl, and *p*-trifluoromethylphenyltellanyl group in St polymerization ($C_{ex} = 28$ –41) takes place much faster than that of methyltellanyl group and very similar to that of dimethylstibanyl and dimethylbismuthanyl groups.

Among the same methyl-substituted heteroatom groups, bismuth is the fastest followed by antimony and then tellurium for the DT reaction. The kinetic data are also consistent with the general trend that organostibine, such as **Sb-2** and **Sb-3**, and organobismuthine CTAs, such as **Bi-1**, show higher MWD control than organotellurium CTAs **Te-1** and **Te-7** do. The kinetic data are also consistent with the observed higher MWD control using CTAs **Te-3**–**Te-5** possessing aryl substituents than that using methyltellanyl derivative **Te-1**.

The DT of diphenylstibanyl group at PS polymer end in St polymerization ($C_{ex} = 118$) occurs faster than that of dimethylstibanyl group. However, the MWD control using diphenylstibanyl CTA **Sb-4** was lower than that using dimethylstibanyl CTA, such as **Sb-1**. The insufficient control of diphenylstibanyl group is attributed to the occurrence of frequent termination.¹⁵² The results indicate that the rate of DT is not the exclusive factor for the MWD control.

The kinetic parameters in the polymerization of MMA, methyl acrylate (MA), and VAc involving an organotellurium dormant species with a methyltellanyl group are also summarized in Table 3.¹¹⁶ The DT mechanism is the predominant activation mechanism in all cases. The rate of DT of PMMA polymer end radical with PMMA-TeMe dormant species takes place about two times slower than that of a PS polymer-end species, and the propagation rate of the MMA polymerization is about 2.5 times faster than that of St. Consequently, C_{ex} ($= 3.6$) of the MMA polymerization becomes about five times smaller than that of the St polymerization. This C_{ex} value is too small to yield PMMAs with narrow MWDs. The result is consistent with the fact that the MWD control of the TERP of MMA was not sufficient ($M_w/M_n > 1.35$), and the addition of ditellurides was required to yield PMMA with a narrow MWD ($M_w/M_n \approx 1.1$).²⁸

SBRP and BIRP of MMA gave PMMA with a low MWD ($M_w/M_n < 1.25$) without the addition of the cocatalyst. The results suggest that the C_{ex} values under SBRP and BIRP must be larger than that under TERP, as in the polymerization of St,

and that organostibines and bismuthines generally have a higher reactivity in the DT reaction than organotellurium compounds have.

The rate of propagation of MA is about 70 times faster than that of St. However, as the rate of DT of the MA polymer-end species is about 80 times faster than that of PS, the C_{ex} (=19) in MA polymerization was similar to that in St polymerization. The result is also consistent with the fact that the polymerization of acrylates usually gives resulting polymers with a low MWD ($M_w/M_n < 1.2$).

SBRP, TERP, and IRP of VAc afforded PVAc with a low MWD when the degree of polymerization was low, but the control decreased with the increase in the degree of polymerization due to the formation of H–H addition (Section 3.5.5 and Scheme 8). Kinetic experiments revealed that DT of the PVAc polymer-end radical species with head-to-tail (H–T) dormant species in TERP ($X = \text{TeMe}$) was very fast with $k_{\text{ex}} = 1.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.¹¹⁶ Although the propagation rate constant of VAc ($k_p = 9.5 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$) is relatively high, C_{ex} is 110, a value large enough to give PVAc with a narrow MWD. In contrast, k_{ex} of the H–H dormant species ($X = \text{TeMe}$) was about 100 times slower than that of the H–T adduct ($C_{\text{ex}} = 1.2$), indicating that the activation from the H–H adduct was insufficient. Therefore, the H–H adduct virtually behaves as a dead polymer and is gradually accumulated in the reaction mixture as the polymerization progressed. Consequently, the MWDs gradually increased with an increase in monomer feed.

Although RAFT also proceeds by DT polymerization,^{19,20} the microscopic energy profiles of the DT in RAFT are completely different from those of SBRP, BIRP, TERP, and IRP as schematically shown in Figure 3. The DT in RAFT proceeds stepwise with the addition of radical P to thiocarbonyl compound **28** (a RAFT reagent) to form intermediate radical **29** (Figure 3a). Subsequent fragmentation of the S–P' bond in **29** generates RAFT reagent **28'** and radical P'. All the elementary processes are reversible, and the addition of radical P' to **28'** also generates radical P and **28** through intermediate **29**.¹⁵³ Although the lifetime of **29** must be short in order to minimize unwanted radical–radical termination process, the cross-termination involving **29** occurs as ascertained by Monteiro and de Brouwer¹⁵⁴ and Fukuda and coworkers.^{155,156} This chain breaking reaction causes the rate retardation observed in acrylate

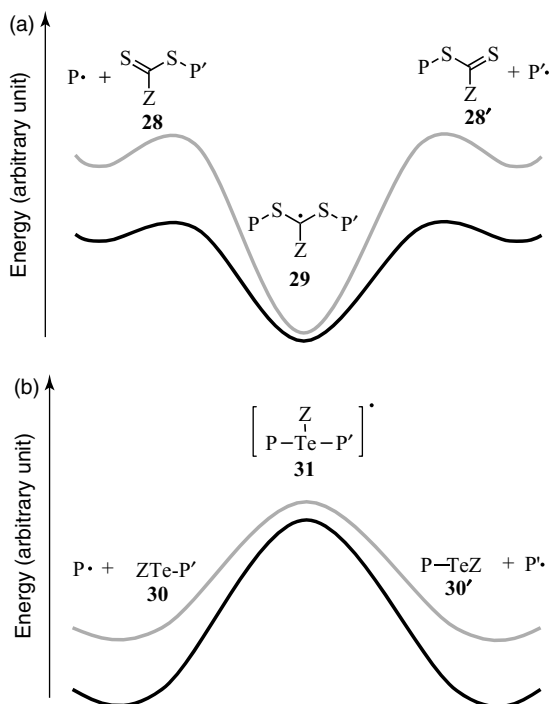


Figure 3 Hypothetical reaction coordinate of DT in (a) RAFT and (b) TERP. The lines in gray show the energy diagram when less stabilized radical P and P' are involved. [Reprinted from Ref. 93. © American Chemical Society, 2009.]

polymerization, especially when phenyl-substituted RAFT CTA ($Z = \text{Ph}$) was used. Stability of **29** is strongly affected by Z substituent because it directly attaches to the radical center, while effects of P and P' radicals on **29** are marginal. When the same Z group is considered, relative stability and, thus, concentration of **29** increases as the polymer-end radical P and P' become less stable as shown by the gray line. This enhances the probability of **29** undergoing the chain breaking reaction. Therefore, appropriate choice of Z group is necessary depending on the monomer families being polymerized so as to undergo efficient degenerative transfer reaction.

In sharp contrast, the DT in TERP proceeds through hypervalent tellurium intermediate or transition state **31**, which forms by the reaction of radical P with organotellurium dormant species **30** to generate radical P' and new dormant species **30'** (Figure 3b). Although the existence of a trivalent tellurium radical intermediate is still a controversial issue,^{89, 157–159} the intermediate, if any, should

Table 4 Kinetic parameters for the deactivation of polymer-end radicals by ditelluride¹⁰⁵ and metaliodide¹⁶³ “cocatalyst.”^a

Monomer	Cocatalyst	<i>T</i> (°C)	<i>K</i> _{da} (M ⁻¹ s ⁻¹)	<i>k</i> _p (M ⁻¹ s ⁻¹)	<i>C</i> _{da}
St	(MeTe) ₂	60	3.4–6.8 × 10 ⁵	3.4 × 10 ²	1000–2000
	GeI ₄	80	9.0 × 10 ⁵	6.6 × 10 ²	1400
	SnI ₄	80	5.7 × 10 ⁵	—	860
	NIS	80	4.3 × 10 ⁵	—	650
	Tolyl-GeI ₃	80	2.5 × 10 ⁵	—	380
	PI ₃	80	1.2 × 10 ⁵	—	180
MMA	(MeTe) ₂	60	1.2–2.4 × 10 ⁵	8.3 × 10 ²	150–290
	Tolyl-GeI ₃	70	3.1 × 10 ⁷	1.1 × 10 ³	30 000

^aThe *k*_{da} and *k*_p are the rate constants for deactivation of polymer-end radical (Scheme 23) and propagation, respectively. *C*_{da} refers to the deactivation constant (= *k*_{da}/*k*_p).

be very close in energy to the transition state. Therefore, the DT in TERP virtually proceed in a concerted manner, and involvement of a long-lived intermediate, which may cause unwanted side reactions, is unlikely. In addition, since the DT process becomes faster when less stable polymer-end radicals are involved as shown by the gray line, CTAs with the same Z group can be used for controlling LRP of various families of monomers. Energy profiles of SBRP, BIRP, and IRP should be very similar to TERP, though more experimental and theoretical investigations are needed.^{160,161}

The contribution of RT is small compared to DT, but it plays a crucial role in BIRP and TERP under condition A (Tables 2 and 3).¹¹⁶ The rate of RT reaction of PS-TeMe is very similar to that of NMP, PS-TEMPO,¹⁵⁰ and the results are consistent with the similarity of BDEs of structurally related organotellurium and nitroxide compound²⁷ and the similarity of the polymerization condition of TERP under condition A and NMP. The results indicate that CTAs in BIRP and TERP also serve as radical initiators. As the rate of thermal dissociation of organobismuth compounds is about two times faster than that of organotellurium compounds, the former is the best radical initiator among the heteroatom compounds.

4.2 Role of Diheteroatom Compounds

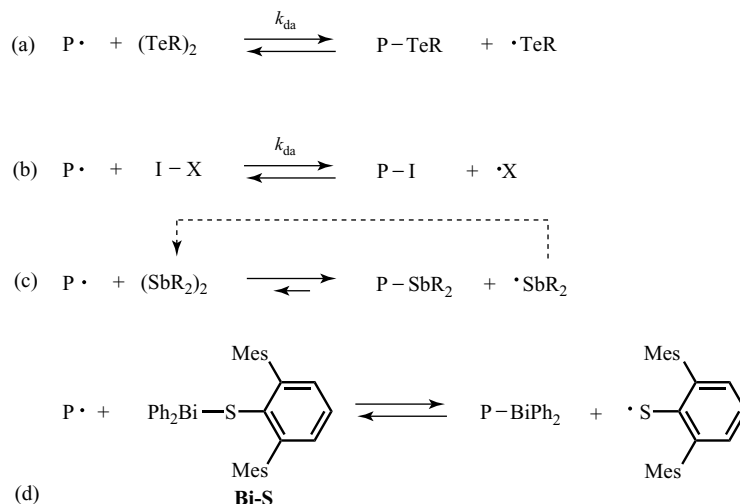
Addition of distibines, ditellurides, and various inorganic and organic cocatalysts in SBRP, TERP, and IRP, respectively, is effective for increasing MWD control in St and methacrylate polymerization (Section 3.5.1).^{23,28} Thiobismuthine **Bi-S** is also

effective for the controlled synthesis of ultrahigh molecular weight PSs and polyacrylates.

Kinetic studies to elucidate the effect of ditellurides have revealed that polymer-end radicals are effectively deactivated by ditelluride via a homolytic substitution reaction to form the dormant species (Table 4, Scheme 23a).¹¹⁶ The second-order rate constant (*k*_{da}) for the deactivation of PS polymer-end radical by dimethylditelluride at 60 °C is 3.4–6.8 × 10⁵ M⁻¹ s⁻¹, which corresponds to the deactivation constant *C*_{da} (= *k*_{da}/*k*_p) of 1000–2000. These values are about 100 times faster than the rate constant of DT (*k*_{ex}) and the *C*_{ex} of PS polymer-end radical with PS dormant species as shown in Table 3. The *k*_{da} for the deactivation of PMMA polymer-end radical by dimethylditelluride at 60 °C is 1.2–2.4 × 10⁵ M⁻¹ s⁻¹ (*C*_{da} = 150–290), the value of which is also 40–80 times faster than the DT rate constant *k*_{ex} of PMMA polymer-end radical by PMMA dormant species. These values are high enough to obtain PS and PMMA with narrow MWD.

The liberated tellanyl radical reacts with an organotellurium dormant species to regenerate a polymer-end radical and ditelluride. Therefore, the deactivation/activation mechanism of the dormant/radical species completely changes from the DT to the ditelluride trapping by the addition of sub-stoichiometric amount of ditelluride. The occurrence of more frequent deactivation/activation of the dormant/radical species is responsible for the increased MWD control by the addition of ditelluride.

Despite the high reactivity of tellanyl radical to organotellurium dormant species, it is virtually inert to monomer and does not initiate new polymer chains.¹⁶² If it did, the observed high controllability would not be realized. These seemingly conflicting reactivities of tellurium-centered radicals also play



Scheme 23 Deactivation mechanism of polymer-end radical P by diheteroatom compounds.

crucial roles in the control of MWD in TERP in the presence of ditellurides.

Inorganic and organic cocatalysts used in RCTP also serve as a deactivator for the polymer-end radicals leading to a dormant species (Scheme 23b).¹⁶³ The rate constants k_{da} of GeI_4 , SnI_4 , NIS, TolyI- GeI_3 , and PI_3 are also summarized in Table 4. GeI_4 showed most active cocatalyst for the deactivation among these cocatalysts, and the k_{da} for the deactivation of PS polymer-end radical by GeI_4 at 80 °C is $9.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. The deactivation constant is $C_{da} = 1400$, which is 400 times faster than the C_{ex} of PS-I dormant species and is very similar to the capping reaction by dimethyl ditelluride. The C_{da} of SnI_4 , NIS, TolyI- GeI_3 , and PI_3 are 860, 650, 380, and 180, respectively, and these values are sufficiently high to obtain PS with narrow MWD. The k_{da} for the deactivation of PMMA polymer-end radical by TolyI- GeI_3 at 80 °C is $3.1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ($C_{da} = 30\,000$), which is extremely fast and sufficiently high enough to control the polymerization of MMA.

When cocatalysts having X-H (X = heteroatom and carbon) are used, such as phenol and carbon catalysts shown in Scheme 5, the X-H bond is transformed *in situ* to X-I bond on hydrogen abstraction of X-H by a radical generated from an initiator followed by the trapping of X radical by iodine source. Once the X-I compound forms, an equilibrium between the polymer-end radical/X-I and the dormant species/X radical is established.

When such X-H-type cocatalysts are used, the hydrogen serves as a reducing agent for radicals generated in the reaction mixture. In addition, when the amount of cocatalyst was increased, rate retardation of the polymerization was observed due to the cross-termination reaction of the X radical with a polymer-end radical.⁷⁶ Therefore, the amount of cocatalyst must be tuned to maximize the advantage of the cocatalyst.

Although there are no kinetic studies on the effects of distibines in SBRP, the increased MWD control in the presence of distibine can also be ascribed to the higher efficiency of the deactivation of the polymer-end radical by distibine via a homolytic substitution reaction (Scheme 22c). The effect on the control using distibine is more noticeable than ditelluride, and this may be attributed to the higher reactivity of distibine than ditelluride, as in the DT reaction of polymer-end dormant species (Section 4.1).²³ The observed rate retardation in the presence of distibine is likely to shift the equilibrium from the polymer-end radical to the dormant species. This shift is probably due to the low reactivity of the dimethylstibanyl radical compared to that of an organostibine dormant species. In such a case, the stibanyl radical may dimerize to a distibine. Cross-termination between the stibanyl radical and a polymer-end radical may also occur to regenerate a dormant species.

The role of thiobismuthine **Bi-S** is to react reversibly with the polymer-end radical to

generate an organobismuthine dormant species and 2,6-dimesitylphenylthiyl radical (Scheme 22d).¹⁶⁴ The bulky 2,6-dimesitylphenyl group attached to the sulfur atom may prevent the addition of thiyl radicals to the vinyl monomers generating a new polymer chain, as thiyl radicals are reactive toward alkenes.¹⁶⁵ Since thiyl radicals are highly reactive toward organobismuthines,¹²⁷ the liberated thiyl radical reacts with the organobismuthine dormant species to regenerate the polymer-end radical P and Bi-S.

5 SYNTHESIS OF FUNCTIONAL POLYMERS BY TERP

5.1 Thermosensitive Micelles

Yusa *et al.*³² have reported the synthesis of diblock copolymers composed of PNIPAM and PNVP and their solution properties in water. The synthesis was achieved by successive TERP of NIPAM and NVP using **Te-2** as a CTA. Since the consumption of NIPAM was quantitative, no purification was necessary before the addition of NVP. By changing the amount of each monomer, diblock copolymers with different block lengths were also prepared in a controlled manner ($M_n = 17\,000$ – $36\,700$ g mol⁻¹, $M_w/M_n = 1.09$ – 1.15) (Figure 4a).

PNIPAM is a representative thermosensitive polymer and has a LCST in water,¹⁶⁶ and PNVP

is a water soluble polymer.^{167,168} Therefore, the block copolymers reversibly form micelles in water depending on the solution temperature (Figure 4b). Each block copolymer reversibly forms spherical core-corona micelles above T_a with unique aggregation numbers (300–27 000) depending on the block lengths of each segment.

Although there have been a number of reports concerning the synthesis of thermoresponsive block copolymers containing PNIPAM segment,^{169–171} this is the first example of the synthesis of diblock copolymer micelle comprising PNIPAM and PNVP. Since PNVP is a water soluble and biocompatible polymer, this block copolymer is a good candidate for several biological applications, such as in thermosensitive drug delivery vehicles.¹⁷²

The same diblock copolymer encapsulates gold nanoparticles in water via coordination of the PNVP block to the gold particle, as schematically shown in Figure 4b.¹⁷³ The polymer-coated gold nanoparticles show a temperature-dependent color change of the solution from pink to bluish-purple above the LCST of PNIPAM determined on the basis of the surface plasmon band. The polymer-coated gold nanoparticles may be separately dissolved in water when the temperature is below the LCST for the PNIPAM block. However, they may associate with each other due to hydrophobic interactions between the dehydrated PNIPAM blocks at temperatures above LCST, inducing a color change. This phenomenon may be applied to colloidal sensors.

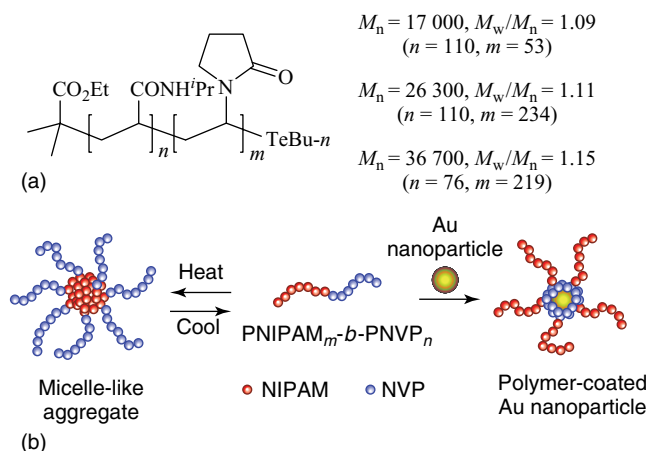


Figure 4 (a) Chemical structure of thermoresponsive diblock copolymer PNIPAM-*block*-PNVP and (b) schematic illustration of the micellization of the block copolymer as a function of temperature and the formation of a polymer-coated gold nanoparticle (M_n was given in g mol⁻¹). [Reprinted from Ref. 32. © American Chemical Society, 2007.]

5.2 Polymer Monoliths

Kanamori and coworkers have reported that TERP of 1,4-divinylbenzene in the presence of poly(dimethylsiloxane) and 1,3,5-trimethylbenzene gave macroporous cross-linked polymeric gels (Figure 5a).¹⁷⁴ Well-defined macroporous monolithic dried gels with bicontinuous structures on the micrometer scale were obtained after removing poly(dimethylsiloxane) and 1,3,5-trimethylbenzene by simple washing and drying (Figure 5b). Inside the skeletons that comprise the macroporous structure, “skeletal pores” with various sizes on the nanometer scale were found. The controlled pore formations are based on polymerization-induced phase separation by spinodal decomposition in the course of the homogeneous network formation during LRP. An unreactive polymeric agent present in solution during the polymerization induces spinodal decomposition during gelation to give a

well-defined bicontinuous porous structure. Pore size and volume can be independently controlled by changing the starting composition.¹⁷⁵

Conventional free radical polymerization in the presence of a “porogen,” which is usually a poor solvent for the network-forming components and induces phase separation, is widely used for the preparation of porous polymeric materials (polymer monoliths).^{176–178} Polymer monoliths thus prepared have been applied especially as liquid-phase separation or reaction media.^{179,180} However, fine-tuning of the pore properties, such as pore size, volume, and morphology, is relatively difficult because the pores are formed between segregated microgel particles that aggregate at random. Since the more homogeneous macroporous morphology with a bicontinuous structure was obtained, this type of materials will improve liquid transport throughout the media and liquid-phase applications, such as chromatography and catalyst supports, are expected.

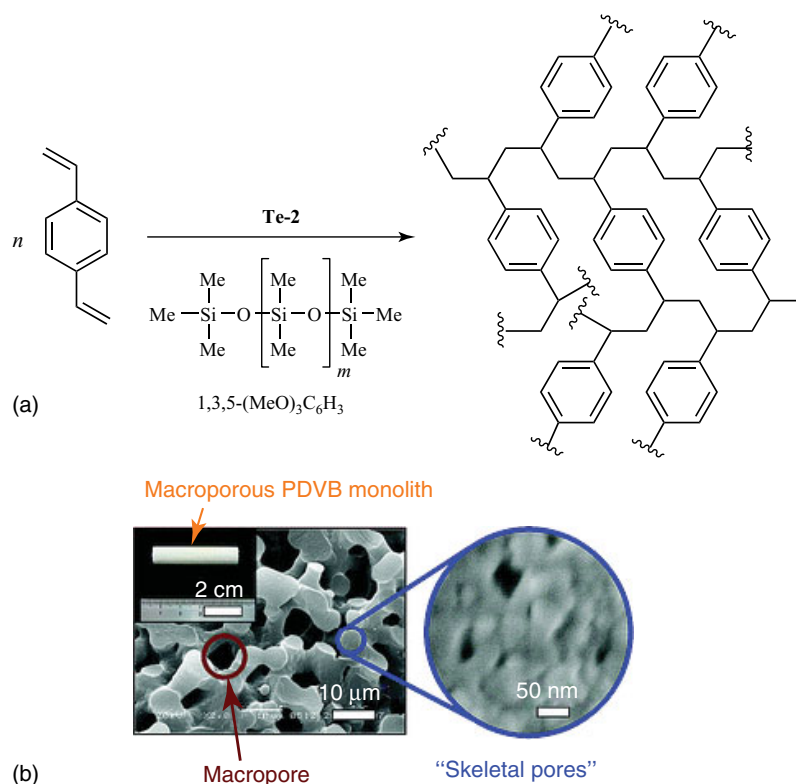


Figure 5 (a) Synthesis and (b) morphology of polydivinylbenzene (PDVB) gel prepared using TERP of 1,4-divinylbenzene. [Reprinted from Ref. 174. © American Chemical Society, 2009.]

The same group has also reported the synthesis of rigid cross-linked polyacrylamide monoliths with well-defined macropores derived from *N,N*-methylenebis(acrylamide) using TERP accompanied by spinodal decomposition with polyethylene oxide as a porogen.¹⁸¹ They are promising materials with highly hydrophilic polyacrylamide surfaces and have enough strength to withstand the surface tension arising from repetitive swelling and drying, which is inevitable in many applications. Kanamori *et al.* has also reported the synthesis of polymer monoliths with controlled pore properties using NMP of 1,4-divinylbenzene¹⁷⁵ and ATRP of 1,3-glycerol dimethacrylate.¹⁸² Therefore, the synthesis of polymer monoliths with controlled pore sizes is not limited to TERP. However, the synthetic advantages of TERP, such as high functional compatibility and high versatility of polymerizable monomer families, should be beneficial for the future design of new monoliths with various functionalities.

5.3 Adhesives, Dispersants, and Compatibilizers

Otsuka Chemical Co. recently announced that they had started selling several adhesives prepared using TERP (<http://chemical.otsukac.co.jp/advanced/about01.html>). Although detailed polymer compositions and chain lengths are not shown, control of MWD and the distribution of the cross-linking functionality of the polymer is the key for improving the properties. For example, a model random copolymer formed by TERP with an M_w of 581 600 with a narrow MWD ($M_w/M_n = 1.24$), whereas a control polymer prepared by conventional radical copolymerization had a broad MWD ($M_w = 703\,800\text{ g mol}^{-1}$, $M_w/M_n = 3.44$). A model adhesive prepared from the model polymer by cross-linking reaction had about 10 times stronger holding power than a control adhesive prepared from the control polymer, although they had similar adhesive powers. The properties of adhesives, such as the adhesive power and the tack, are easily tuned by changing the composition of functional groups and/or chain lengths. Otsuka Chemical Co. has also succeeded in the development of polymer compatibilizers and pigment dispersants consisting of block copolymers prepared by TERP.

6 CONCLUSION

SBRP, BIRP, TERP, and RTCP are versatile and robust methods for the preparation of structurally well-controlled macromolecules. Characteristic features of these methods include wide applicability to the polymerization of a variety of monomer families, high functional group compatibility, and a strong ability for the syntheses of block copolymers and end-modified polymers. These features clearly demonstrate that SBRP, BIRP, TERP, and RTCP could rival current LRP methods for the preparation of functionalized macromolecules with well-defined structures.

The development of these polymerization methods also clarified the unique reactivities of heteroatom compounds under radical conditions, especially toward the DT reaction. The rate of the DT reaction can be highly tuned by changing the central heteroatom and also substituent on the heteroatom. In addition, several diheteroatom, inorganic, and organic cocatalysts show ultrafast reaction toward radical species and highly effective to increase MWD control. Since methods to control the radical reaction is limited so far, these findings will offer a new strategy for highly controlled radical reactions in both polymer and organic synthesis. With the aid of such basic understandings, one can create truly powerful and useful LRP method to overcome the scientific and technical problems hindering industrial applications of LRP.

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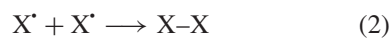
Photoinduced Reactions of Radical Ions via Charge Separation

Shunichi Fukuzumi^{1,2} and Kei Ohkubo¹

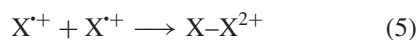
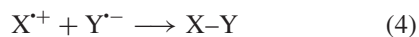
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1 INTRODUCTION

Free radicals are highly versatile and reactive intermediates, allowing many synthesis to be carried out under relatively mild conditions in chemical and biological systems (1).^{1–5} However, the high reactivity of free radicals usually results in low selectivity (2) and (3). Thus, it has been difficult to utilize reactions between free radicals for selective bond formation^{1–5}:



In contrast to neutral free radicals, reactions of radical ions are well controlled by charges: radical cations are expected to react selectively with radical anions (4) as compared with reactions of radical ions with the same charge (5) and (6):

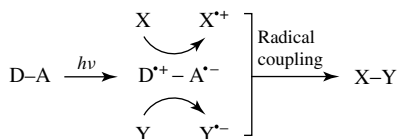


Thus, reactions between radical cations and radical anions have profound fundamental and

synthetic interest for selective bond formation.^{6–13} Radical cations and radical anions are formed using electron donor–acceptor-linked molecules, because the photoexcitation results in the formation of the radical ion pair, which can oxidize and reduce substrates to generate the corresponding radical cations and radical anions, respectively.^{14–17} Radical cations ($X^{\bullet+}$) and radical anions ($Y^{\bullet-}$) thus produced may couple selectively to produce the coupling products ($X-Y$) (4) in competition with back electron transfer from $Y^{\bullet-}$ to $X^{\bullet+}$.

Extensive studies have so far been devoted to mimic the function of the photosynthetic reaction center by developing electron donor–acceptor-linked molecules, which undergo a cascade of electron-transfer steps leading to long-range charge separation with prolonged lifetime of the charge-separated (CS) state.^{18–40} In a view of synthetic feasibility and their applications, it is important to develop electron donor–acceptor dyads in which the CS states have long lifetimes without losing energy by multistep electron-transfer processes.

This article focuses on reactions of radical ions produced by electron-transfer reactions of the CS state of electron donor–acceptor dyads (D–A) as shown in Scheme 1. First an electron donor–acceptor dyad capable of efficient photoinduced electron transfer to produce a long-lived CS



Scheme 1 Radical coupling reaction of X^{*+} and Y^{*-} produced by electron-transfer reactions of substrates (X and Y) with the CS state of an electron donor–acceptor dyad (D–A).

state ($D^{*+}-A^{*-}$) is described. Then, the long-lived CS state is utilized for generation of radical cations (X^{*+}) and radical anions (Y^{*-}), which are coupled to afford the coupling products (X–Y) (Scheme 1). Radical cations can also be converted to the corresponding neutral radicals by deprotonation, whereas radical anions can be converted to the corresponding neutral radicals by protonation. Thus, combination of deprotonation of radical cations and protonation of radical anions leads to facile reactions of neutral radicals. The reactions of radical cations, which are produced by electron-transfer reactions of the CS state of an electron donor–acceptor dyad, with nucleophiles are also described in this article.

2 FORMATION OF LONG-LIVED CHARGE-SEPARATED STATES

In order to produce radical ions by electron-transfer reactions with a CS state, the CS lifetime must be long enough to compete with back electron transfer to the ground state. The lifetime of the CS state has been reported to be elongated by decreasing the distance between the donor and acceptor in the dyads, which results in a decrease in the solvent reorganization energy of electron transfer.⁴¹ Among many electron donor–acceptor-linked molecules, an acridinium ion is the best candidate as a chromophore as well as an electron acceptor, because of the efficient electron self-exchange between the acridinium ion and the corresponding one-electron reduced radical^{7,42} and the high triplet excited energy.⁴³ Thus, an electron donor moiety (mesityl group) is directly connected at the 9-position of the acridinium ion to yield 9-mesityl-10-methylacridinium ion (Acr^+-Mes , Figure 1),⁴⁴ in which the solvent reorganization of electron transfer is minimized, because the overall charge remains the same in the charge-shift electron transfer with the short

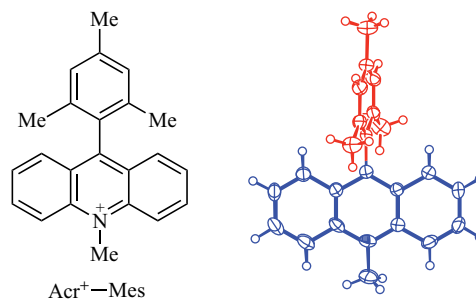
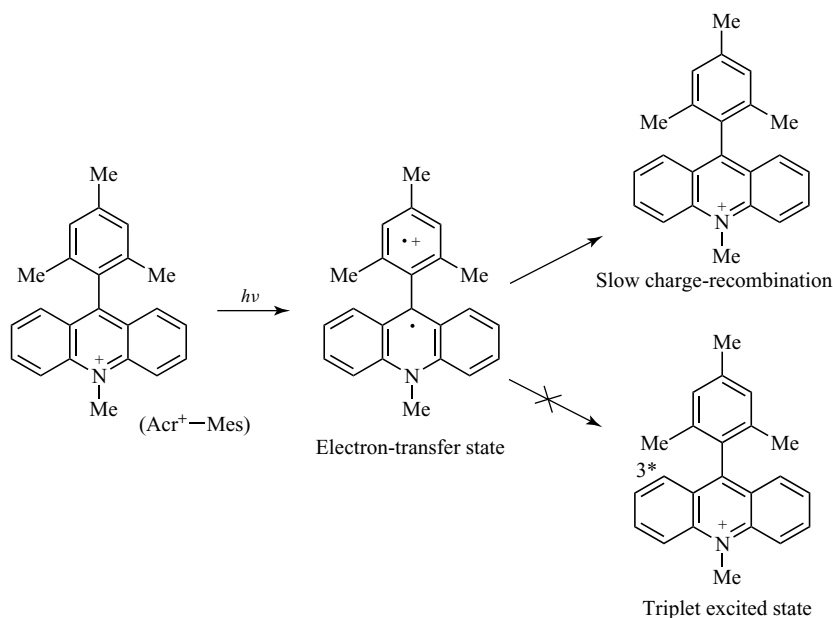


Figure 1 Chemical structure and crystal structure of Acr^+-Mes .⁴⁴

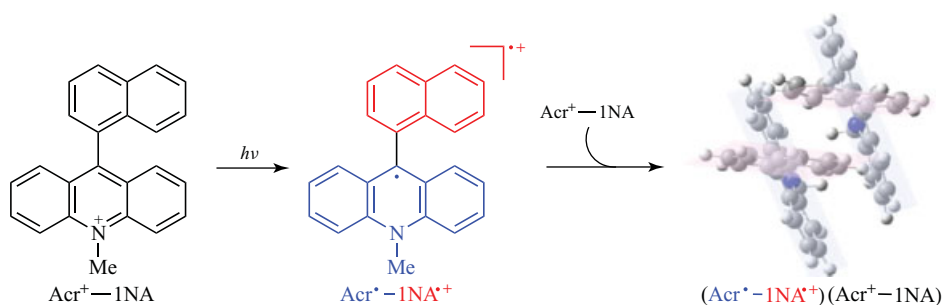
linkage between the donor and acceptor moieties. Acr^+-Mes affords the electron-transfer state on photoexcitation with not only a much longer lifetime (e.g., 2 h at 203 K) and a high quantum yield close to unity (98%) but also a much higher energy (2.37 eV) than the natural system.⁴⁴

The rate of intramolecular electron transfer from the Acr^+ moiety to the Mes^{*+} moiety in the same Acr^+-Mes^{*+} molecule is highly temperature dependent and the lifetime of the electron-transfer state becomes almost infinite (10^{29} years extrapolated from the Arrhenius plot for BET rates) at 77 K in solid state.⁴⁴ Nuclear tunneling usually becomes more apparent at lower temperatures, but this seems not to be the case for Acr^+-Mes^{*+} . The X-ray crystal structure of Acr^+-Mes in Figure 1 exhibits that the dihedral angle is perpendicular between the Mes and Acr^+ moieties of Acr^+-Mes .⁴⁴ In such a case, the orbital interaction between the donor and acceptor moieties is minimized. This is the key point to attain the long lifetime of the electron-transfer state. The simple molecular dyad (Acr^+-Mes) capable of fast photoinduced electron transfer but relatively slow back electron transfer to the ground state has clear advantages with regard to synthetic feasibility and its application as an organic photocatalyst.⁴⁵

The electron-transfer state of Acr^+-Mes has both strong oxidizing and reducing ability that would never be attained by the excited state of the electron acceptor moiety.^{44,46} However, there have been some reports on possible formation of the triplet excited state of the acridinium ion moiety rather than the electron-transfer state (Scheme 2).^{47–51} It was reported that the photoexcitation of 9-(1-naphthyl)-10-methylacridinium ion (Acr^+-1NA) resulted in the formation of the



Scheme 2 Reaction course of Acr^+-Mes on photoexcitation.



Scheme 3 π -Dimer formation of the electron-transfer state of Acr^+-1NA with the ground state of Acr^+-1NA .

triplet excited state, because of the absence of the transient absorption due to the radical cation at 700 nm.^{52–54} The reason why the electron-transfer state of Acr^+-1NA was overlooked was later shown by clear cut evidence of the formation of the electron-transfer state (NOT the triplet excited state) of Acr^+-1NA , which forms the π -dimer radical cation complex with the ground state of Acr^+-1NA (Scheme 3).⁵⁵ The nanosecond laser excitation of a deaerated acetonitrile (MeCN) solution of Acr^+-1NA at 355 nm resulted in the appearance of the new absorption band at 1050 nm due to the naphthalene π -dimer radical cation as shown in Figure 2a.⁵⁵ The equilibrium between monomer naphthalene radical cation and dimer naphthalene

radical cation is observed in intermolecular photoinduced electron transfer from naphthalene to the singlet excited state of 10-methylacridinium ion ($^1\text{AcrH}^{+*}$) as shown in Figure 2b.⁵⁵ When the concentration of naphthalene is 10 mM, the transient absorption due to monomer radical cation of naphthalene is clearly seen at 700 nm together with the near-infrared (NIR) absorption at 1050 nm due to the dimer naphthalene radical cation (Figure 2b). When the concentration of naphthalene is increased to 100 mM, the transient absorption at 700 nm due to monomer radical cation of naphthalene disappears, accompanied by an increase in the absorbance at 550 and 1050 nm due to the naphthalene π -dimer radical cation (Figure 2b). The

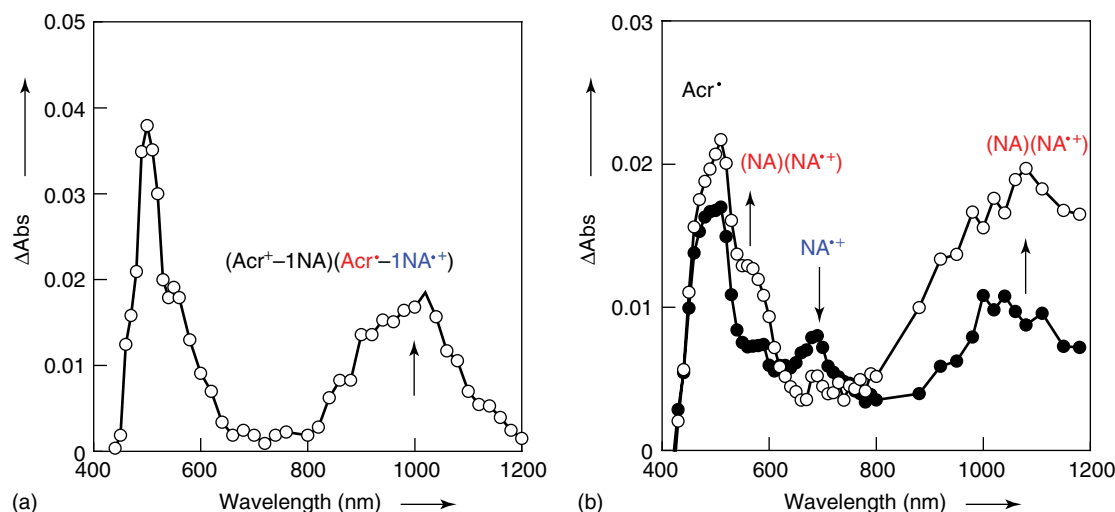


Figure 2 Transient absorption spectra of (a) Acr^+-1NA ($5.0 \times 10^{-5}\text{ M}$) and (b) AcrH^+ ($3.0 \times 10^{-5}\text{ M}$) with 10 mM (●) and 100 mM (○) of naphthalene in deaerated MeCN at 298 K taken at 2 μs after laser excitation at 355 nm.⁵⁵

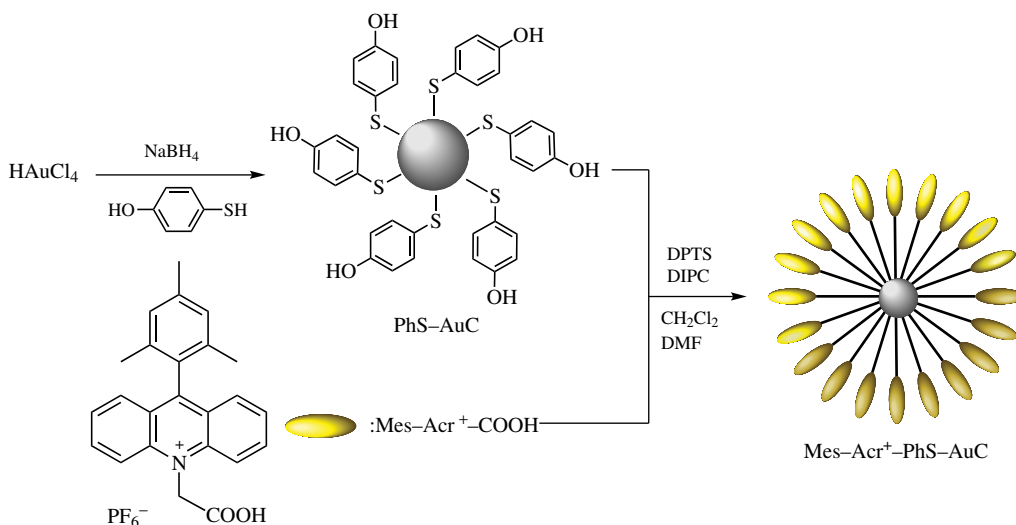
broad absorption band in the NIR region due to the π -dimer radical cation was also clearly observed in the case of Acr^+-Mes .⁵⁵ This is different from the band at 960 nm due to the T–T absorption of 9-phenylacridine.^{46,56–58} The formation of stable π -dimer radical cations and anions of aromatic compounds has been well known as a result of π -bonding of neutral π -compounds with the radical cations and radical anions, respectively.^{59–66}

The light-harvesting capability of Acr^+-Mes is significantly improved by assembling Acr^+-Mes molecules on Au nanoclusters ($\text{Mes}-\text{Acr}^+-\text{PhS}-\text{AuC}$) as shown in Scheme 4.⁶⁷

The $\text{Mes}-\text{Acr}^+-\text{PhS}-\text{AuC}$ nanocluster was prepared by the coupling between the functional molecules and Au nanoclusters. Carboxyl-terminated $\text{Mes}-\text{Acr}^+-\text{COOH}$ ^{67,68} is directly coupled to 4-mercaptophenol-functionalized Au nanoclusters ($\text{PhS}-\text{AuC}$) in the presence of *N,N'*-diisopropylcarbodiimide and 4-(*N,N*-dimethylamino)pyridinium-4-toluene-sulfonate as the standard coupling agents (Scheme 4).⁶⁷ The reference compound ($\text{Mes}-\text{Acr}^+-\text{COOPh}$) was synthesized by condensation of $\text{Mes}-\text{Acr}^+-\text{COOH}$ and phenol.⁶⁷

Femtosecond laser excitation of $\text{Mes}-\text{Acr}^+-\text{PhS}-\text{AuC}$ at 420 nm results in appearance of a transient absorption band at 490 nm and a broad transient absorption band in the NIR region as shown in Figure 3a.⁶⁷ Such a broad NIR band is assigned to the π -dimer radical

cation of the electron-transfer state of $\text{Mes}-\text{Acr}^+$ ($\text{Mes}^{*+}-\text{Acr}^+-\text{PhS}-\text{AuC}$) with the neighboring $\text{Mes}-\text{Acr}^+$ molecule. This is made possible by the close proximity of $\text{Mes}-\text{Acr}^+$ molecules on AuC via an intramolecular π – π interaction on photoinduced electron transfer from the Mes moiety to the singlet excited state of the Acr^+ moiety. In contrast to this, no transient absorption band in the NIR region was observed in the case of the reference compound ($\text{Mes}-\text{Acr}^+-\text{COOPh}$), when only the transient absorption band at 490 nm due to the electron-transfer state of $\text{Mes}-\text{Acr}^+-\text{COOPh}$ ($\text{Mes}^{*+}-\text{Acr}^+-\text{COOPh}$) is observed at 10 ps (Figure 3b).⁶⁷ The π -dimer radical cation of $\text{Mes}^{*+}-\text{Acr}^+-\text{COOPh}$ with $\text{Mes}-\text{Acr}^+-\text{COOPh}$ was formed by the intermolecular reaction at 10 μs , in sharp contrast to intramolecular formation of the π -dimer radical cation at 1 ps as shown in Figure 3a.⁶⁷ Thus, the photoexcitation of gold nanoclusters (AuC) functionalized with $\text{Mes}-\text{Acr}^+$ resulted in rapid formation of the electron-transfer state ($\text{Mes}^{*+}-\text{Acr}^+$) to produce the π -dimer radical cation with the neighboring $\text{Mes}-\text{Acr}^+$ molecule on AuC, whereas such π -dimer radical cation formation occurs at much slower timescale for the reference compound ($\text{Mes}-\text{Acr}^+-\text{COOPh}$) by the intermolecular reaction between $\text{Mes}^{*+}-\text{Acr}^+-\text{COOPh}$ and $\text{Mes}-\text{Acr}^+-\text{COOPh}$.



Scheme 4 Preparation of 9-mesitylacridinium ion-monolayer-protected gold nanoclusters ($\text{Mes-Acr}^+\text{-PhS-AuC}$).⁶⁷

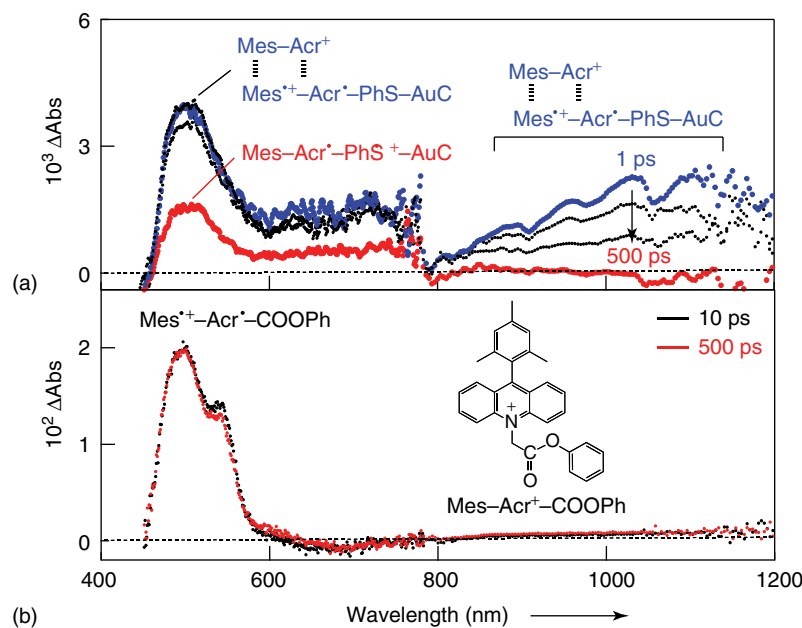
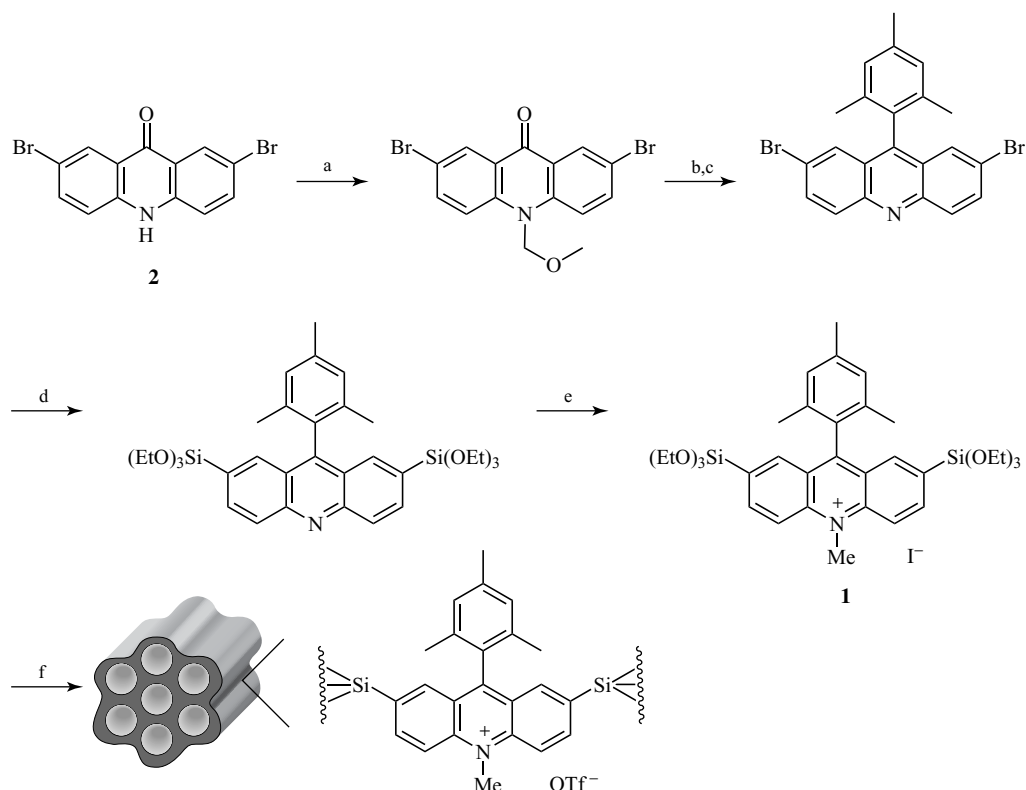


Figure 3 Transient absorption spectra observed in femtosecond laser flash photolysis ($\lambda_{\text{ex}} = 420 \text{ nm}$) of (a) $\text{Mes-Acr}^+\text{-PhS-AuC}$ at 2 and 500 ps and (b) $\text{Mes-Acr}^+\text{-COOPh}$ at 10 and 500 ps in MeCN at 298 K.⁶⁷

Immobilization of $\text{Acr}^+\text{-Mes}$ molecules in a solid porous framework provides a wide range of potential applications, including as solid-state photocatalysts and in electrical devices. Periodic mesoporous organosilicas (PMOs) prepared

by surfactant-directed self-assembly of bridged organosilane precursors ($(\text{R}'\text{O})_3\text{Si-R-Si}(\text{OR}')_3$, R: organic bridging group) have been used to immobilize $\text{Acr}^+\text{-Mes}$ (Scheme 5).⁶⁹ PMOs with a high surface area are promising candidates as



Scheme 5 Synthetic route for the preparation of Mes-Acr⁺ organosilane precursor **1** and mesostructured organosilica. (a) NaH, MOMCl, dimethylformamide (DMF); (b) MesMgBr, tetrahydrofuran; (c) HCl aq; (d) HSi(OEt)₃, NEt₃, *n*-Bu₄NI, [Rh(cod)(CH₃CN)₂]BF₄, DMF; (e) MeOTf, CH₂Cl₂ (X = OTf); (f) Brij76, HCl aq, EtOH.⁶⁹

solid-state functional materials, because their function and morphology can be readily controlled by appropriate selection of organic bridges (–R–) within the framework.^{70–77} The mesostructured materials were successfully obtained from the newly designed precursor **1** (Scheme 5) without dilution of the scaffold silica sources (e.g., tetraethoxysilane).⁶⁹ The Acr⁺–Mes-bridged precursor **1** was prepared starting from commercially available 2,7-dibromoacridone **2** in 74% overall yield (five steps) (Scheme 5). Photoinduced electron transfer within the Acr⁺–Mes–silica hybrid framework was demonstrated to afford the electron-transfer state over a microsecond timescale.⁶⁹

The following sections describe the development photocatalytic oxidation, cycloaddition, and bromination via the long-lived electron-transfer state of Acr⁺–Mes.

3 PHOTOOXYGENATION VIA ELECTRON TRANSFER

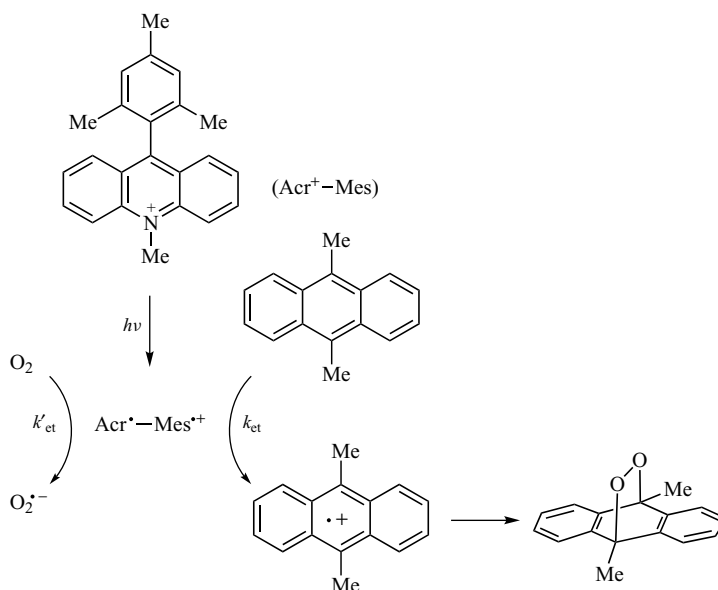
3.1 Photooxygenation of Anthracene via Radical Ion Coupling

As described above, photoexcitation of Acr⁺–Mes results in the formation of the electron-transfer state (Acr[•]–Mes^{•+}), which has an extremely long lifetime (e.g., 2 h at 203 K) as well as both highly oxidizing and reducing ability.^{44,78} In such a case, Acr⁺–Mes acts as an efficient electron-transfer photocatalyst for highly selective oxygenation of various substrates with O₂ via selective radical ion coupling of the donor radical cation and superoxide anion (O₂^{•–}) under visible light irradiation (vide infra).

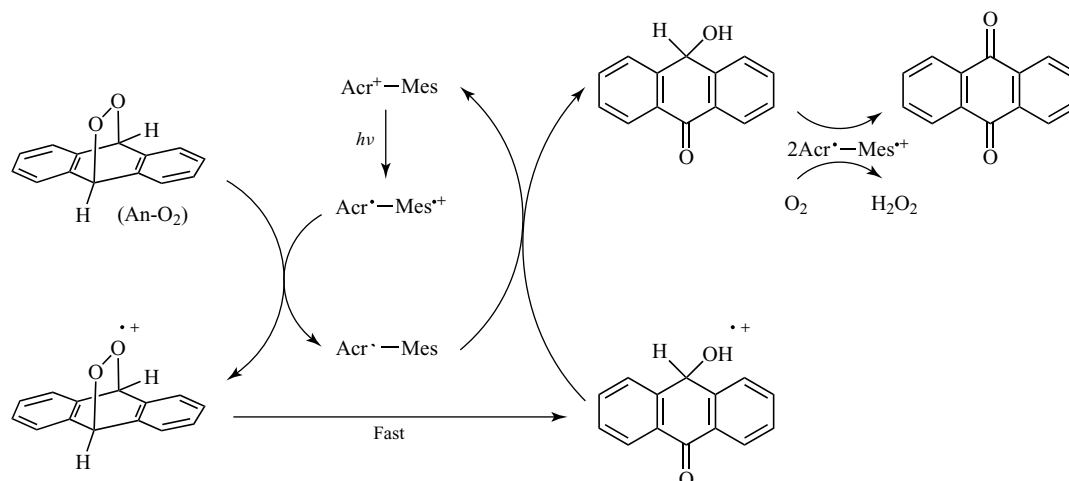
Visible light irradiation (λ > 430 nm) of the absorption band of Acr⁺–Mes in an O₂-saturated

MeCN solution containing 9,10-dimethylantracene (Me_2An) results in the formation of oxygenation product, that is, dimethylepidioxanthracene ($\text{Me}_2\text{An-O}_2$) via efficient [4 + 2] coupling between the radical cation of 9,10-dimethylantracene ($\text{Me}_2\text{An}^{\bullet+}$) and $\text{O}_2^{\bullet-}$, which are produced by the electron-transfer oxidation of Me_2An and the electron-transfer reduction of O_2 with the electron-transfer state of Acr^+-Mes , respectively, as shown in Scheme 6.⁷⁸ Anthracene and 9-methylantracene also undergo the photocatalytic oxygenation by O_2 with Acr^+-Mes to afford the corresponding epidioxanthracenes (An-O_2 and MeAn-O_2 , respectively) under visible light irradiation.⁷⁸ Epidioxanthracenes are known to be formed by the reaction of anthracenes with singlet oxygen ($^1\text{O}_2$).⁷⁹ However, the rate constant of the reaction of $^1\text{O}_2$ with Me_2An ($2.4 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$) is much smaller than the rate constant of the radical coupling reaction of $\text{Me}_2\text{An}^{\bullet+}$ and $\text{O}_2^{\bullet-}$ ($1.7 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$) in MeCN at 298 K.⁷⁸ It was confirmed that no singlet oxygen emission was observed during the photocatalytic oxygenation of Me_2An in an O_2 -saturated CD_3CN .⁷⁸ Thus, $\text{Me}_2\text{An-O}_2$ is formed exclusively by the radical ion coupling between $\text{Me}_2\text{An}^{\bullet+}$ and $\text{O}_2^{\bullet-}$ rather than the reaction of Me_2An and $^1\text{O}_2$ as shown in Scheme 6.

In the case of anthracene, further photoirradiation results in the formation of anthraquinone as the final six-electron oxidation product via 10-hydroxyanthrone, accompanied by generation of H_2O_2 as shown in Scheme 7.⁷⁸ The photocatalytic oxygenation of anthracenes is initiated by photoexcitation of Acr^+-Mes , which results in the formation of the electron-transfer state ($\text{Acr}^{\bullet}-\text{Mes}^+$), followed by electron transfer from anthracenes to the Mes^+ moiety together with electron transfer from the $\text{Acr}^{\bullet}$ moiety to O_2 .^{44,78} The resulting anthracene radical cation undergoes radical coupling reactions with $\text{O}_2^{\bullet-}$ to produce the epidioxanthracene (An-O_2).^{44,78} The mechanism of the photocatalytic conversion of An-O_2 to 10-hydroxyanthrone is shown in Scheme 7.⁷⁸ The electron transfer from An-O_2 to the Mes^+ moiety of $\text{Acr}^{\bullet}-\text{Mes}^+$, produced on photoexcitation of Acr^+-Mes , results in the O–O bond cleavage of An-O_2 , followed by facile intramolecular hydrogen transfer to produce 10-hydroxyanthrone radical cation. Then the back electron transfer from $\text{Acr}^{\bullet}-\text{Mes}$ to 10-hydroxyanthrone radical cation yields 10-hydroxyanthrone to regenerate Acr^+-Mes . 10-Hydroxyanthrone is further oxidized to anthraquinone with $\text{Acr}^{\bullet}-\text{Mes}^+$, accompanied by reduction of O_2 to yield H_2O_2 (Scheme 7).



Scheme 6 Photocatalytic oxygenation of Me_2An by O_2 with Acr^+-Mes .⁷⁸



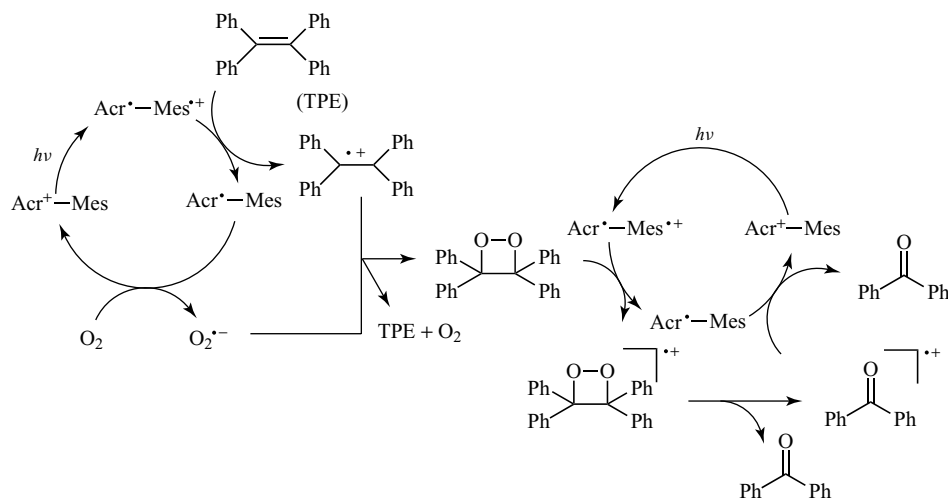
Scheme 7 Photocatalytic oxygenation of anthracene by O_2 with Acr^+-Mes .⁷⁸

3.2 Photocatalytic Oxygenation of Tetraphenylethylene to 1,2-Dioxetane

The Acr^+-Mes can also act as an efficient organic photocatalyst for the synthesis of 1,2-dioxetane of tetraphenylethylene (TPE), which would otherwise be impossible to synthesize.⁷⁹ 1,2-Dioxetanes have attracted considerable interest because of the key roles in chemiluminescence and bioluminescence,^{80–82} which have a broad range of biological, chemical, and medical applications.^{83–86} The most common preparation of 1,2-dioxetanes is through the formal [2 + 2] cycloaddition of singlet oxygen (1O_2) to electron-rich alkenes.^{87,88} Diastereoselective formation of dioxetanes has also been achieved by a chiral-auxiliary induced [2 + 2] cycloaddition of 1O_2 with a chiral allylic alcohol and enecarbamates.^{89–93} If alkenes are too electron-poor to react with 1O_2 , however, no oxygenated products were obtained. For example, no products were formed in an oxygen-saturated MeCN solution of TPE in the presence of 1O_2 sensitizers such as C_{60} or tetraphenylporphyrin under photoirradiation.⁴⁷ In contrast, the photocatalytic oxygenation of TPE by O_2 occurs efficiently with Acr^+-Mes via the radical ion coupling between TPE radical cation ($TPE^{+\bullet}$) and $O_2^{\bullet-}$, both of which are produced by electron-transfer reactions of TPE and O_2 with the photogenerated electron-transfer state of Acr^+-Mes ($Acr^+-Mes^{+\bullet}$),

leading to successful isolation of the corresponding 1,2-dioxetane.⁷⁹

Electron transfer from TPE to the $Mes^{+\bullet}$ moiety in $Acr^+-Mes^{+\bullet}$ is energetically feasible, because the one-electron reduction potential of $Acr^+-Mes^{+\bullet}$ in MeCN ($E_{red} = 1.88$ V vs SCE, saturated calomel electrode)⁴⁴ is more positive than the one-electron oxidation potential of TPE ($E_{ox} = 1.31$ V vs SCE in $CHCl_3$).⁷⁹ The second-order rate constant of electron transfer from TPE to $Acr^+-Mes^{+\bullet}$ was determined by laser flash photolysis measurements to be 2.5×10^9 $M^{-1} s^{-1}$ in $CHCl_3$, which is close to be the diffusion-limited value as expected from the exergonic electron transfer.⁷⁹ The second-order rate constant of the electron-transfer reduction of O_2 by the Acr^+ moiety was also determined to be 3.8×10^8 $M^{-1} s^{-1}$ in $CHCl_3$.⁷⁹ The formation of $O_2^{\bullet-}$ was confirmed by electron spin resonance (ESR), which was measured at 123 K immediately after the photoirradiation of a chloroform solution of TPE (1.0×10^{-3} M) and Acr^+-Mes (1.0×10^{-4} M) at 233 K.⁷⁹ The observed g values agree with those reported for $O_2^{\bullet-}$ ($g_{||} = 2.1050$ and $g_{\perp} = 2.0032$).^{94,95} The transient absorption band of $TPE^{+\bullet}$ decays second-order kinetics.⁷⁹ The second-order rate constant was determined to be 6.0×10^9 $M^{-1} s^{-1}$, which is close to the diffusion-limited value in $CHCl_3$.⁷⁹ The bimolecular process involves both the radical coupling between $TPE^{+\bullet}$ and $O_2^{\bullet-}$ to afford the corresponding dioxetane and the back electron transfer from $O_2^{\bullet-}$

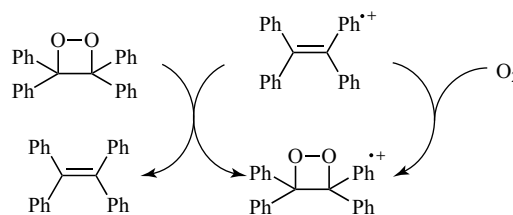


Scheme 8 Photocatalytic oxygenation of TPE by O_2 with Acr^+-Mes .⁷⁹

to $TPE^{\bullet+}$ to regenerate the reactant pair as shown in Scheme 8.

The E_{ox} and E_{red} values of the dioxetane were determined by second-harmonic ac voltammetry as 1.56 V and -0.95 V versus SCE, respectively.⁷⁹ The E_{ox} value is less positive than the E_{red} value (1.88 V vs SCE in PhCN)⁴⁴ of the $Mes^{\bullet+}$ moiety of $Acr^+-Mes^{\bullet+}$, whereas the E_{ox} value of the $Acr^{\bullet}$ moiety (-0.57 V vs SCE) is less negative than the E_{red} value of the dioxetane. In such a case, the dioxetane is further oxidized by $Acr^+-Mes^{\bullet+}$ rather than by being reduced to produce the dioxetane radical cation, which undergoes the O–O bond homolysis to produce benzophenone and the radical cation as shown in Scheme 8.⁷⁹ The benzophenone radical cation is reduced by Acr^+-Mes to produce another benzophenone molecule, accompanied by regeneration of Acr^+-Mes (Scheme 8). The thermal oxygenation reaction of TPE with oxygen has previously been proposed to proceed via radical chain processes as shown in Scheme 9.^{96–98} The dioxetane is assumed to be produced by direct oxygenation of the dioxetane radical cation with O_2 . However, the saturated dependence of Φ on $[TPE]$ and also on $[O_2]$ indicates that such an electron-transfer radical chain process (Scheme 9) is not operative as the major pathway under the photocatalytic reaction conditions.⁷⁹

The formation of the dioxetane radical cation was confirmed by ESR measurements under photoirradiation at low temperature as shown in Figure 4.⁷⁹



Scheme 9 Radical chain process of photooxygenation of TPE via the dioxetane.

A deaerated chloroform solution of Acr^+-Mes with TPE dioxetane was irradiated by a high-pressure Hg lamp at 223 K. The resulting ESR spectrum observed at 143 K exhibits anisotropic signals at $g_{||} = 2.020$ and $g_{\perp} = 2.004$. The isotropic g value (g_{iso}) is determined as 2.009 ± 0.001 , which agrees with the reported value of a dioxetane radical cation (2.0099).⁹⁹ The formation of TPE dioxetane radical cation was also confirmed by photoinduced electron-transfer oxidation of TPE dioxetane with the singlet excited state of 9,10-dicyanoanthracene (DCA) ($^1E_{red}^* = 1.97$ V vs SCE) in frozen deaerated $CHCl_3$ at 143 K.⁷⁹ The resulting ESR signal was virtually the same as that shown in Figure 4a.⁷⁹ The singly occupied molecular orbital (SOMO) of dioxetane radical cation involves O–O antibonding orbital (Figure 4b).⁷⁹ This may be the reason why the facile cleavage of the O–O bond of the dioxetane radical cation occurs to yield benzophenone.¹⁰⁰

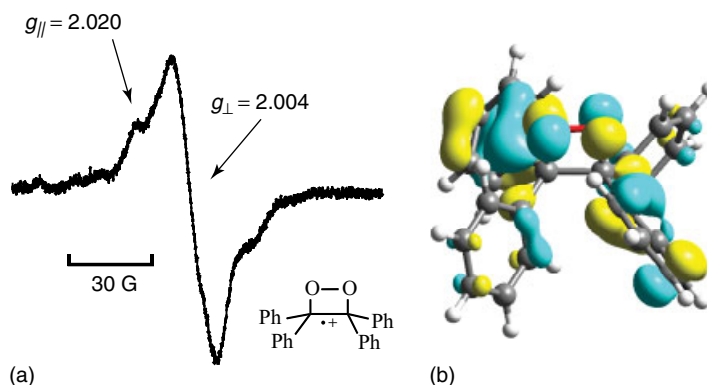


Figure 4 (a) ESR spectrum of TPE dioxetane radical cation observed under irradiation of a deaerated CHCl_3 solution containing TPE dioxetane (3.0×10^{-3} M) and Acr^+-Mes (3.7×10^{-2} M) at 223 K measured at 143 K (frozen). (b) The SOMO orbital of TPE dioxetane radical cation, calculated by DFT method using UB3LYP/6-31G* basis set.⁷⁹

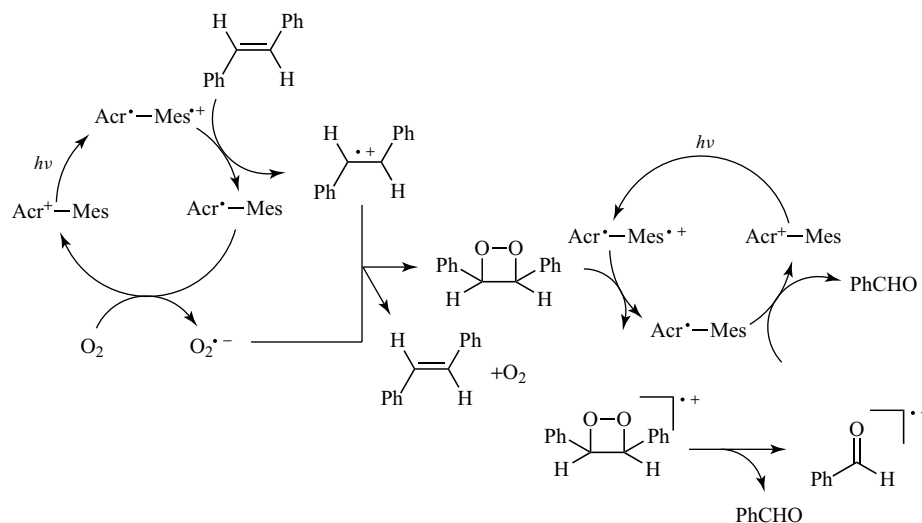
Photocatalytic oxygenation of olefins such as stilbene derivatives also occurs with Acr^+-Mes in MeCN and CHCl_3 .¹⁰¹ In contrast to the case of TPE, the dioxetane intermediates were not detected under the same experimental conditions as employed for TPE.¹⁰¹ This indicates that the stilbene dioxetanes decompose to the corresponding benzaldehydes spontaneously under the photoirradiation. The yields of benzaldehyde derivatives obtained from *trans*-stilbene derivatives increase in order: $\text{R}^1, \text{R}^2 = \text{H}, \text{H} < \text{Me}, \text{Me} < p\text{-MeO}, \text{H}$, as the one-electron oxidation potential (E_{ox}) values of stilbene derivatives decrease.¹⁰¹ The photooxygenation mechanism of *cis*-stilbene catalyzed by Acr^+-Mes is shown in Scheme 10,¹⁰¹ which is similar to that of TPE (Scheme 8). Electron transfer from stilbene derivatives to the Mes^{++} moiety of $\text{Acr}^+-\text{Mes}^{++}$ is energetically feasible, because the E_{ox} values of stilbene derivatives (0.55–1.58 V vs SCE) are less positive than the E_{red} value of the Mes^{++} moiety of $\text{Acr}^+-\text{Mes}^{++}$ in PhCN (1.88 V vs SCE).⁴⁴ Because stilbene radical cation has low reactivity toward O_2 ,^{102–112} the photocatalytic oxygenation of stilbene with Acr^+-Mes occurs via the radical ion coupling between stilbene radical cation and $\text{O}_2^{\cdot-}$ rather than via the reaction of stilbene radical cation with O_2 , accompanied by the isomerization of the stilbene radical cation.¹⁰¹ The stilbene radical cation reacts with $\text{O}_2^{\cdot-}$ to produce the dioxetane that decompose spontaneously to benzaldehyde and benzaldehyde radical cation by the electron-transfer oxidation with the Mes^{++} moiety of $\text{Acr}^+-\text{Mes}^{++}$. The back electron transfer from Acr^+-Mes to benzaldehyde radical

cation yields benzaldehyde to regenerate Acr^+-Mes (Scheme 10).

Photocatalytic isomerization of *cis*-stilbene to *trans*-stilbene also occurs with Acr^+-Mes in an O_2 -saturated MeCN as shown in Scheme 10.¹⁰¹ The concentration of *cis*-stilbene decreases with a concomitant increase due to *trans*-stilbene, when the total concentration of *cis*- and *trans*-stilbene only slightly decreases together with an accompanied increase in the photooxygenation product, benzaldehyde.¹⁰¹ The observed yield of *trans*-stilbene was 96% after 60-min photoirradiation ($\lambda > 430$ nm), when the total consumption of *cis*- and *trans*-stilbene is still 4%.¹⁰¹ It is well known that *cis*-*trans* isomerization occurs rapidly in the stilbene radical cation.^{113–116} The steady-state *cis*-*trans* ratio of stilbene has been reported to be 99:1.¹¹⁶ Thus, Acr^+-Mes acts as a photocatalyst for the *cis*-*trans* isomerization of stilbene via the radical cation (Scheme 10).

3.3 Photocatalytic Oxygenation of *p*-Xylene and Reduction of Oxygen

As described above, photocatalytic oxygenation of aromatic substrates occurs via radical ion coupling of the substrate radical cation and $\text{O}_2^{\cdot-}$. This section describes photocatalytic oxygenation via the electron-transfer state of Acr^+-Mes without radical coupling. Oxygenation of aromatic compounds to produce aromatic aldehydes is key chemical reactions for production of precursors of a variety of

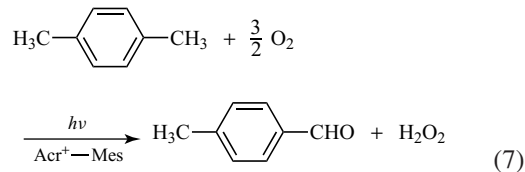


Scheme 10 Photocatalytic isomerization and oxygenation of stilbene by O_2 with Acr^+-Mes .¹⁰¹

fine or specialty chemicals such as pharmaceutical drugs, dyestuffs, pesticides, and perfume compositions. A number of methods using inorganic heavy metal oxidants have so far been reported for oxygenation of aromatic compounds to produce the corresponding aldehydes.^{117–122} However, their synthetic utility has been limited because of low yield and poor selectivity. Moreover, the use of stoichiometric amounts of inorganic oxidants should be avoided because of the environmental problems.¹²³ For this reason, catalytic oxygenation processes with molecular oxygen or hydrogen peroxide (H_2O_2) have merited increasing attention.¹²⁴ H_2O_2 is in brisk demands for clean and mild oxidant because the byproduct in oxygenation of substrates is only H_2O .^{124,125} There have been extensive studies on photocatalytic formation of H_2O_2 ^{126,127} or photocatalytic oxygenation of aromatic substrates.^{128–133} If valuable aromatic aldehydes can be produced together with H_2O_2 in the photocatalytic oxygenation of alkyl aromatic compounds by O_2 , such a process would be superior as compared to the conventional methods to produce either or both H_2O_2 and aromatic aldehydes.

Such selective photocatalytic oxygenation has been made possible using Acr^+-Mes and its derivative, which act as efficient photocatalysts for simultaneous production of aromatic aldehydes and H_2O_2 in the photocatalytic oxygenation of alkyl aromatic compounds by O_2 under

visible light irradiation.¹³⁴ Visible light irradiation of $[\text{Acr}^+-\text{Mes}]\text{ClO}_4^-$ ($\lambda_{\text{max}} = 430 \text{ nm}$, 0.20 mM) in oxygen-saturated MeCN containing *p*-xylene (4.0 mM) with a xenon lamp attached with a color glass filter ($\lambda = 380\text{--}500 \text{ nm}$) for 80 min resulted in formation of an oxygenated product, *p*-tolualdehyde (34%), *p*-methylbenzyl alcohol (10%), and H_2O_2 (30%). The overall stoichiometry of the photocatalytic reaction is given by (7).¹³⁴ *p*-Methylbenzyl alcohol is an intermediate in the photocatalytic oxygenation (*vide infra*):



The photocatalytic reactivity was enhanced by the presence of H_2O (0.9 M) and sulfuric acid (1.0 mM) to yield *p*-tolualdehyde (75%), *p*-methylbenzyl alcohol (15%), and H_2O_2 (74%) with a high quantum yield (0.25).¹³⁴ The 100% yields of *p*-tolualdehyde and H_2O_2 with a higher quantum yield (0.37) were achieved using 9-mesityl-2,7,10-trimethylacridinium ion ($\text{Me}_2\text{Acr}^+-\text{Mes}$), where the hydrogens at 2 and 7 positions of the acridinium ring are replaced by the methyl groups (Table 1).¹³⁴

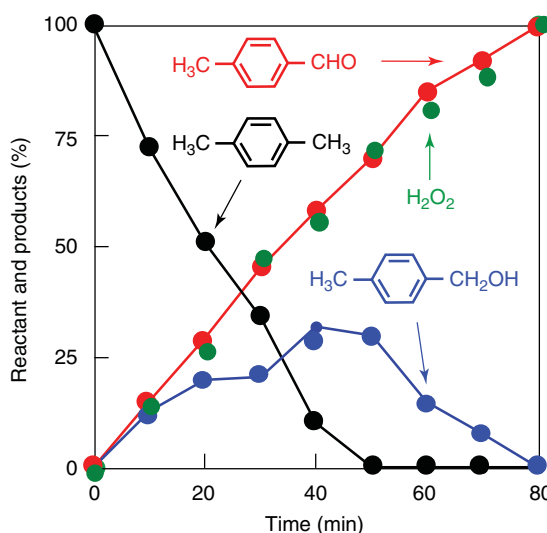
Table 1 Products and quantum yields for photocatalytic oxygenation of methyl-substituted benzenes with acridinium ion derivatives in O₂-saturated MeCN.¹³⁴

Photocatalyst	Substrate	E_{ox} vs SCE (V) ^a	Yield (%) ^b aldehyde/alcohol/H ₂ O ₂	Quantum yield ^{b,c}
Acr ⁺ –Mes	<i>p</i> -Xylene	1.93	75/15/74 (34/3/30)	0.25 (0.13)
	Mesitylene	1.71	77/19/75 (47/3/44)	0.30 (0.078)
	Durene	1.63	75/15/70 (35/1/33)	0.30 (0.065)
Me ₂ Acr ⁺ –Mes	<i>p</i> -Xylene	1.93	100/0/100 (54/5/52)	0.37 (0.13)
	Mesitylene	1.71	66/2/65 (40/1/39)	0.26 (0.14)
	Durene	1.63	64/10/62 (37/2/36)	0.25 (0.15)
Acr ⁺ –Ph	<i>p</i> -Xylene	1.93	12/18/10 (5/2/4)	0.042 (0.019)

^aTaken from Ref. 42.^bValues are determined after photoirradiation for 80 min. Conditions: [photocatalyst] = 0.2 mM, [substrate] = 4.0 mM, [H₂O] = 0.9 M, [H₂SO₄] = 1.0 mM. Values in parentheses are determined without H₂O and H₂SO₄.^cOn the basis of formation of the corresponding aldehyde.

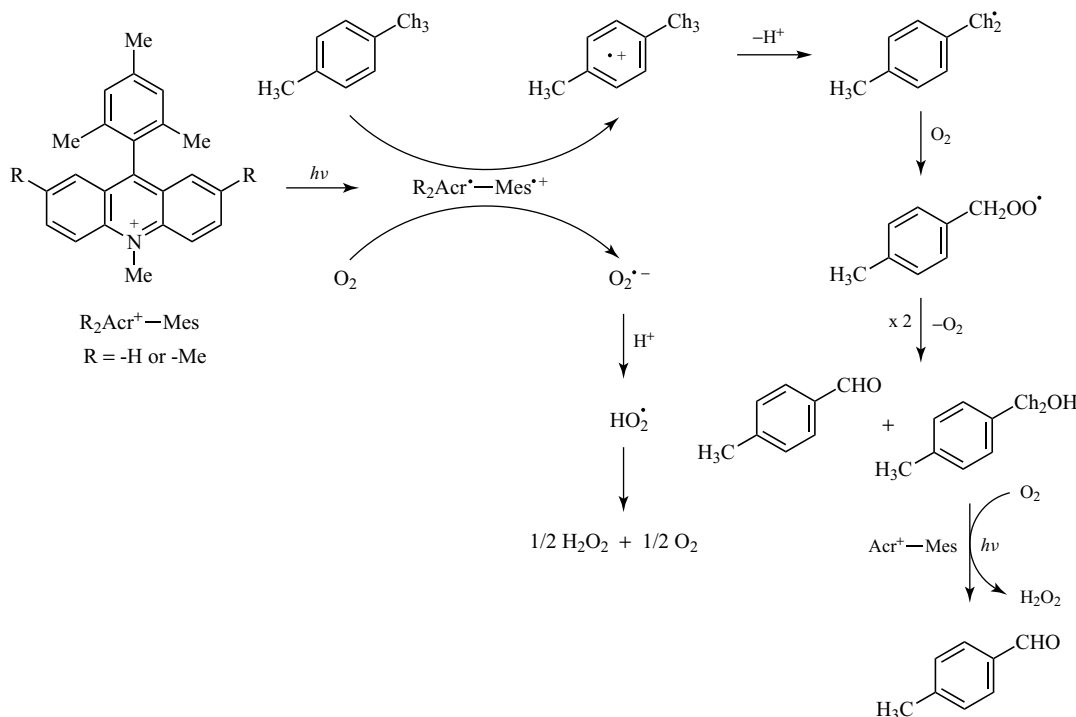
No further oxygenated product, *p*-toluic acid or *p*-phthalaldehyde, was produced during the photocatalytic reaction. When the concentration of Me₂Acr⁺–Mes (1.0×10^{-4} M) was decreased, turnover number (TON) was increased to 200. A preparative scale photocatalytic reaction with *p*-xylene (0.5 g, 4.7 mmol) and Me₂Acr⁺–Mes (60 mg, 0.14 mmol) in MeCN (150 ml) under irradiation with a xenon lamp for 48 h afforded *p*-tolualdehyde (59%), *p*-methylbenzyl alcohol (28%), and H₂O₂ (51%) with 87% conversion of substrate.¹³⁴ The catalyst can be recyclable because no decomposition of photocatalyst occurred under the present experimental conditions.¹³⁴ Figure 5 shows the time profiles of the reactant and products in optimized photocatalytic reaction conditions. *p*-Methylbenzyl alcohol was formed as a reaction intermediate and this was readily oxygenated to form *p*-methylbenzaldehyde.¹³⁴

The photocatalytic oxygenation also occurred in the case of durene and mesitylene.¹³⁴ The one-electron oxidation potentials (E_{ox}) of toluene derivatives in MeCN are listed in Table 1. The E_{ox} values of toluene derivatives given in Table 1 are lower than the one-electron reduction potential (E_{red}) of the electron-transfer state of Acr⁺–Mes (Acr^{•+}–Mes^{•+}: 2.06 V vs SCE in MeCN).¹³⁴ Thus, electron transfer from toluene derivatives such as *p*-xylene to the Mes^{•+} moiety of Acr^{•+}–Mes^{•+} is energetically feasible, whereas electron transfer from toluene ($E_{\text{ox}} = 2.20$ V)^{42,134} to the Mes^{•+} moiety is energetically unfavorable when no photocatalytic oxidation of toluene by O₂ occurred with Acr⁺–Mes under the same experimental conditions.¹³⁴

**Figure 5** Irradiation time profiles of photooxygenation of *p*-xylene (4.0×10^{-3} M) catalyzed by Me₂Acr⁺–Mes in oxygen-saturated MeCN (0.6 ml) at 298 K; [Me₂Acr⁺–Mes] = 2.0×10^{-4} M; [H₂O] = 0.9 M; [H₂SO₄] = 1.0×10^{-3} M.¹³⁴

The E_{ox} values of the oxygenated products of the corresponding benzaldehydes are also higher than the E_{red} value of Acr^{•+}–Mes^{•+} (2.06 V).¹³⁴ This is the reason why the oxygenated product of *p*-xylene was only *p*-tolualdehyde and no further oxygenated product such as *p*-phthalaldehyde was formed.

The photocatalytic reaction is initiated by intramolecular photoinduced electron transfer from the mesitylene moiety to the singlet excited state of the Acr⁺ moiety of Acr⁺–Mes, which affords the electron-transfer state (Acr^{•+}–Mes^{•+}).^{44,134} Electron transfer from *p*-xylene to the Mes^{•+}



Scheme 11 Photocatalytic oxygenation of *p*-xylene by O_2 with Acr^+-Mes .¹³⁴

moiety occurs to produce *p*-xylene radical cation, which undergoes deprotonation to afford the deprotonated radical. This is followed by rapid O_2 addition to afford the peroxy radical as shown in Scheme 11.¹³⁴ The disproportionation of the peroxy radical affords *p*-tolualdehyde, *p*-methylbenzyl alcohol, and O_2 . *p*-Methylbenzyl alcohol is readily oxygenated to yield *p*-tolualdehyde with Acr^+-Mes .¹³⁴ On the other hand, $O_2^{\bullet-}$ disproportionates with proton to yield H_2O_2 and O_2 (Scheme 11). The radical intermediates involved in Scheme 11 were detected by ESR ($g_{||} = 2.101$, $g_{\perp} = 2.009$ for $O_2^{\bullet-}$ and $g_{||} = 2.033$, $g_{\perp} = 2.006$ for *p*-methylbenzyl peroxy radical) in frozen MeCN.¹³⁴

Addition of aqueous sulfuric acid enhanced the deprotonation of *p*-xylene radical cation and the disproportionation process of $O_2^{\bullet-}$, respectively, leading to a remarkable enhancement of photocatalytic reactivity as mentioned above (Table 1).¹³⁴ The reaction pathway of photocatalytic oxygenation of *p*-xylene by O_2 with Acr^+-Mes is not the radical chain process, because there was no dependence of the product quantum yield on concentration

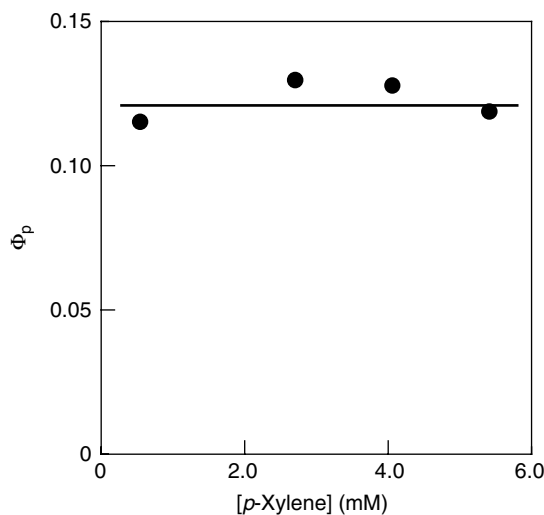


Figure 6 Dependence of quantum yield of formation of *p*-tolualdehyde on concentration of *p*-xylene in the photocatalytic oxygenation of *p*-xylene with Me_2Acr^+-Mes (0.2 mM) in O_2 -saturated MeCN.¹³⁴

of *p*-xylene (Figure 6) and irradiation light intensity.¹³⁴ If the radical chain (autoxidation) process is

involved in the photocatalytic reaction, the quantum yield would increase linearly with increasing concentration of *p*-xylene, because the rate-determining step in the radical chain process would be the hydrogen abstraction from *p*-xylene by the peroxy radical. In addition, there is no induction period that is typically observed for an autoxidation process. Thus, disproportionation of the peroxy radicals (*p*-methylbenzyl peroxy radical and hydrogen peroxy radical as shown in Scheme 11) is the major pathway in the photocatalytic oxygenation of *p*-xylene by O₂ with Acr⁺–Mes.

In contrast to the case of Acr⁺–Mes, the photocatalytic oxygenation of *p*-xylene by O₂ with Acr⁺–Ph that contains no electron donor moiety proceeds via electron transfer from *p*-xylene to the singlet excited state of Acr⁺–Ph. However, the lifetime of the singlet excited state of Acr⁺–Ph ($\tau = 1.5$ ns in MeCN)¹³³ is much shorter than that of the electron-transfer state of Acr⁺–Mes. A high concentration of substrate is thereby needed to quench the short-lived singlet excited state of Acr⁺–Ph.

2-Methylnaphthalene that does not react with singlet oxygen (i.e., no conversion under irradiation conditions in the presence of tetraphenylporphyrin as a singlet oxygen photosensitizer) is also efficiently oxygenated by O₂ with Acr⁺–Mes acting as a photocatalyst to yield the corresponding naphthaldehyde.^{135,136} DCA also acts as a photocatalyst for the oxygenation of 2-methylnaphthalene by O₂ as a result of the photoinduced oxidation of 2-methylnaphthalene, followed by deprotonation from the methyl group, and O₂ addition,¹³⁵ which is similar to photocatalytic oxygenation of *p*-xylene by O₂ with Acr⁺–Mes as shown in Scheme 11.

The reducing ability of the electron-transfer state of Acr⁺–Mes is improved by the electron-donating methyl substitution of the acridinium ring of Acr⁺–Mes.¹³⁴ Cyclic voltammograms of Acr⁺–Mes and Me₂Acr⁺–Mes in deaerated MeCN are shown in Figure 7 to compare the reducing abilities of the electron-transfer states of Acr⁺–Mes and Me₂Acr⁺–Mes.¹³⁴ The E_{red} value of Me₂Acr⁺–Mes (–0.67 V vs SCE) is 0.1 eV more negative than that of Acr⁺–Mes (–0.57 V).¹³⁴

The difference in dynamics of the electron-transfer reduction of O₂ by the electron-transfer states of Acr⁺–Mes and Me₂Acr⁺–Mes was determined by nanosecond laser flash photolysis.¹³⁴ As shown in Figure 8a, the rates of the electron-transfer reduction were determined

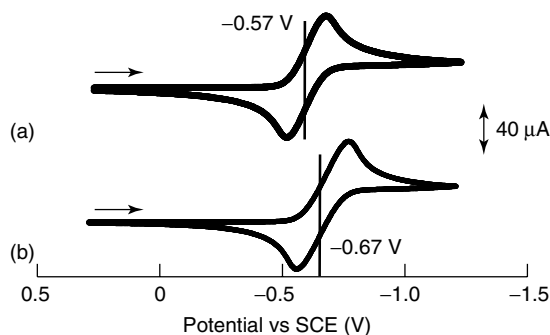


Figure 7 Cyclic voltammograms of (a) Acr⁺–Mes and (b) Me₂Acr⁺–Mes (10 mM) in deaerated MeCN containing TBAPF₆ (0.1 M) at 298 K.¹³⁴

from the quenching of the transient absorption due to the electron-transfer state by O₂ to be $6.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for Acr⁺–Mes^{•+}⁷⁸ and $2.0 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ for Me₂Acr⁺–Mes^{•+} (Figure 8b).¹³⁴ Thus, the reducing ability of Me₂Acr⁺–Mes^{•+} was indeed significantly enhanced by the methyl substitution. This may be the reason why the 100% yield of tolualdehyde and H₂O₂ with a higher quantum yield (0.37) was achieved using Me₂Acr⁺–Mes (Table 1).

As described above, the electron-transfer state of Me₂Acr⁺–Mes, which has both the high oxidizing and reducing ability, make it possible to produce both aromatic aldehydes and H₂O₂ selectively in the photocatalytic oxygenation of alkylaromatic compounds with oxygen. After aromatic aldehydes are formed, no further oxidation takes place because electron transfer from aromatic aldehydes to the Mes^{•+} moiety is thermodynamically unfavorable. Thus, the use of charge-separation dyads as photocatalysts paves a new way for the selective oxygenation of alkylaromatic compounds with simultaneous formation of H₂O₂.

3.4 Photocatalytic Oxygenation of Triphenylphosphine

The photocatalytic oxygenation of triphenylphosphine by O₂ also occurs with Acr⁺–Mes.¹³⁷

Visible light irradiation ($\lambda > 430 \text{ nm}$) of the absorption band of Acr⁺–Mes in an O₂-saturated chloroform (CHCl₃) solution containing triphenylphosphine (Ph₃P) for 30 min by xenon lamp

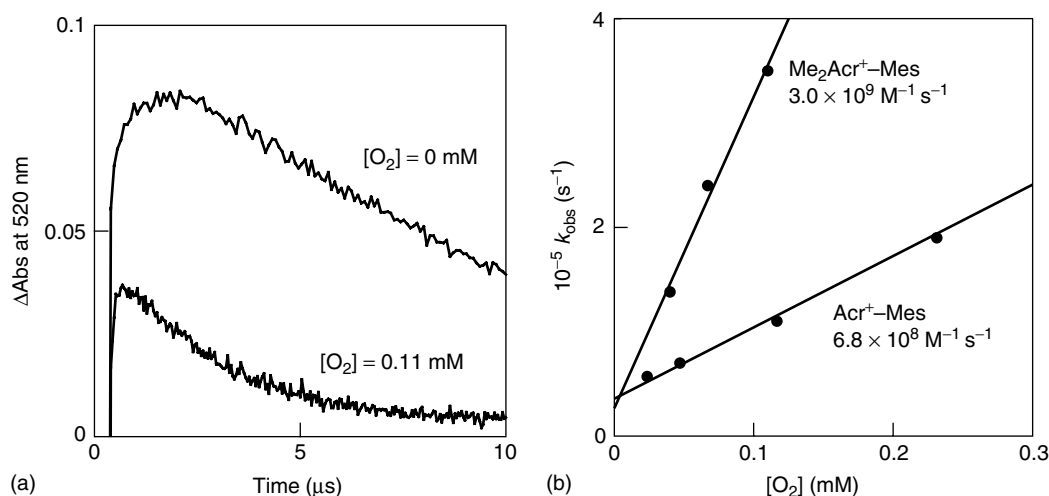
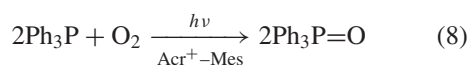


Figure 8 (a) Absorbance time profiles at 520 nm due to $\text{Me}_2\text{Acr}^+-\text{Mes}^{*+}$ in aerated and deaerated MeCN containing $\text{Me}_2\text{Acr}^+-\text{Mes}$ ($1.0 \times 10^{-4} \text{ M}$). (b) Plot of the pseudo-first-order rate constant (k_{obs}) for electron transfer from the Acr^+ moiety of $\text{Acr}^+-\text{Mes}^{*+}$ and $\text{Me}_2\text{Acr}^+-\text{Mes}^{*+}$ to O_2 versus $[\text{O}_2]$.

results in formation of an oxygenated product, that is, triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) with 99% yield¹³⁷:



When Acr^+-Mes is replaced by 10-methyl-acridinium ion (AcrH^+) which has no electron donor moiety, $\text{Ph}_3\text{P}=\text{O}$ was also produced quantitatively after 60-min photoirradiation.¹³⁷ No photooxygenation of Ph_3P occurs without Acr^+-Mes or AcrH^+ under otherwise the same experimental conditions.¹³⁷ The dependence of the quantum yields (Φ_P) of formation of $\text{Ph}_3\text{P}=\text{O}$ on concentration of Ph_3P is shown in Figure 9 (closed circle).¹³⁷ The limiting value (Φ_∞) in air-saturated CHCl_3 is constant (0.58) at any Ph_3P concentrations. Judging from the constant dependence of Φ_P on $[\text{Ph}_3\text{P}]$ in Figure 9 (closed circle), a reactive intermediate of photooxygenation is assigned as an extremely long-lived species, which is the electron-transfer state of Acr^+-Mes .⁴⁴ Thus, the rate-determining step in the photocatalytic reaction is proposed to be electron transfer from Ph_3P to $\text{Acr}^+-\text{Mes}^{*+}$.¹³⁷

In the case of AcrH^+ (closed square in Figure 9), the Φ_P values increase on increasing the Ph_3P to higher concentrations than in the case of Acr^+-Mes . From the saturated dependence of Φ_P on $[\text{Ph}_3\text{P}]$ and the lifetime of $^1\text{AcrH}^{*+}$ ($\tau = 31 \text{ ns}$),^{131–133} the

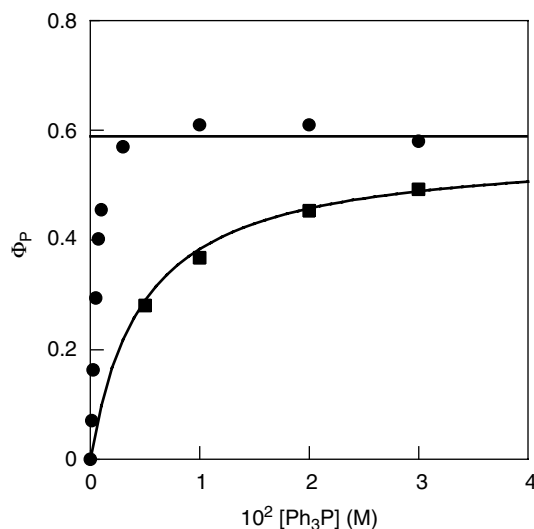


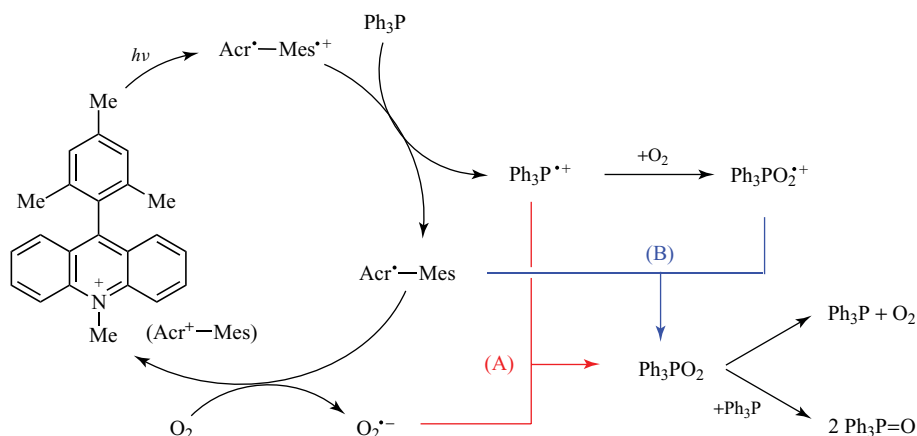
Figure 9 Dependence of quantum yield (Φ_P) on concentrations of Ph_3P for the photocatalytic oxygenation of Ph_3P by O_2 with Acr^+-Mes ($8.0 \times 10^{-5} \text{ M}$, ●) and AcrH^+ ($8.0 \times 10^{-5} \text{ M}$, ■) in air-saturated CHCl_3 .

rate constant of the reaction of $^1\text{AcrH}^{*+}$ with Ph_3P is $6.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, which agrees with the value obtained from the fluorescence quenching of AcrH^+ ($9.0 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$).¹³⁷ Such agreement strongly indicates that the photooxygenation of Ph_3P with AcrH^+ proceeds via photoinduced electron transfer

from Ph_3P to $^1\text{AcrH}^{+*}$. However, AcrH^{+} -catalyzed photooxygenation requires the high concentrations of Ph_3P and O_2 because the lifetime of $^1\text{AcrH}^{+*}$ is too short to quench the excited state.¹³⁷

Electron transfer from Ph_3P to the Mes^{++} moiety in $\text{Acr}^+-\text{Mes}^{++}$ is energetically feasible, because the one-electron reduction potential of $\text{Acr}^+-\text{Mes}^{++}$ ($E_{\text{red}} = 2.06 \text{ V vs SCE}$)¹³⁴ is more positive than the one-electron oxidation potential of Ph_3P ($E_{\text{ox}} = 1.20 \text{ V vs SCE}$).¹³⁷ The formation of Ph_3P radical cation (Ph_3P^{+*} ; $\lambda_{\text{max}} = 330 \text{ nm}$)¹³⁷ was confirmed by the laser flash photolysis.¹³⁷ The second-order rate constant of electron transfer from Ph_3P to the Mes^{++} moiety of $\text{Acr}^+-\text{Mes}^{++}$ was determined to be $9.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$,¹³⁷ which is close to the diffusion-limited value as expected from the exergonic electron transfer. Photoinduced electron transfer from Ph_3P to $^1\text{AcrH}^{+*}$ also occurs to yield Ph_3P^{+*} , which reacts with O_2 . The rate constant of the reaction of Ph_3P^{+*} with O_2 was determined to be $1.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.¹³⁸

The mechanism of the photocatalytic oxygenation of Ph_3P by O_2 with Acr^+-Mes is shown in Scheme 12. Triphenylphosphine peroxide (Ph_3PO_2) is produced via addition of O_2 to Ph_3P^{+*} to give Ph_3P peroxide radical cation ($\text{Ph}_3\text{PO}_2^{+*}$), which undergoes back electron transfer from Acr^+-Mes to $\text{Ph}_3\text{PO}_2^{+*}$ (reaction pathway A in Scheme 12) and via radical coupling between Ph_3P^{+*} and $\text{O}_2^{\cdot-}$ (reaction pathway B in Scheme 12). Ph_3PO_2 reacts with Ph_3P to produce $\text{Ph}_3\text{P}=\text{O}$ via O–O bond cleavage.^{139,140}



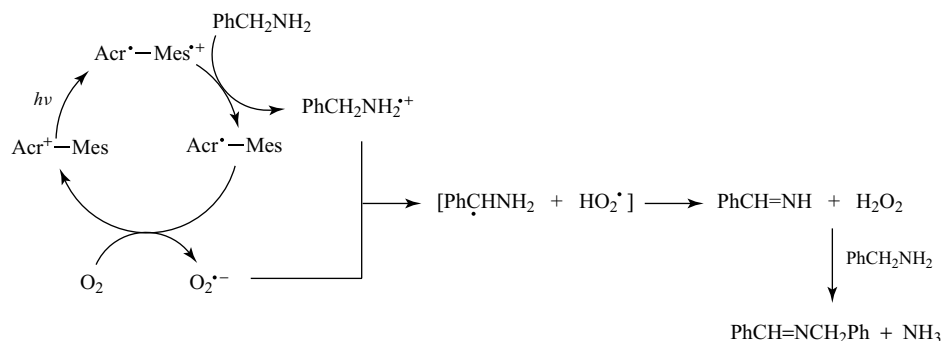
Scheme 12 Photocatalytic oxygenation of Ph_3P by O_2 with Acr^+-Mes .¹³⁷

3.5 Photocatalytic Oxidation of Benzylamine

Benzylamine is also oxidized by the photogenerated electron-transfer state of Acr^+-Mes in O_2 -saturated MeCN to yield *N*-benzylidenebenzylamine, $\text{PhCH}_2\text{N}=\text{CHPh}$.¹³⁷ The reaction mechanism of the photocatalytic oxidation of benzylamine by O_2 with Acr^+-Mes is shown in Scheme 13.¹³⁷ The photogenerated electron-transfer state of Acr^+-Mes ($\text{Acr}^+-\text{Mes}^{+*}$) oxidizes benzylamine and reduces O_2 by electron transfer to produce the benzylamine radical cation and $\text{O}_2^{\cdot-}$, respectively. The subsequent proton transfer occurs from benzylamine radical cation to $\text{O}_2^{\cdot-}$ to give the α -hydrogen abstracted radical of benzylamine and hydrogen peroxyl radical ($\text{HO}_2^{\cdot}$). The α -hydrogen abstracted radical spontaneously reacts with $\text{HO}_2^{\cdot}$ to form benzylimine ($\text{PhCH}=\text{NH}$) and hydrogen peroxide (H_2O_2). $\text{PhCH}=\text{NH}$ reacts with benzylamine to produce the primary product $\text{PhCH}_2\text{N}=\text{CHPh}$ (Scheme 13).^{141–143}

3.6 Photocatalytic Oxidation and Cleavage of DNA

Photoinduced DNA cleavage has attracted considerable interest because of the biological significance of DNA damage and repair (see **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA and Oxidatively Formed Sugar Radicals in Nucleic Acids**).^{144–149}



Scheme 13 Photocatalytic oxidation of benzylamine by O₂ with Acr⁺-Mes.¹³⁷

The DNA cleavage resulted from efficient electron-transfer oxidation by the electron-transfer state of Acr⁺-Mes.^{150,151} The reduction potential of Acr^{*}-Mes^{•+} ($E_{\text{red}} = 2.06 \text{ V}$ vs SCE in MeCN)¹³⁴ is much more positive than the one-electron oxidation potential of guanosine-5'-monophosphate (GMP, $E_{\text{ox}} = 1.07 \text{ V}$ vs SCE in an aqueous solution).¹⁵² Thus, electron transfer from GMP to the Mes^{•+} moiety of Acr^{*}-Mes^{•+} is energetically feasible.¹⁵⁰ Formation of GMP radical cation (GMP^{•+}; $\lambda_{\text{max}} = 510 \text{ nm}$) is observed by the laser photoirradiation of a buffer solution of Acr⁺-Mes at pH 2.0 containing GMP as shown in Figure 10a (closed rectangles).¹⁵⁰ At pH 7.0, a transient absorption at the long wavelength region circa at 650 nm appears because of the deprotonation of GMP^{•+} (closed circles in Figure 10a).^{153,154} The difference spectra given in Figure 10b, obtained by subtracting the spectra in the absence of GMP from those in the presence of GMP at pH 2.0 and 7.0, correspond to those between GMP^{•+} (positive absorption) and the Mes^{•+} moiety (negative absorption), because the spectra in the absence and the presence of GMP are those of Acr^{*}-Mes^{•+} and those of GMP^{•+} and Acr^{*}-Mes, respectively.¹⁵⁰ The rate of formation of GMP^{•+} obeyed pseudo-first-order kinetics and the pseudo-first-order rate constant increased linearly with increasing concentration of GMP at pH 2.0.¹⁵⁰ The second-order rate constant (k_{et}) of electron transfer from GMP to the Mes^{•+} moiety of Acr^{*}-Mes^{•+} was determined to be $4.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ in the buffer solution at 298 K.¹⁵⁰ The k_{et} value of electron transfer from GMP to the Mes^{•+} moiety of Acr^{*}-Mes^{•+} was also determined to be $2.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at pH 7.0, which is much larger than the value ($4.3 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$) at pH 2.0, but

still smaller than the diffusion limit.¹⁵⁰ The larger k_{et} value at the higher pH indicates the involvement of deprotonation associated with electron transfer (proton-coupled electron transfer).^{155,156}

The transient absorption spectrum of oxidized DNA shown in Figure 11 is similar to that of GMP^{•+} in Figure 10.¹⁵⁰ The k_{et} value of the electron-transfer oxidation of DNA was determined to be $4.8 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, which is larger than the k_{et} value of GMP.¹⁵⁰ The electron-transfer oxidation of DNA results in the cleavage of DNA.¹⁵⁰ The DNA cleavage activity with Acr⁺-Mes in the absence of O₂ was much higher than that in the presence of O₂ at pH 5.0 and 7.0.¹⁵⁰ This indicates that O₂ acts as an apparent inhibitor for the DNA cleavage. When DNA is oxidized by the Mes^{•+} moiety of Acr^{*}-Mes^{•+}, O₂ is reduced by the Acr^{*} moiety to produce O₂^{•-}.^{78,150} The retarding effect of O₂ may result from more efficient back electron transfer from O₂^{•-} to DNA radical cation as compared with that from the Acr^{*} moiety to DNA radical cation before oxidizing DNA as shown in Scheme 14.¹⁵⁰

Although all DNA bases can be oxidized by the Mes^{•+} moiety of Acr^{*}-Mes^{•+}, the largest k_{et} value of the electron-transfer oxidation of GMP together with the lowest oxidation potential of GMP among DNA bases indicate that guanine is eventually oxidized in electron transfer from DNA to the Mes^{•+} moiety of Acr^{*}-Mes^{•+}, leading to efficient DNA cleavage.¹⁵⁷ In the present case, however, no hydroxyl radical (HO^{*}) was formed because the photoexcitation of Acr⁺-Mes affords the electron-transfer state, which oxidizes DNA without involvement of the triplet excited state.¹⁵⁸ The higher DNA cleavage activity at pH 5.0 as compared with that at pH 7.0 suggests

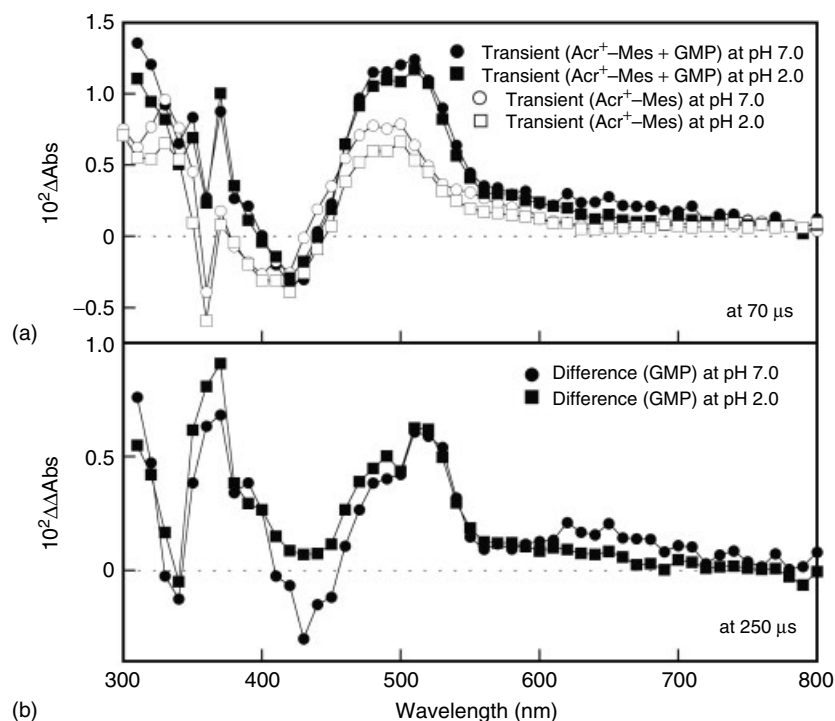


Figure 10 (a) Transient absorption spectra of Acr^+-Mes in the presence and absence of GMP (1.0×10^{-2} M) at pH 2.0 and 7.0; (b) difference transient absorption spectra of GMP^{++} (pH 2.0) and $(\text{GMP}-\text{H})^+$ (pH 7.0), obtained by subtracting the spectra in the absence of GMP from those in the presence of GMP at pH 2.0 and 7.0, respectively.¹⁵⁰

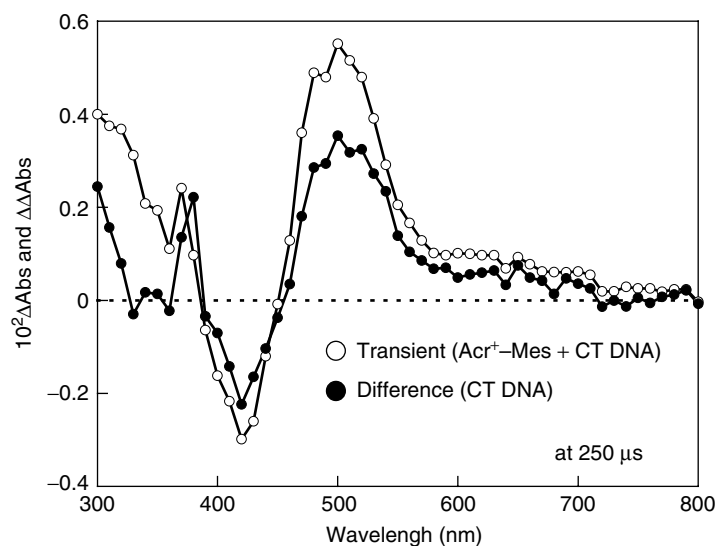
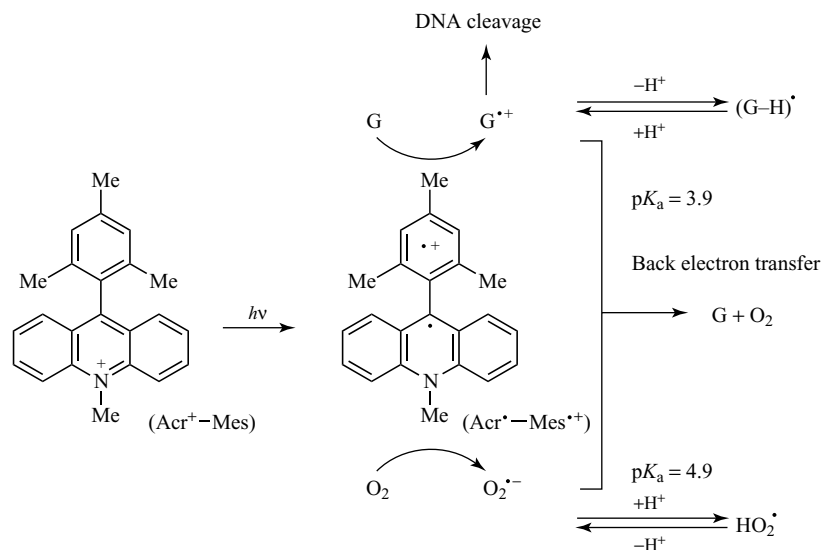


Figure 11 Transient absorption spectrum of Acr^+-Mes (6.0×10^{-5} M) in the presence of calf thymus DNA (CT DNA) (1.0×10^{-3} M) and the difference spectrum of DNA radical cation at pH 7.0 measured at 250 μs after laser excitation at $\lambda = 355$ nm at 298 K.¹⁵⁰



Scheme 14 Photocatalytic oxidation and cleavage of DNA by O_2 with Acr^+-Mes .¹⁵⁰

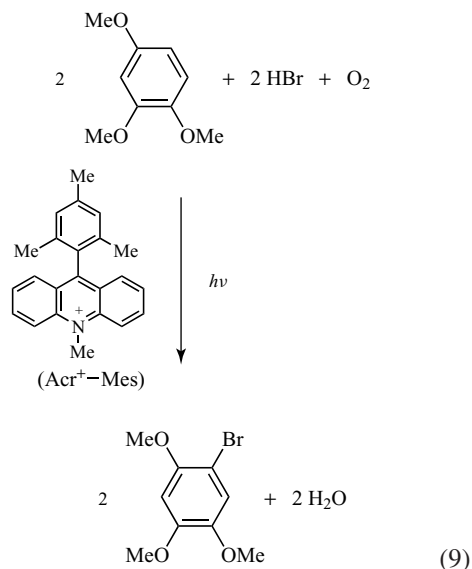
that guanine radical cation has a higher reactivity for the DNA cleavage than the deprotonated radical (Scheme 14), judging from the pK_a value of guanine radical cation ($pK_a = 3.9$).¹⁵⁴

4 PHOTOCATALYTIC BROMINATION VIA CHARGE SEPARATION

Acr^+-Mes was found to act as an efficient photocatalyst for selective bromination of aromatic hydrocarbons and thiophenes with aqueous HBr as a Br source without using a toxic bromine source and O_2 as a green oxidant under visible light irradiation.¹⁵⁹ It should be noted that bromination of thiophenes is particularly important in the preparation of oligothiophenes and polythiophenes,^{160–174} which have many applications as conductive, semiconductive, nonlinear optical, and liquid crystalline materials.¹⁷⁵

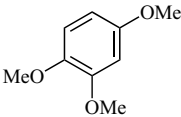
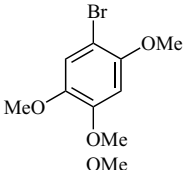
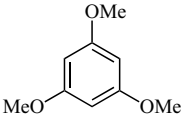
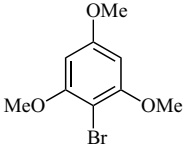
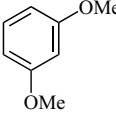
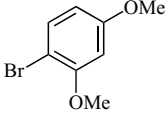
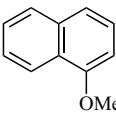
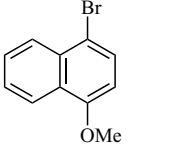
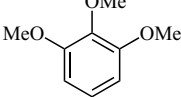
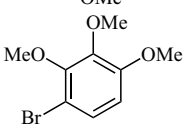
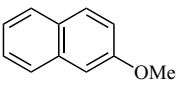
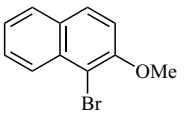
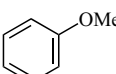
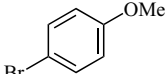
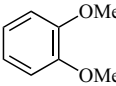
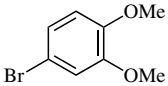
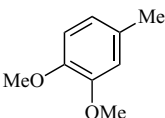
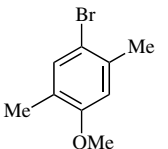
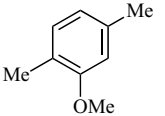
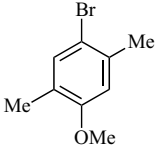
Visible light irradiation of $[Acr^+-Mes]ClO_4^-$ ($\lambda_{max} = 430$ nm, 0.20 mM) in an oxygen-saturated MeCN solution containing 1,2,4-trimethoxybenzene (TMB, 4.0 mM), 50% aqueous HBr ($[HBr] = 20$ mM, $[H_2O] = 100$ mM) with a xenon lamp attached with UV-cut glass filter ($\lambda < 320$ nm) for 20 min resulted in formation of a brominated product, 2,4,5-trimethoxybromobenzene.¹⁵⁹ The overall stoichiometry of the photocatalytic reaction is given by

the following equation:



The yield and selectivity of 2,4,5-trimethoxybromo-benzene is nearly 100%, because no further brominated product, dibromo- or tribromo-derivative, was produced in these reaction conditions.¹⁵⁹ The products and quantum yields are listed in Table 2.¹⁵⁹ Photocatalytic bromination reactions of various aromatic compounds also occurred as shown in Table 2. A preparative scale

Table 2 Product and quantum yields for photocatalytic bromination of organic compounds by O₂ and HBr with Acr⁺–Mes in MeCN, and one-electron oxidation potentials of substrates.¹⁵⁹

Entry	Substrate	Product	Conversion ^a (%)	Yield ^a (%)	Time (h)	Quantum yield ^a (%)	E _{ox} ^b (V)
1			>99	>99	0.3	4.3	0.96
2			>99	>99	0.3	4.8	1.43
3			>99	>99	0.3	3.9	1.49
4			>99	>99	0.5	3.1	1.34
5			>99	>99	1.5	1.1	1.42
6			>99	>99	2	0.26	1.47
7			>99	>99	16	0.01	1.76
8			>99	78 ^c	3	0.10	1.45
9			>99	53	2	0.36	1.33
10			>99	44	2	0.32	1.47

^a Conditions: [substrate] = 4.0 mM; [Acr⁺–Mes] = 0.20 mM; [HBr] = 20 mM; [H₂O] = 100 mM.^b Values are determined by cyclic voltammetry and second harmonic ac voltammetry.^c Minor product is mainly the dibromo compound.

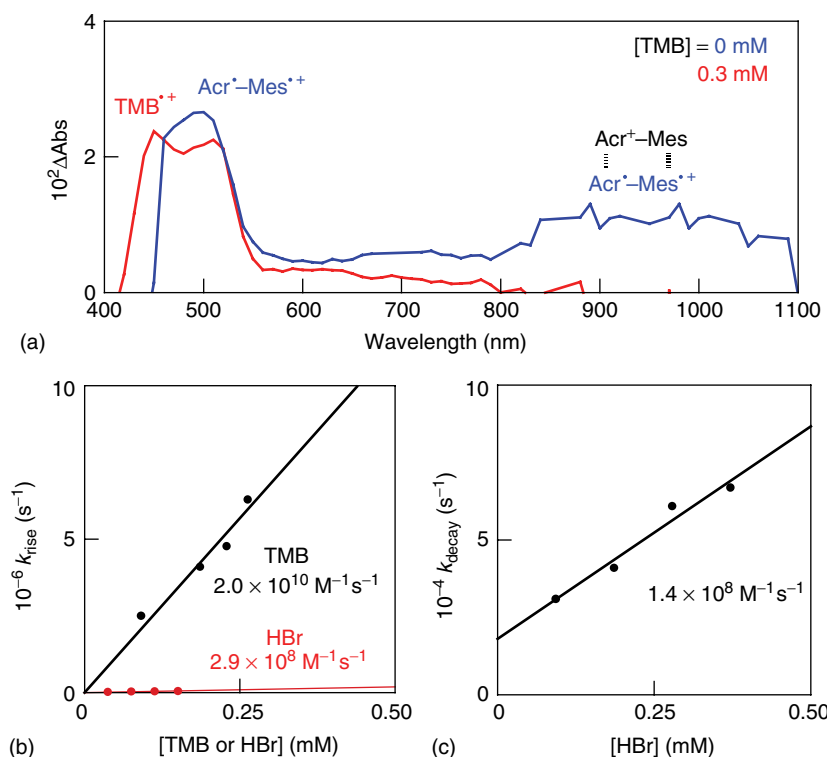


Figure 12 (a) Transient absorption spectra of the electron-transfer state of Acr⁺-Mes (0.2 mM) in the absence and presence of TMB (0.3 mM) in deaerated MeCN after nanosecond laser excitation at 430 nm. (b) Plot of k_{rise} versus [TMB] or [HBr] for the reaction of Acr⁺-Mes⁺ with TMB or HBr. (c) Plot of k_{decay} versus [HBr] for the reaction of TMB⁺ with HBr.¹⁵⁹

photocatalytic reaction of TMB (200 mg, 1.2 mmol) with 50% aqueous HBr (160 μ l 1.5 mmol) in the presence of Acr⁺-Mes (0.044 mmol) in an oxygen-saturated MeCN under photoirradiation by a xenon lamp for 24 h affords the brominated product in 100% selectivity and in 81% yield.¹⁵⁹

The photodynamics of the photocatalytic bromination of TMB with HBr in the presence of Acr⁺-Mes was revealed by nanosecond laser flash photolysis.¹⁵⁹ A transient absorption spectrum due to the electron-transfer state of Acr⁺-Mes (Acr⁺-Mes⁺) is observed after the laser pulse excitation at 430 nm of an MeCN solution of Acr⁺-Mes as shown in Figure 12 (blue line).¹⁵⁹ The broad absorption band in the NIR region is attributed to the π -dimer of Acr⁺-Mes⁺ with the ground state of Acr⁺-Mes as described earlier.⁵⁵ In the presence of TMB, a new band at 450 nm appeared at 12 μ s as shown in Figure 12 (red line), which is assigned to TMB radical cation (TMB⁺).¹⁵⁹ The rate constant for electron transfer from TMB to the

Mes⁺ at the electron-transfer state of Acr⁺-Mes was determined from the slope of the linear plot of k_{rise} versus [TMB] to be $k_{\text{TMB}} = 2.0 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (Figure 12b).¹⁵⁹ The rate of disappearance of TMB⁺ was accelerated by increasing the concentration of HBr.¹⁵⁹ The observed decay rate constant (k_{decay}) increases linearly with increasing concentrations of HBr as shown in Figure 12c.¹⁵⁹ Thus, TMB⁺ efficiently reacts with Br⁻ to form the Br adduct radical [TMB(Br)[•]]. The rate constant of the addition of Br⁻ was determined from the slope of k_{decay} versus [HBr] to be $k_{\text{HBr}} = 1.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ (Figure 12c).¹⁵⁹ The electron-transfer oxidation of Br⁻ in the photocatalytic reaction was also revealed by quenching of Acr⁺-Mes⁺ by HBr. The quenching rate constant of Acr⁺-Mes⁺ with HBr is two orders of magnitude smaller ($2.9 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) than the k_{TMB} value (Figure 12b).¹⁵⁹ Thus, the electron-transfer oxidation of hexamethylbenzene (HMB) predominated over the oxidation of Br⁻.

The one-electron oxidation potentials (E_{ox}) of aromatic compounds in deaerated MeCN (0.96–1.76 V) listed in Table 2 are lower than the one-electron reduction potential of the electron-transfer state of Acr^+-Mes ($\text{Acr}^{\bullet}-\text{Mes}^{++}$; $E_{\text{red}} = 2.06 \text{ V}$ vs SCE).^{134,159} Thus, electron transfer from aromatic compounds such as TMB to $\text{Acr}^{\bullet}-\text{Mes}^{++}$ is energetically favorable, whereas electron transfer from toluene ($E_{\text{ox}} = 2.20 \text{ V}$) and benzene (2.32 V) to the Mes^{++} moiety of $\text{Acr}^{\bullet}-\text{Mes}^{++}$ is energetically unfavorable. In such a case, no photocatalytic bromination of benzene or toluene occurs under the same experimental conditions as TMB. The decreased reactivity of methoxybenzene (entry 7 in Table 2) is attributed to the high E_{ox} value (1.76 V). On the other hand, the one-electron reduction of O_2 by the electron-transfer state of Acr^+-Mes in the presence of an acid is known to occur efficiently, producing $\text{HO}_2^{\bullet}$ that disproportionates to yield H_2O_2 and O_2 .¹⁷⁶ The rate constant of electron-transfer reduction of O_2 (k_{O_2}) was reported to be $6.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.¹³⁴

The photocatalytic bromination of TMB by HBr with Acr^+-Mes is initiated by intramolecular photoinduced electron transfer from the Mes moiety to the singlet excited state of the Acr^+ moiety of Acr^+-Mes to generate $\text{Acr}^{\bullet}-\text{Mes}^{++}$ as shown in Scheme 15.^{44,159}

The Mes^{++} moiety of $\text{Acr}^{\bullet}-\text{Mes}^{++}$ can oxidize TMB to produce TMB^{++} , whereas the $\text{Acr}^{\bullet}$ moiety can reduce O_2 to $\text{HO}_2^{\bullet}$.¹⁵⁹ The TMB^{++} thus produced reacts with Br^- to form the Br adduct radical, which undergoes dehydrogenation with protonated $\text{HO}_2^{\bullet}$ to afford the corresponding brominated product and hydrogen peroxide.¹⁵⁹ Hydrogen peroxide further reacts with HBr and substrate to

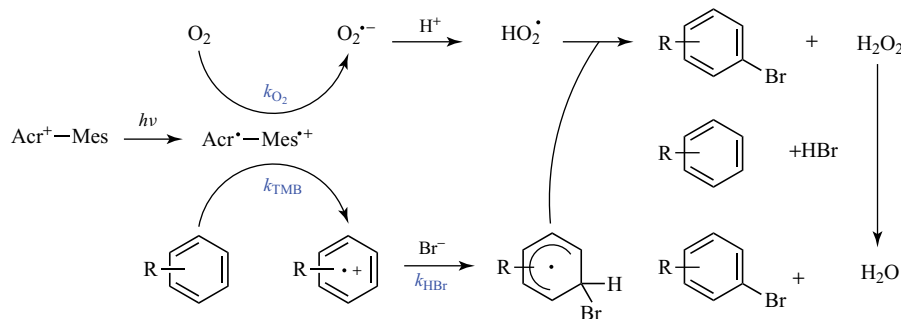
produce another brominated product and H_2O .¹⁷⁷ The quantum yield remained constant on increasing the concentration of TMB and the light intensity under the present experimental conditions.¹⁵⁹ This suggests that no radical chain process is involved in the present photocatalytic aerobic bromination of substrates with HBr.

5 CARBON–CARBON BOND FORMATION VIA CHARGE SEPARATION

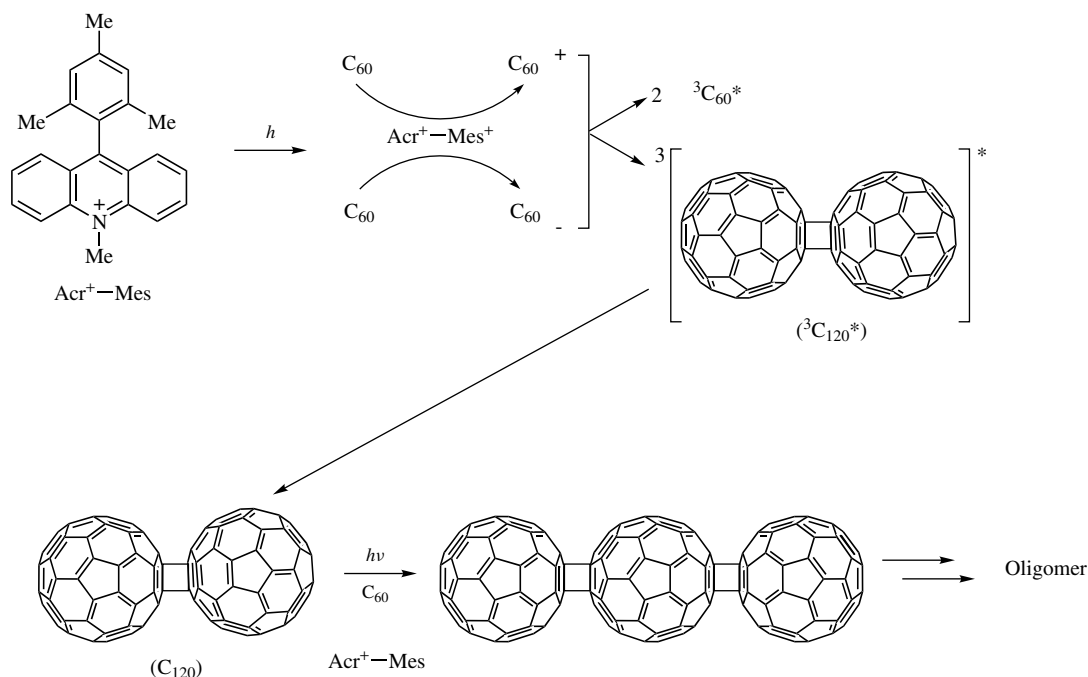
5.1 Oligomerization of Fullerene

Because the photogenerated electron-transfer state of Acr^+-Mes ($\text{Acr}^{\bullet}-\text{Mes}^{++}$) has both the highly oxidizing and reducing ability, the same substrate (S) can be oxidized and reduced by $\text{Acr}^{\bullet}-\text{Mes}^{++}$ to produce the radical cation ($\text{S}^{+\bullet}$) and the radical anion ($\text{S}^{-\bullet}$), which can be coupled to yield the dimer ($\text{S}-\text{S}$). Such an example has been reported for the coupling of fullerene radical cation ($\text{C}_{60}^{+\bullet}$) and fullerene radical anion ($\text{C}_{60}^{-\bullet}$), which are produced by electron-transfer oxidation and reduction of C_{60} with $\text{Acr}^{\bullet}-\text{Mes}^{++}$ as shown in Scheme 16.¹⁷⁸ The coupling products were fullerene oligomers, C_{120} , C_{180} , and C_{240} .¹⁷⁸

Nanosecond laser excitation at 430 nm of a deaerated PhCN solution containing Acr^+-Mes and C_{60} results in the appearance of new transient absorption bands in the NIR region, which are the superposition of those due to $\text{C}_{60}^{+\bullet}$ (960 nm) and $\text{C}_{60}^{-\bullet}$ (1080 nm) as shown in Figure 13a.^{178–180} The transient absorption bands of $\text{C}_{60}^{+\bullet}$ and $\text{C}_{60}^{-\bullet}$ disappear, accompanied by appearance of a new absorption band at 740 nm due to the triplet excited



Scheme 15 Photocatalytic bromination of alkylbenzenes by HBr and O_2 with Acr^+-Mes .¹⁵⁹



Scheme 16 Photocatalytic oligomerization of fullerene with Acr^+-Mes .¹⁷⁸

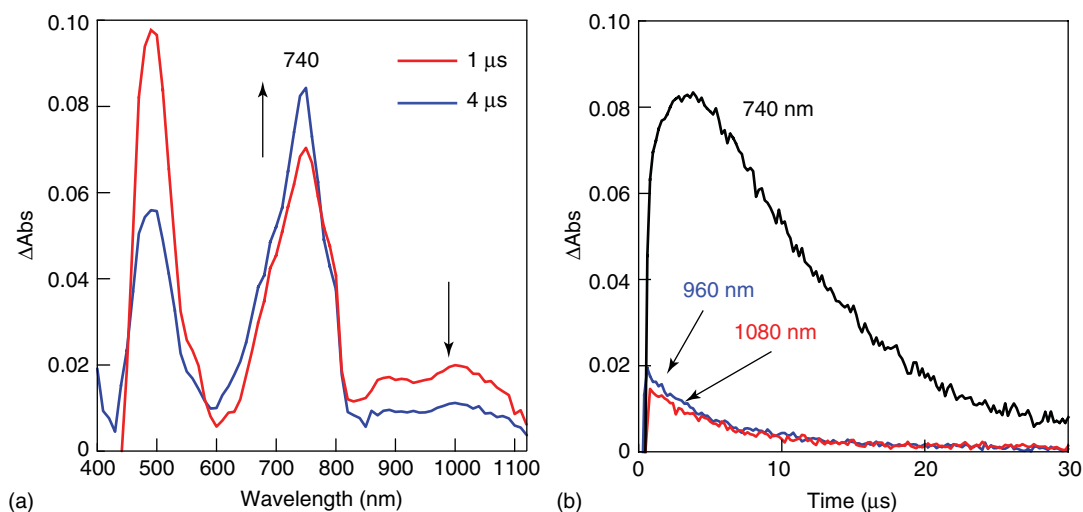


Figure 13 (a) Transient absorption spectra in PhCN observed in photoinduced electron-transfer oxidation of C_{60} (1.0×10^{-4} M) with $\text{Acr}^+-\text{MesClO}_4^-$ (1.0×10^{-4} M) taken 1.0 and 4.0 μs after laser excitation at 430 nm at 298 K. (b) Time profiles at 740, 960, and 1080 nm in PhCN.¹⁷⁸

state of C_{60} ($^3\text{C}_{60}^*$) (Figure 13b). The reaction mechanism of photoinduced oligomerization of C_{60} with Acr^+-Mes is summarized in Scheme 16, where only a linear isomer is shown for C_{180} .¹⁷⁸

Because the free energy change of electron transfer (ΔG_{et}) from C_{60} ($E_{\text{ox}} = 1.73$ V vs SCE)^{180,181} to the Mes^+ moiety of the electron-transfer state of Acr^+-Mes in PhCN ($E_{\text{ox}} = 1.88$ V)^{44,78} is negative

($\Delta G_{\text{et}} = -0.15$ eV), the electron-transfer oxidation C_{60} is energetically feasible to form $\text{C}_{60}^{\bullet+}$. On the other hand, the electron-transfer reduction of C_{60} ($E_{\text{red}} = -0.43$ V)¹⁸² with the $\text{Acr}^{\bullet}$ moiety ($E_{\text{red}} = -0.49$ V)^{44,78} is also thermodynamically feasible to give $\text{C}_{60}^{\bullet-}$ ($\Delta G_{\text{et}} = -0.06$ eV). Thus, C_{60} acts as both an electron donor and acceptor in electron-transfer reactions of $\text{Acr}^{\bullet}\text{-Mes}^+$ with C_{60} to produce $\text{C}_{60}^{\bullet+}$ and $\text{C}_{60}^{\bullet-}$ at the same time. The [2 + 2]cycloaddition occurs efficiently between $\text{C}_{60}^{\bullet+}$ and $\text{C}_{60}^{\bullet-}$ to afford ${}^3\text{C}_{120}^*$ rather than C_{120} , because the driving force of charge recombination (2.16 eV) is larger than the triplet excited state energy of C_{120} (circa 1.5 eV).^{178,183} The radical coupling between $\text{C}_{60}^{\bullet-}$ and $\text{C}_{60}^{\bullet+}$ also affords the triplet excited state of C_{60} (${}^3\text{C}_{60}^*$). Further oligomerization occurs by the same process.

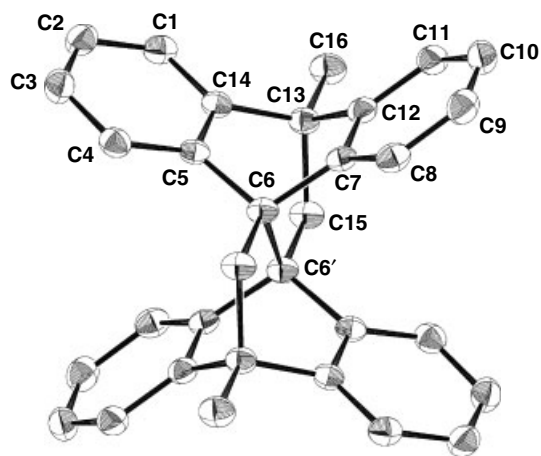


Figure 14 Crystal structure of dimethylllepidoptere produced in the Acr^+-Mes -catalyzed photochemical reaction of DMA.¹⁸⁴

5.2 Photocatalytic Dimerization of Anthracene

Photodimerization of anthracene is made possible using Acr^+-Mes as a photocatalyst in CHCl_3 .¹⁸⁴ When the photochemical reaction of 9,10-dimethylantracene with Acr^+-Mes was carried out without O_2 in CHCl_3 , photocatalytic carbon-carbon bond formation occurred efficiently to give dimethylllepidoptere (5,6,11,12-tetrahydro-5,12-dimethyl-4*b*,12[1',2']: 6,10*b*[1'',2'']-dibenzo-chrysene).¹⁸⁴ The X-ray crystal structure of dimethylllepidoptere is shown in Figure 14.¹⁸⁴ In the crystal structure, the bond length of the newly formed C-C bond (C6-C6') is 1.629(2) Å, which is much longer than normal C-C single bonds, indicating severe distortion of this compound.¹⁸⁴ The synthesis of another type of anthracene dimer such as lepidoptere has previously been carried out by intramolecular Diels-Alder reaction of 9-anthrylmethyl *a,p*-dimer,¹⁸⁵⁻¹⁸⁹ dehalogenation of 9-chloromethylantracene,^{190,191} oxidation of 9-methylantracene with copper(II)/peroxy-disulfate,¹⁹² photolysis of 9-(*N,N*-dimethylamino)-anthracene,¹⁹³ 9-(phenoxymethyl)anthracene,¹⁹⁴ and 9-anthracenylmethylsulfides and selenides.¹⁹⁵

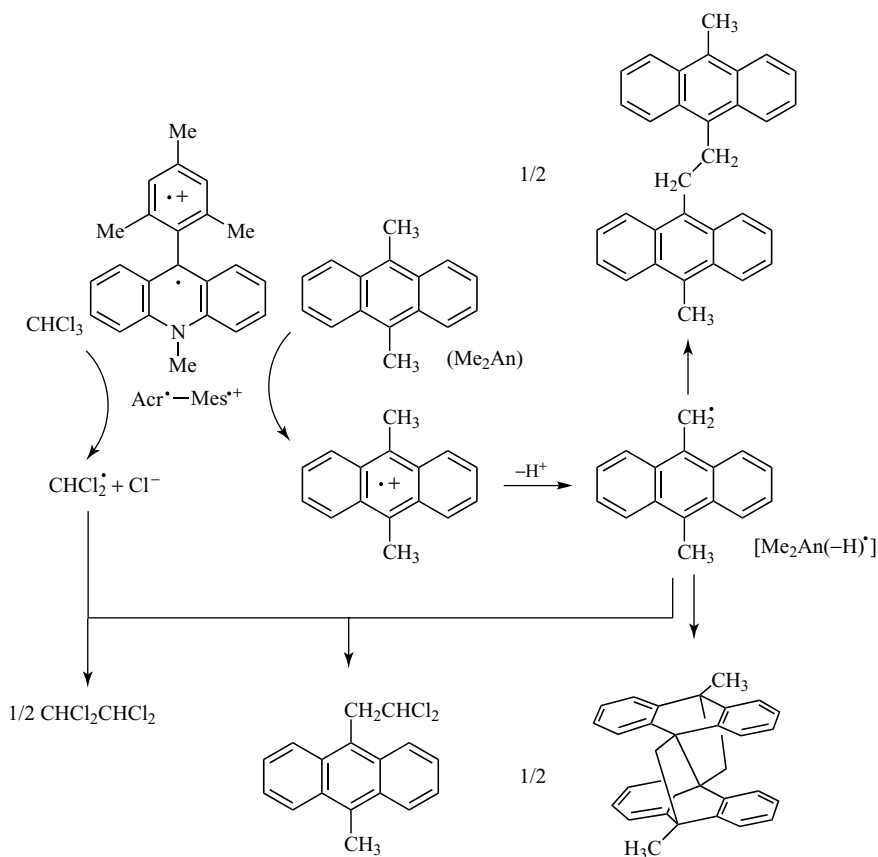
The one-pot synthesis of the lepidoptere from the corresponding anthracene has been made possible using Acr^+-Mes as a photocatalyst as shown in Scheme 17.¹⁸⁴ Photoirradiation of Acr^+-Mes

affords the electron-transfer state ($\text{Acr}^{\bullet}-\text{Mes}^+$), followed by electron transfer from DMA to $\text{Acr}^{\bullet}-\text{Mes}^+$ to produce $\text{DMA}^{\bullet+}$ and $\text{Acr}^{\bullet}-\text{Mes}$. The deprotonation from the methyl group of $\text{DMA}^{\bullet+}$ is the key step for the formation of dimethylllepidoptere as shown in Scheme 17. There are two ways of radical coupling of the deprotonated radicals to produce the dimers: lepidoptere and 1,2-bis(9-anthracenyl)ethane (Scheme 17). The $\text{Acr}^{\bullet}$ moiety of $\text{Acr}^{\bullet}-\text{Mes}$, produced by electron transfer from DMA to $\text{Acr}^+-\text{Mes}^+$, is oxidized by dissociative electron transfer to CHCl_3 to produce $\text{CHCl}_2^{\bullet}$ and Cl^- . The $\text{CHCl}_2^{\bullet}$ radicals dimerize to yield 1,1,2,2-tetrachloroethane ($\text{CHCl}_2\text{CHCl}_2$) as shown in Scheme 17.¹⁸⁴

The improvement of the dimer product yield can be achieved by the addition of a base such as tetrabutylammonium hydroxide (TBAOH), which accelerates deprotonation of $\text{DMA}^{\bullet+}$.¹⁸⁴ When TBAOH was introduced to a CHCl_3 solution containing DMA and Acr^+-Mes , the isolated yield of dimethylllepidoptere was increased to 21%, as compared with the yield in the absence of the base (12%).¹⁸⁴

6 SUMMARY

As described above, a variety of photocatalytic reactions are made possible using the electron-transfer state of Acr^+-Mes , which can oxidize and reduce



Scheme 17 Photocatalytic formation of dimethylepidoptere with Acr^+-Mes .¹⁸⁴

external electron donors and acceptors to produce the radical cations and anions, respectively. The reactions of radical cations with superoxide anion ($\text{O}_2^{\cdot-}$) can efficiently compete with the back electron transfer to yield the oxygenated products. Substrates that cannot react with singlet oxygen can be readily oxygenated by oxygen with Acr^+-Mes under visible light irradiation. The oxygenated products become much more difficult to be oxidized by the electron-transfer state of Acr^+-Mes , when the selective photocatalytic oxygenation of substrates, which would otherwise be very difficult to achieve, has been made possible with Acr^+-Mes . The reactions of radical cations produced by electron transfer from electron donor substrates to the electron-transfer state of Acr^+-Mes with nucleophiles such as Br^- can also afford the adducts with nucleophiles, when the electron-transfer oxidation of substrates with the electron-transfer state

of Acr^+-Mes is much faster than that of nucleophiles. In addition, the radical coupling of neutral radicals produced by deprotonation of the produced radical cations can be utilized for the C–C bond formation reactions. Thus, photocatalytic reactions of Acr^+-Mes under visible light irradiation provide new ways to design environmentally benign synthesis.

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Conducting Polymers: Applications in Electronics and Photovoltaics

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1 INTRODUCTION

1.1 Prologue

The Nobel Prize for Chemistry in 2000 was awarded to Professors Alan Heeger, Alan MacDiarmid, and Hideki Shirakawa for their great discovery of conducting polymer that “doped” polyacetylene can conduct electricity, which immediately shocked the world and changed the initial way in which polymers were only viewed as insulators. Since then, significant academic and commercial interest in conjugated polymers was evoked for their wide region of physical properties from insulating, semiconducting to highly conducting (metallic) state through reasonable molecular tailoring^{1–4} and their superior solution-processed ability over the traditional inorganic materials for promising applications in the context of flexible, low-cost, and large-area optoelectronic devices.^{5–9} Till date, this field has evolved three typical generation processes from the early work on polyacetylene (the first generation) to a special focus on soluble and processable polymers (the second generation) and then to currently the more complex copolymer materials (the third generation),¹⁰ aiming to meet different application areas. Among them, polymer-based light-emitting diodes (PLEDs), polymer-based field-effect transistors (PFETs), and polymer-based solar cells (PSCs) are the most representative application fields for

conducting polymers and have received particular and extensive attention over the past decades. Encouragingly, till date, PLEDs are becoming commercially available, representing the final step in the advance of organic electronics from laboratory curiosity to a part of daily life. In contrast, PFETs and PSCs have been left behind. Nevertheless, the past success in PLEDs provides scientists enough confidence that in near future there will be vital alternatives of PFETs and PSCs in commercial world to their inorganic counterparts. Figure 1 shows the number of publications versus years for PFETs and PSCs obtained from the ISI web of knowledge, clearly indicating the increasing research interest in these fields.

In spite of current success for PLEDs in the market place, such as most notably the displays of several mobile electronic applications,^{8,9,11,12} the goal of this article will mainly focus on the important and updated development in fields of PFETs and PSCs, in order to give a concise review especially regarding those which play important role in leading the development trend in terms of both new materials and device applications, in order to provide a valuable guideline for driving their true commercialization. Before discussing these representative developments, it is quite necessary to give a basic introduction to PFETs and PSCs, including their device structures, principles of operation, as well as the research background and the state-of-the-art.

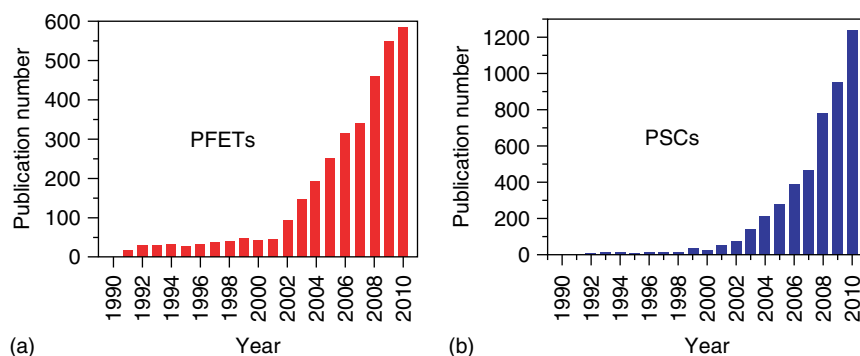


Figure 1 Number of literature publications versus years for (a) PFETs and (b) PSCs obtained from ISI web of knowledge searching with the keywords “polymer field-effect transistor(s)” and “polymer solar cells or polymer photovoltaics”, respectively.

1.2 Basic Knowledge of PFETs

An organic field-effect transistor (OFET) is a three-terminal device composed of a gate electrode, a gate insulator layer, a semiconducting layer, and the source/drain electrodes. According to the relative position of every component, field-effect transistor has four typical device structures (as shown in Figure 2a). In principle, bottom-gate top-contact (BGTC) is the most usually investigated device

structures for PFETs due to its intimate contact between the semiconducting layer and source/drain electrodes and thus resulting in low contact resistance and higher device performance. However, from the viewpoint of large-area applications, top-gate bottom-contact (TGBC) and bottom-gate bottom-contact (BGBC) are the ideal device structures because they can be easily manipulated with inexpensive fabrication techniques, such as gravure printing, flexographic, inkjet printing, and so on.

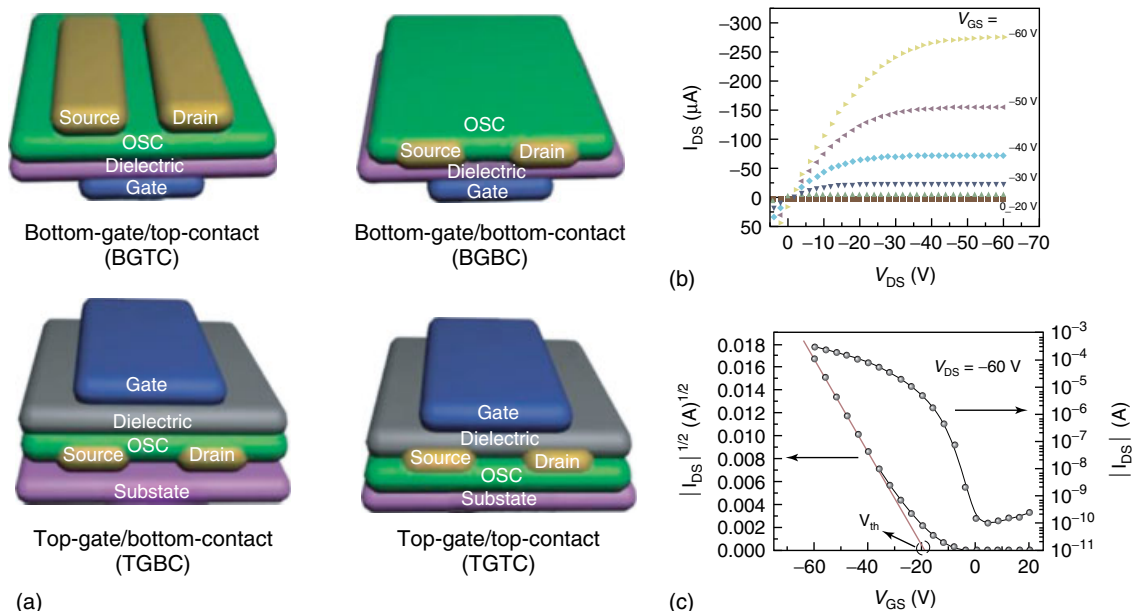


Figure 2 (a) The common structures of OFETs. Typical I - V characteristics of a pentacene-based BGTC p-channel OFET with gate dielectric of PS (15 nm)-modified 300 nm SiO_2 , (b) output, and (c) transfer curves. [Reproduced from Ref. 13. © Wiley-VCH Verlag GmbH & Co. KGaA, 2010.]

Simply speaking, OFETs can be seen as a capacitor between the gate electrode and semiconductor layer. Under applying a gate voltage, there are induced charges (holes for p-type or electrons for n-type) occurring in the semiconductor thin film near the insulator, and then these induced charges transport from the source electrode to the drain electrode by applying a certain source-drain voltage and produce current. Compared to that of no applied gate voltage, the channel current can be significantly increased by several orders, depending on the applied gate voltage. The performance of OFETs is usually characterized by parameters such as field-effect mobility ($\mu/(\text{cm}^2 \text{Vs}^{-1})$), on/off ratio ($I_{\text{on/off}}$), and threshold voltage (V_{th}/V), which can be calculated through the transfer and output curves (as shown in Figure 2b and c).

In the linear region, the μ value is given as following:

$$I_{\text{DS}} = \frac{W}{L} \mu C_i (V_{\text{GS}} - V_{\text{th}}) V_{\text{DS}} \quad (1)$$

While in the saturation region, the μ value is given as follows:

$$I_{\text{DS}} = \frac{W}{2L} \mu C_i (V_{\text{GS}} - V_{\text{th}})^2 \quad (2)$$

Beside this, the $I_{\text{on/off}}$ is the ratio of the highest current value/the lowest current value in the transfer curve, the V_{th} can be determined by extrapolating a plot of $(I_{\text{DS,sat}})^{1/2}$ versus V_{GS} to $I_{\text{DS}} = 0$. Field-effect mobility, as one of the most important parameters, refers to the absolute value of the ratio of the velocity to the electric field, which is affected by many factors, such as semiconductor materials, device fabrication process, interface properties as well as measurement conditions.^{14,15} Since the first report of PFETs (mobility was only $10^{-5} \text{ cm}^2 \text{Vs}^{-1}$),¹⁶ they have undergone remarkable progress and the highest field-effect mobility reported so far for PFETs has been up to $1.4 \text{ cm}^2 \text{Vs}^{-1}$,¹⁷ which has been comparable to amorphous silicon, indicating their tremendous potential for future applications.

1.3 Basic Knowledge of PSCs

Different from field-effect transistor, solar cell is a kind of device that operates in converting light into

electricity through the following steps: absorption of photons leading to the formation of excitons, that is, the bond electron-hole pairs; exciton diffusion for dissociation, that is, charge separation occurs; and then charges transport within organic semiconductor to electrodes and connect by electrodes to generate photocurrent and photovoltage. Under the consideration of energy sustainability and environmental protection, PSCs have received widespread attention as a source of clean and renewable energy particularly due to its potential for large-area and low-cost applications. The first PSC device was reported by Karg *et al.* 1993¹⁸ based on poly(*p*-phenylene-vinylene) with a single layer device structure, and only about 0.1% conversion efficiency was obtained for such solar cells. And then, in 1986, Tang *et al.*¹⁹ introduced the concept of two-layer device architecture into the organic solar cells, and much progress has been made for organic photovoltaic cells due to the incorporation of a donor-accept interface in the active layer, which generates the charge separation and produces higher photocurrent. However, the small interfacial areas and the limited thickness for exciton diffusion make it very difficult for the further enhancement of such two-layer device performance. To overcome these limitations, a concept of bulk heterojunction (BHJ) solar cells (as shown in Figure 3a) was proposed by Yu *et al.*²⁰ in 1995. By blending donor and acceptor materials together, an interpenetrating network with a large D–A interfacial area can be achieved through controlling the phase separation between the two components in bulk. In this way, any absorbing site in the composite is within a few nanometers to the donor–acceptor interface, leading to much enhanced quantum efficiency of charge separation. The formation of the continuous network creates two channels to transport holes in the donor domain and electrons in the acceptor domain, resulting in an efficient charge collection.²¹ So far, this structure strategy has become the research mainstream in PSCs and has obtained very good success. The device efficiency has been significantly improved from the initial report value of 0.1%¹⁸ to current value of approaching 8%,²² representing a breakthrough in the PSCs' performance and bringing a bright future for PSCs' future applications.

The performance of PSCs can be characterized by the following essential parameters, such as J_{sc} (the short-circuit current), V_{oc} (the open-circuit voltage), J_{mp} , and V_{mp} referring to the current and voltage,

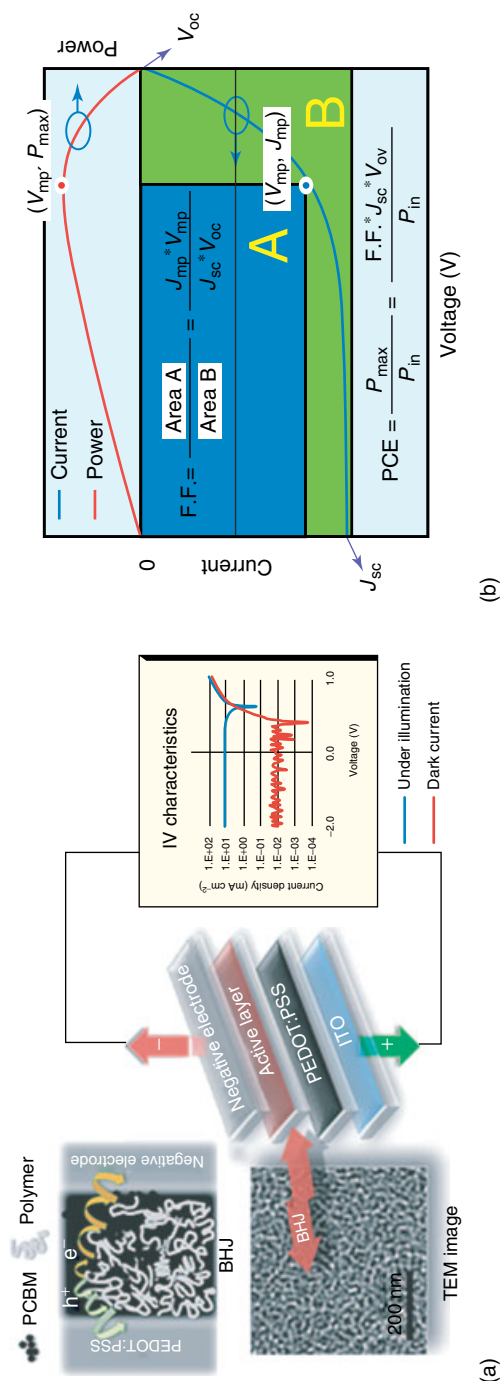


Figure 3 (a) Architecture of a bulk heterojunction photovoltaic device using indium tin oxide (ITO) as the electrode and poly[3,4-(ethylenedioxy)thiophene] poly(styrenesulfonate) (PEDOT:PSS) as the hole-conducting layer. The enlarged area shows the active layer consisting of a conjugated polymer [6,6]-phenyl-C₆₁-butyric acid methyl ester (PCBM) composite with a bicontinuous interpenetrating morphology with domain sizes between 10 and 20 nm. (The bottom one is a TEM image, and the top one is a drawing illustration.) (b) Current voltage ($J-V$) characteristics and the corresponding power voltage curve for a BHJ solar cell under illumination. [Reprinted with permission from Ref. 21. Copyright 2009 American Chemical Society.]

respectively, at which a given device's electrical power output is the maximum, $P_{\max}$, the fill factor (FF) (a graphic measure of the square of the I - V curve), and the power conversion efficiency (PCE) (which is defined as the ratio of maximum power output ($P_{\max}$) to power input (P_{in})). They are usually obtained through the current-voltage (I - V) curves with corresponding equations shown in Figure 3b.

From the above brief introduction, we can see that the current breakthrough development has been made in both PFETs and PSCs, specifically in terms of field-effect mobility for PFETs and device efficiency for PSCs. However, to combine all these essential parameters for PFETs or PSCs into a useful technology, further research in device science and new materials is needed. As the core component of PFETs and PSCs, semiconducting layer plays the crucial role in determining the whole device performance. So, in the following sections, we will firstly give a relatively comprehensive summary on the recent important and representative progresses in both these two fields, with special emphasis on novel concepts of molecular designs, optimizing the device fabrication from a view point of materials, such as thermal annealing, interface modification as well as solvent effect, and so on, for the enhancement of device performance. Then, we will briefly introduce some of their prospective applications in flexible and large-area organic electronics. Finally, a conclusion and outlook is presented with a discussion on the chances and challenges facing PFETs and PSCs in their future commercial applications.

2 ADVANCED PFET MATERIALS

As mentioned above, as a key element of PFETs, the properties of semiconducting polymers, including the local intramolecular and the intermolecular packing between molecules, the molecular ordering and orientation at the semiconductor/dielectric layer as well as material itself directly affect the charge transport properties and thus the device performance. Thus, except of device structure optimization, the development of superior polymer semiconductors is crucial for the further enhancement of device performance. In order to obtain high device performance, polymer semiconductors should firstly meet some stringent criteria relating to the current carrying

and charge injection: (i) ideal coplanar structure conformation for maximized molecular orbital overlaps, (ii) good self-organization properties for preferable molecular orientation, especially at the semiconductor/dielectric interface, and (iii) proper energy gap and energy alignment for efficient charge injection as well as high ambient stability resistance to environmental O_2 or H_2O molecules.¹⁴ Moreover, the solubility, film-forming property, film morphology, and material purity are all also needed to be taken into account in designing a new high-performance polymer semiconductor. Recently, except for liquid-crystalline polymer semiconductors, easily processable, "annealing free," and "fabrication method independent" amorphous polymers have also received increasing attention for their promising commercial applications since its charge transport properties are isotropic in whole thin film along any direction and independent of fabrication conditions.^{23–25} Here, we will summarize these important and outstanding high-performing semiconducting polymers both for p-type and n-type from the viewpoint of novel molecular design.

2.1 High-Performance p-Type Polymers

2.1.1 Polythiophenes

Among the number of p-type semiconducting polymers, polythiophenes are one of the most and widely investigated materials, and the first OFET reported in 1986 was also based on the unsubstituted polythiophene.¹⁶ Since then, in a very long time, a large part of the research for polythiophene materials has focused on the improvement of solubility, exploration of easy synthetic methods, purification of materials, maximization of the molecular regioregularity, optimization of the molecular weight, and so on.^{26–28} Among all the polythiophene materials, regioregular poly(3-hexylthiophene) (P3HT) is the most representative semiconducting material with relatively high charge transport properties due to its highly crystalline microstructure as well as the very good solubility for solution processing.^{29,30} Various studies demonstrated that this mobility of P3HT device depended sensitively on the degree of head-to-tail (HT) regioregularity. For example, with high HT regioregularity (>91%) and low molecular weight, P3HT molecules generally preferentially

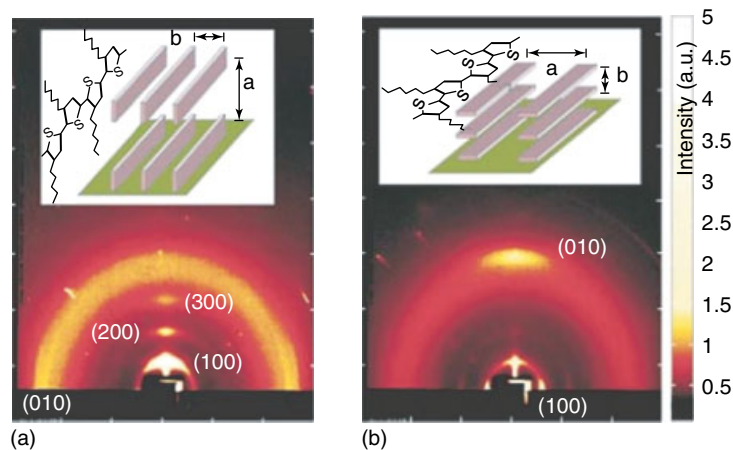


Figure 4 Two different orientations of ordered P3HT domains with respect to the FET substrate. The wide-angle X-ray scattering images are a color representation of the two-dimensional distribution of scattered Cu K α X-ray intensity from spin-coated, 70- to 100-nm-thick P3HT films with regioregularity of 96% (a) edge-on orientation and 81% (b) face-on orientation on SiO₂/Si substrates. The vertical (horizontal) axes correspond to scattering normal (parallel) to the plane of the film. The insets show schematically the different orientations of the microcrystalline grains with respect to the substrate. [Reprinted by permission from Macmillan Publishers Ltd: Nature (Ref. 31), Copyright (1999).]

form high orientation of crystalline domains with the backbone long axis in the plane and the π - π stacking direction parallel to the substrate (as shown in Figure 4a), promoting two-dimensional charge transport and resulting in high field-effect mobility of $0.1 \text{ cm}^2 \text{ Vs}^{-1}$; however, in contrast, with low HT regioregularity (81%) and high molecular weight, P3HTs tend to orient with their thiophene ring planes in the substrate plane and the π - π stacking direction normal to the substrate (as shown in Figure 4b), leading to low field-effect mobility ($\sim 10^{-4} \text{ cm}^2 \text{ Vs}^{-1}$).³¹ This important discovery sparks many new ideas in device science by optimizing the molecular orientation for high device performance. Kim *et al.*³² found that the preferential orientation of P3HT molecules in thin films could also be manipulated through controlling the intermolecular interactions at the interface between P3HT and the insulate substrate using self-assembling monolayer functionalized with various groups. For instance, on insulators with unshared electron pairs, such as $-\text{NH}_2$ or $-\text{OH}$, the P3HT chains tend to form with the edge-on molecular orientation in the films (Figure 4a), while on an insulator surface without unshared electron pairs, such as $-\text{CH}_3$, they tend to order with the face-on molecular orientation (as shown in Figure 4b), and the resultant different orientations were mainly attributed to the different interactions between the P3HT molecules

and the insulator surface, the existence of π -H interactions between the thienyl-backbone bearing π -system and the H (hydrogen) atoms of $-\text{NH}_2$ or $-\text{OH}$ modified surface facilitated the formation of edge-on molecular orientation in film and resulted in availability of as high as $0.3 \text{ cm}^2 \text{ Vs}^{-1}$ mobility. Additionally, it should be stated that the mobility of P3HT transistor is also affected by many other factors, such as molecular weight,^{33,34} solvent, film morphology,³⁵ and so on, and the approaches to improve the mobility of P3HT-based field-effect transistors are now still being reported; however, the poor stability of P3HT when exposed to oxygen and/or to water has been and continues to be a big barrier for it to commercialization, which mainly is induced by the oxidative instability because of its low ionization potential (IP is around 4.8 eV).³⁶

Recently, chemical modification of the thiophene backbone structure has been employed to provide the controlled manipulation of both the polymer backbone conformation and the microstructure as well as tuning the electronic energy levels of molecular orbitals.³⁶ One effective approach is to reduce the π -overlap by increasing the rotation freedom of the polymer backbone, such as by introducing unsubstituted thiophene units at the proper positions, which results in higher IP levels and simultaneously still retain good molecular orientation in the microstructure, and thus facilitates

the availability of high ambient stability as well as efficient charge transport properties. A prime example is poly(3,3''-dialkyl-quaterthiophene) (PQT), after thermal annealing this material could form highly ordered lamellar thin film microstructures by self-assembly due to the large local free-volume between adjacent alkyl side chains³⁷ and exhibited very high field-effect mobility of $0.2 \text{ cm}^2 \text{ Vs}^{-1}$ and good ambient stability due to the increased IP (4.9 eV).^{38,39} Another promising strategy developed to increase the IP of materials is to incorporate some electron-withdrawing groups or electron poor comonomers, such as perfluorobenzene, thiophene-fused aromatic/heteroarene rings, into the polythiophene backbone, which could result in a lower polymer highest occupied

molecular orbital owing to the reduced delocalization along the backbone, and meanwhile minimize any steric interaction between the neighboring alkyl groups and preserve the backbone planarity, which was very useful for the formation of highly ordered crystalline domains. On the basis of this consideration, various classes of high-performing polymer semiconductors with good ambient stability have been successfully produced. Among them, a copolymer of thieno(3,2-*b*)-thiophene and 4,4-dialkyl 2,2-bithiophene (PBTtT) reported by McCulloch *et al.*⁴⁰ in 2005 is an exemplary liquid crystalline semiconductor with excellent transistor property, good ambient stability, as well as unusual self-assembly properties for large crystalline domains. As shown in Figure 5, after annealing

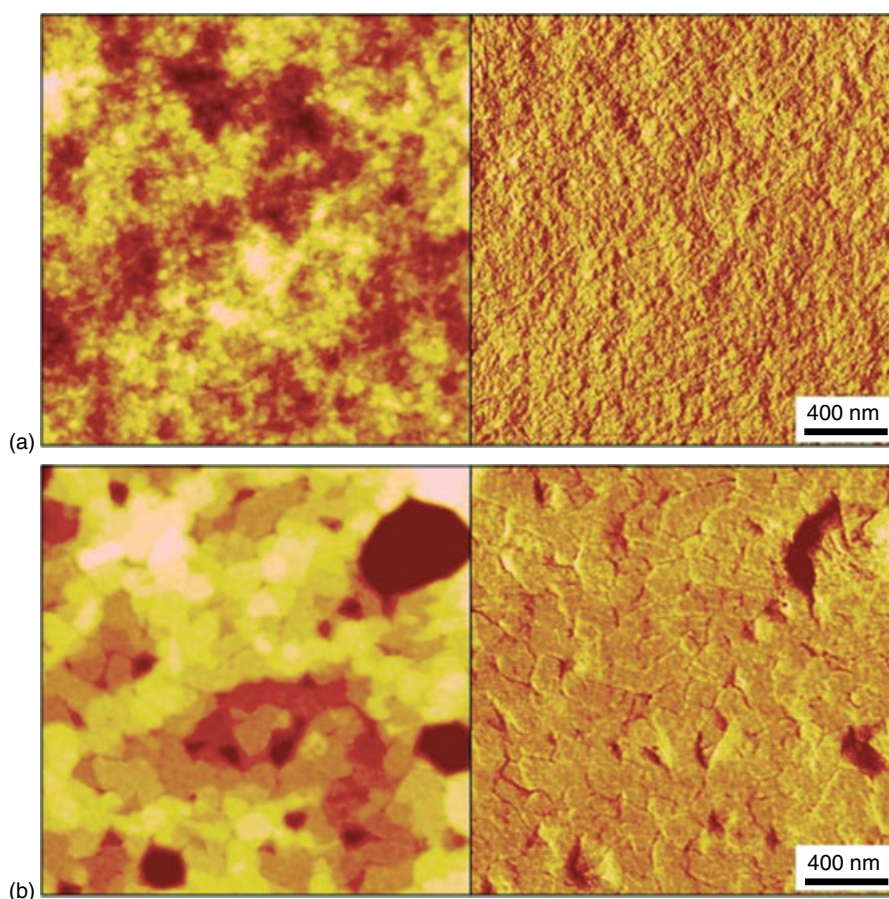


Figure 5 AFM images of PBTtT-C12 (annealed at 180°C). (a) Before and (b) after annealing above the liquid-crystal isotherm. The left-hand side images show the topography and the right-hand side images show the phase image. The dark spots in the topography of the annealed film are voids where the film partially dewetted during annealing. [Reproduced from Ref. 40. © Nature Publishing Group, 2006.]

above its liquid-crystal isomer, PBTTT-C12 formed highly oriented polycrystalline structure with relatively large crystalline domains with diameter of around 200 nm, in which the backbone long axis oriented in the plane of substrate, and the thiophene ring plane ordered orthogonal to the substrate plane with high density of side chain interdigitation, promoting the formation of three-dimensional ordering and facilitating the efficient charge transport in films,⁴¹ which was also manifested by the extremely high charge carrier mobility of $0.2\text{--}0.6\text{ cm}^2\text{ Vs}^{-1}$ (even up to $0.72\text{ cm}^2\text{ Vs}^{-1}$ through optimizing the device structure with reduced channel length).⁴⁰ In contrast, PBTCT molecule, an isomer of PBTTT, exhibited lower field-effect mobility of $0.15\text{ cm}^2\text{ Vs}^{-1}$,⁴² further indicating the importance of molecular structure

itself in designing new high-performing organic semiconductors.

The successful molecular design concept for PBTTT further prompted the development of other high-performance polythiophene derivatives through simply tuning the molecular structure or incorporating more highly fused systems into the backbone under the combining consideration of processability, molecular organization, as well as the electronic properties in solid state. Poly(2,5-bis(2-thienyl)-3,6-di-alkylthieno[3,2-*b*]-thiophene) (PBT) has a similar molecular structure with PBTTT but different side chain positions. On annealing, the devices based on PBT exhibited a field-effect mobility of $0.25\text{ cm}^2\text{ Vs}^{-1}$ with a high on/off ratio of 10^7 .⁴³ Poly(2,6-bis(3-alkylthiophen-2-yl)dithieno[3,2-*b*;2',3'-*d*]thiophene) (PBTDT) exhibited a

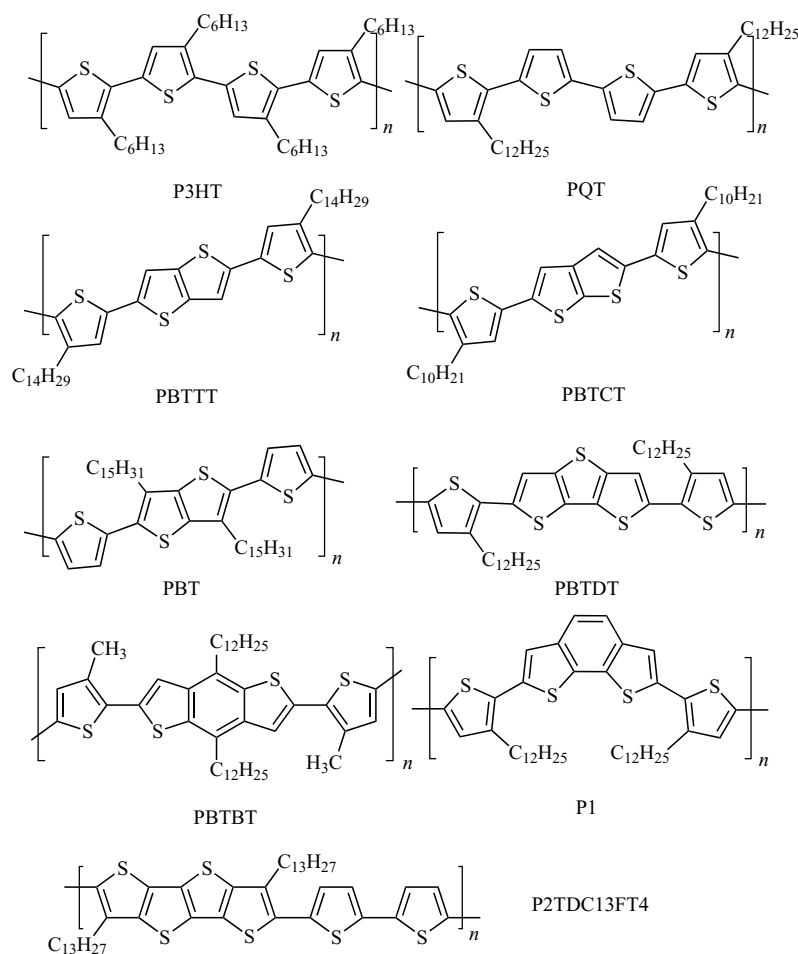


Figure 6 Molecular structures of some representative polythiophene semiconductors.

very good solubility even in the environmentally friendly hydrocarbon solvents and also a very high crystalline properties with a close π - π stacking distance of 3.8 Å. BGBC PBTDT transistors demonstrated as high as $0.3 \text{ cm}^2 \text{ Vs}^{-1}$ field-effect mobility with on/off ratio of over 10^7 .⁴⁴ Poly(4,8-didodecyl-2,6-bis-(3-methylthiophen-2-yl)-benzo[1,2-*b*:4,5-*b'*]dithiophene) (PBTBT) is a typical low-temperature semiconductor, and without thermal annealing process, it could form highly structural thin films and exhibited very high field-effect mobility of $0.15 \text{ cm}^2 \text{ Vs}^{-1}$.⁴⁵ Further extending the π -system, Rieger *et al.*⁴⁶ and Fong *et al.*⁴⁷ designed and synthesized polymer P1 and P2TDC13FT4, respectively. P1 is also a low-temperature material and rendered easily processed with no need of long-term annealing, even on a flexible substrate this material still exhibited very high field-effect mobility of up to $0.5 \text{ cm}^2 \text{ Vs}^{-1}$.⁴⁶ With four fused thiophene rings in the backbone, P2TDC13FT4 possesses higher rigid rod property and closer π - π stacking distance of 3.76 Å, the obtained field-effect mobility was around $0.33 \text{ cm}^2 \text{ Vs}^{-1}$.⁴⁷ The molecular structures of polythiophene semiconductors are shown in Figure 6. The IP values and detailed information of field-effect performance for above-mentioned polythiophene materials are summarized in Table 1.

2.1.2 Copolymers

Recently, a number of groups have started to investigate the field-effect properties of other more complex polymer systems, such as copolymer with expectation of much higher device performance

and already obtained a certain achievement.^{17,48,50} A copolymer of cyclopentabithiophene and benzothiadiazole was initially designed as a low-band gap material for photovoltaic applications.⁵¹ In the early report, field-effect mobility of $0.17 \text{ cm}^2 \text{ Vs}^{-1}$ was obtained for the drop-casted thin film of CDT-BTZ with 2-h thermal annealing processing under 200°C , otherwise, only $10^{-4} \text{ cm}^2 \text{ Vs}^{-1}$ could be examined.⁵⁰ More recently, by further purification of the material and with higher molecular weight, approaching $1.4 \text{ cm}^2 \text{ Vs}^{-1}$ was achieved for CDT-BTZ in its dip-coated thin films, the author claimed that it was because of higher crystalline structures due to the purified material as well as the optimized fabrication process, which is also the highest field-effect mobility value reported so far for PFETs.¹⁷ Becerril *et al.*⁵² reported another donor-acceptor copolymer based on acenaphtho[1,2-*b*]thieno[3,4-*e*]pyrazine and fluorene (ACTP-F), which was designed for a good planar molecular structure to promote an intimate π - π stacking between polymer chains. In N_2 atmosphere, the best field-effect mobility of $0.2 \text{ cm}^2 \text{ Vs}^{-1}$ was achieved for ACTP-F-based transistors. Poly[*N*-9'-hepta-decanyl-2,7-carbazole-alt-5,5-(4',7'-di-2-thienyl-2',1',3'-benzothiadiazole)] (PCDTBT) is another example of photovoltaic material which was used to fabricate the field-effect transistors.^{25,53} The field-effect mobility examined for PCDTBT in PFETs was $0.03 \text{ cm}^2 \text{ Vs}^{-1}$. More importantly, PCDTBT-based PFET devices showed remarkable stability when exposed to elevated temperatures (in air stable up to 150°C and in N_2 stable up to 350°C , as shown in Figure 7a and c). However, in contrast, the mobility of P3HT decreased by more than two orders of magnitude after exposure to 200°C . Additionally, it should also be stated that the high-temperature stability of the transport mobility was strongly dependent on the molecular weight of PCDTBT, that is, the excellent thermal stability is observed for only the highest molecular weight materials, evidently indicative of degradation *via* reactive end groups (as shown in Figure 7b). It is proposed that such high thermal stability of PCDTBT is typically attributed to its fully aromatic backbone as well as the stability of amorphous structure, which provides very useful guidelines for further design and synthesis of new high thermal stable polymer semiconductors. The molecular structures of copolymers discussed above are shown in Figure 8.

Table 1 A summary of IP values and field-effect performance of above-mentioned polythiophenes.

Polymer	IP (eV)	$I_{\text{on/off}}$	Mobility (cm^2/Vs)	Reference
P3HT	4.8		0.28	32
PQT	4.9	$> 10^7$	0.14	38
		$> 10^7$	0.5	43
PBTTT	5.1	$> 10^6$	0.72	40
PBTCT	5.3	10^5	0.15	42
PBT	5.23	$> 10^7$	0.25	43
PBTDT	5.14	$> 10^7$	0.3	44
PBTBT	5.05	10^6	0.15	45
P1	—	10^5	0.5	46
P2TDC13T4	—	$> 10^5$	0.33	47

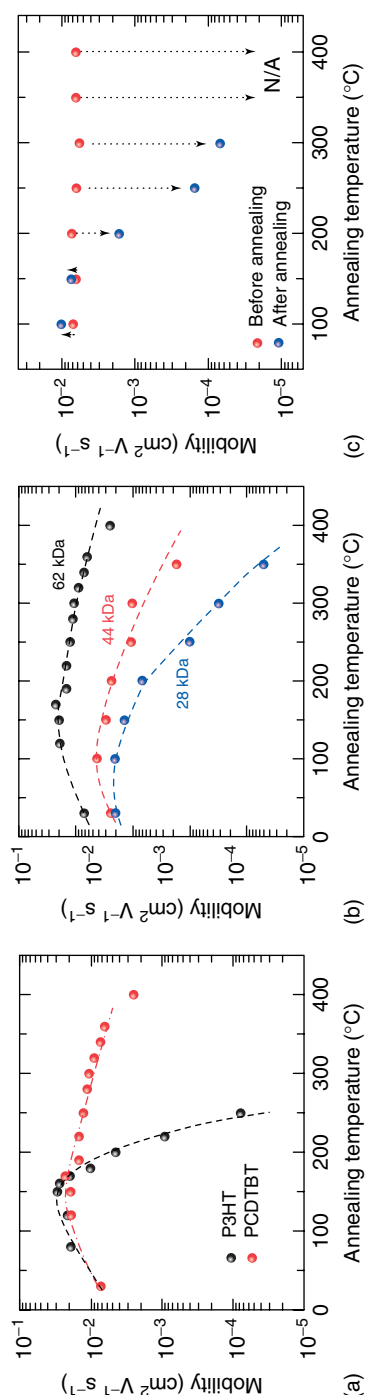


Figure 7 (a) Hole mobility of PCDTBT (red) as a function of annealing temperature from room temperature to 400 °C. Results obtained from a similar device fabricated with P3HT are shown for comparison (black). (b) Effect of weight-average molecular weight on the high-temperature stability of PCDTBT. (c) Mobility before and after annealing in air at elevated temperatures. [Reproduced from Ref. 25. © Wiley-VCH Verlag GmbH & Co. KGaA, 2010.]

2.2 High-Performance n-Type Polymers

N-type materials are crucial for the fabrication of p–n junctions as well as complementary circuits. Over the past years, especially in recent years, there has been tremendous progress in the development of superior n-type semiconducting polymer materials, though the number of reported n-channel polymers in the literature is still far lower than the p-type polymers. Poly(benzobisimidazobenzophenanthroline) (BBL) is the first reported n-type semiconducting polymer and exhibited as high as 0.1 cm² V s⁻¹ electron mobility in air for its spin-coated ladder polymer films from Lewis acid solution.⁵⁴ However, BBL has very low solubility in common organic solvents, which significantly inhibited its potential applications. Recently, perylenes as one of the most interesting electron-depleted cores used for n-channel polymer materials have demonstrated great potential for n-type materials.⁵⁵ A new copolymer of *N,N'*-dialkyl-1,7-dibromo-3,4,9,10-perylene diimide and dithienothiophene (P(PDI2OD-DD)) was recently synthesized by Zhan *et al.*⁵⁶ and a good electron field-effect mobility of 0.02 cm² V s⁻¹ was measured based on top-contact device geometry (with alumina as source and drain electrodes) in vacuum conditions, unfortunately, the corresponding devices do not operate under the ambient condition. More recently, Chen *et al.*⁵⁷ found that a promising strategy to achieve both high-performance n-channel thin-film transistors and stable device operation in ambient conditions is to choose the larger electron affinity of naphthalene core replacing the perylene core in the copolymer backbone, which could stabilize the lowest occupied molecular orbital (LUMO) with a proper level in terms of both efficient electron injection and operation stability. And based on this consideration, they successfully produced a highly stable n-type polymer, P(NDI2OD-T2). A remarkable high electron mobility of approaching 0.85 cm² V s⁻¹ was achieved through optimizing the device architecture, dielectric layer, and channel length. This value is the highest electron mobility reported so far for polymer semiconductors and could also be comparable to amorphous silicon, representing a significant improvement on the benchmark values for n-channel polymers.⁵⁸ Moreover, the great versatile processing such as spin coating, by gravure, flexographic, and inkjet printing for

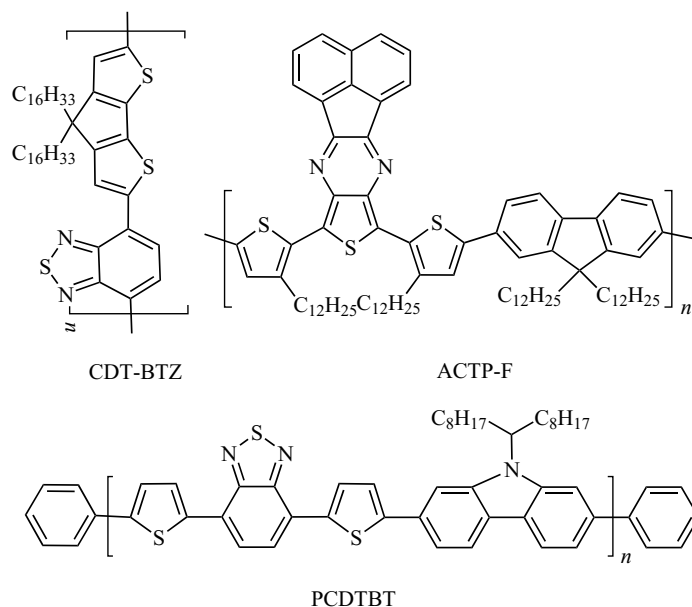


Figure 8 Molecular structures of some representative PFET copolymers.

P(NDI2OD-T2) along with the excellent electron transfer properties indicate its potential application in printed electronics. The molecular structures of n-type polymer semiconductors mentioned above are shown in Figure 9.

3 ADVANCED PSC MATERIALS

As mentioned previously in Section 1.3, BHJ solar cell structure has currently been the mainstream of research due to its maximum interfacial areas and

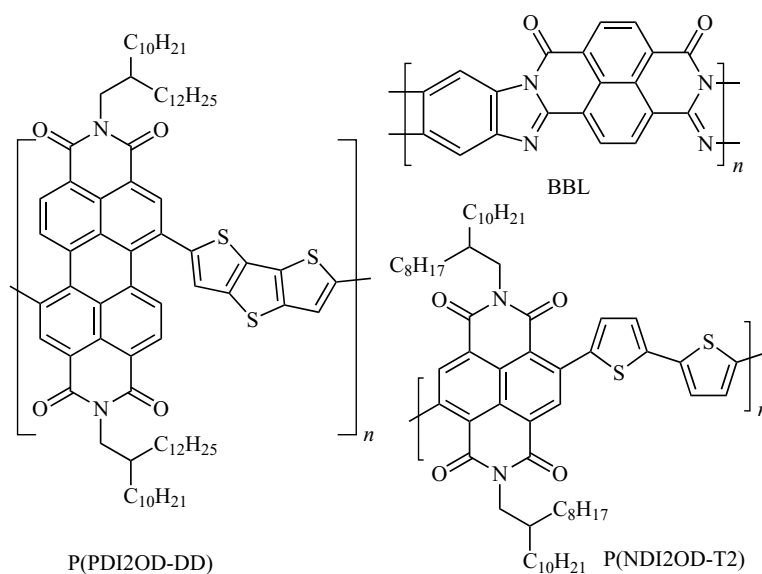


Figure 9 Molecular structures of some n-type polymer semiconductors.

efficient exciton diffusion, facilitating the further enhancement of device efficiency. There are generally two components of donor and acceptor materials in the active layer for BHJ structure and selection of the materials in both components is very important for the solar cell performance.

For acceptor materials, fullerene derivatives with solubilizing groups are the best candidates so far due to their high electron affinity, superior electron mobility, and three-dimensional structure, providing unique packing ability in blend to efficiently form electron transport channels.⁵⁹ Of them, [6,6]-phenyl-C₆₁-butyric acid methyl ester (PC₆₁BM) is the most important acceptor material, which exhibits excellent properties in fabrication of high-performance PSCs. However, weak absorption in the visible region and a low LUMO energy level for PC₆₁BM are its drawbacks, which significantly affect its contribution to light harvesting in the photovoltaic conversion and are unfavorable for availability of larger open circuit voltage (V_{oc}) in PSCs. Thus, some new soluble fullerene derivatives with stronger visible absorption and high LUMO energy levels than PC₆₁BM have been designed and synthesized. [6,6]-Phenyl-C₇₁-butyric acid methyl ester (PC₇₁BM) is one representative of such fullerene derivatives and shows improved

photovoltaic performance over PC₆₁BM in some cases.^{60–64} But the high cost of PC₇₁BM and other larger core fullerene derivatives⁶⁵ will probably limit their future commercial applications in PSCs. Recently, He *et al.*⁶⁶ reported a new C₆₀ derivative, indene-C₆₀ bisadduct with easier synthesis, better solubility, stronger absorption, and also better device performance in P3HT-based PSCs than PC₆₁BM, indicating it as a promising acceptor material for high-performance PSCs. Anyway, till date, polymer-based acceptors for high-performance PSCs have rarely been reported, though which are crucial for all-PSCs,⁵⁶ that is, the most effective component in BHJ solar cells is mainly based on properties of conjugated polymer donors in the blend. The molecular structures of representative fullerene derivatives used as acceptors are shown in Figure 10.

From the above discussion, it is obvious that the development of high-performance polymer donor materials for the active layer in PSCs has become crucial to achieve the desired solar cell performance for practical applications. Over the past years, many groups have made significant efforts in this field.^{60,62,67–69} Till date, the highest PCE reported for PSCs is approaching 8% based on a new polymer with alternating thieno[3,4-*b*]thiophene and

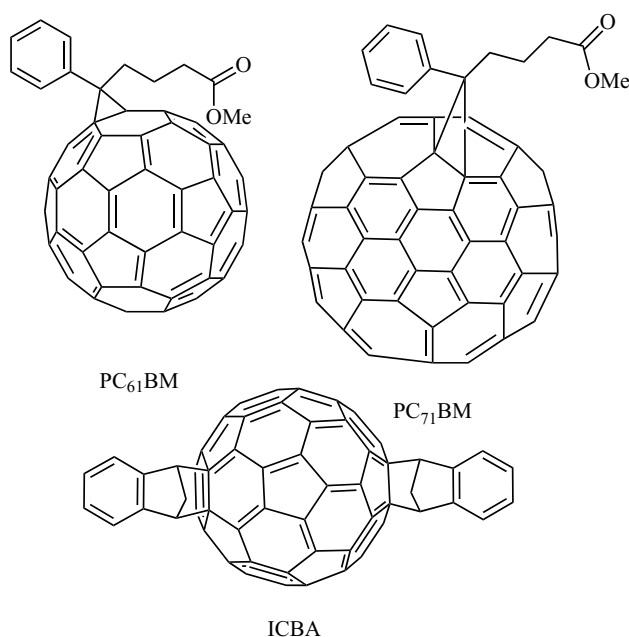


Figure 10 Molecular structures of some representative fullerene derivatives acceptors.

benzodithiophene units (PTB7)/PC₇₁BM system,²² which means a key breakthrough in PSCs. In this section, we give a review on the recent outstanding progress in developing new and promising active materials, especially those that have already shown promising performance in actual PSC devices, or have the potential to show significantly higher efficiencies than those recently achieved.

3.1 Polyphenylenevinylenes

Polyphenylenevinylenes (PPVs) are one of the most well-known conjugated polymer materials and have been widely investigated in many electronic and optoelectronic devices because of their unique light-emitting properties and photovoltaic performance. The original PPVs do not have enough solubility in organic solvents, so PPV derivatives with solubilizing groups, such as poly[2-methoxy-5-(2'-ethylhexyloxy)-1,4-phenylene vinylene] (MEH-PPV) and poly[2-methoxy-5-(3,7-dimethyloctyloxy)-1,4-phenylene vinylene] (MDMO-PPV), are usually used and have exhibited good photovoltaic performance. Till date, high efficiencies

of approaching 2.5% were achieved based on MDMO-PPV/PC₆₁BM blend, confirming the good photovoltaic performance for PPV derivatives.⁷⁰ In 2003, Wienk *et al.*⁶⁴ demonstrated improved efficiency of up to 3.0% for a MDMO-PPV/PC₇₁BM blend by changing the acceptor from PC₆₁BM to PC₇₁BM as well as adjusting the used solvent attributed to more efficient charge separation and the light harvesting, which is also the best efficiency reported so far for PPVs-based solar cells. Weak absorption in the visible region (only up to 500 nm) and the unstable properties in the presence of even small amount air are the main weak points for this class of materials, which dramatically limit the further improvement for their photovoltaic efficiency (because of low sunlight absorbance) as well as the potential applications. One simple design concept to improve the absorption and stability of PPVs is to introduce strong electron-withdrawing group, such as a cyano group into the PPV backbone. CN-PPV is one typical example, and compared with PPV, the highest occupied molecular orbital (HOMO) and LUMO levels of CN-PPV were lowered 0.6 and 0.9 eV, respectively, indicating its strong electron affinity as the polymer acceptors.⁷¹ The all-polymer

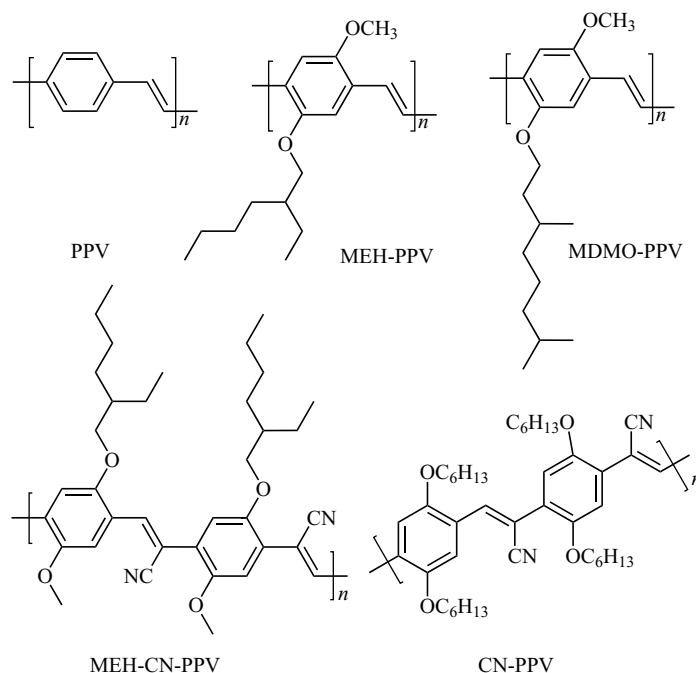


Figure 11 Molecular structures of representative polyphenylenevinylene materials used in PSCs.

BHJ solar cell based on MEH-PPV/CN-PPE blend exhibited PCE of 0.9%,⁷² another all-PSC based on P3HT/MEH-CN-PPV demonstrated quantum efficiency of 29% and an overall PCE of as high as 1.9% under a simulated solar spectrum, providing opportunities for plastic applications.⁷³ It is clear that although much progress has been made in this field, the efficiencies remained at 3.0% at best so far; thus, the general interest in this class of materials gradually faded especially over the past years. The molecular structures of PPVs are shown in Figure 11.

3.2 Polythiophene Materials

In recent years, polythiophenes, specifically speaking P3HT, have received particular attention as the electron-donating materials in polymer photovoltaic devices due to their superior physical properties, good solubility for solution processing, as well as the unique molecular structure facilitating self-assembly in solid state. In 2002, the first encouraging results for P3HT/fullerene derivative blend-based solar cells were reported by Schilinsky *et al.*⁷⁴ and as high as 8.7 mA cm^{-2} of short-circuit current density and good efficiency of 2.8% were achieved with a weight of 1:3 for P3HT and fullerene component. Since then, this experimental result significantly accelerated the development of P3HT-fullerene blend solar cells, and tremendous progresses have been made in this field over the past years, and relatively high efficiency of 4–5% recently could be easily achieved for P3HT/fullerene system in BHJ solar cells, which can be clearly illustrated by Table 2. Actually, on the other hand, such concentrated studies over the past years for P3HT/fullerene system-based solar cells also help us in understanding the optimization of device fabrication process better and also give some novel insights in design of new polymer donor materials to maximize the device performance. For instance, appropriate thermal annealing conditions could result in effective improvement for PSCs, probably due to both the molecular recrystallization as well as the reduced free volume and the density of defects.^{75–77} Another interesting discovery for P3HT-fullerene-based solar cells is about the influence of regioregularity on P3HT-based solar cell performance. Generally, in the same condition,

Table 2 Nonexhaustive survey of reports focusing on photovoltaic devices based on P3HT:PCBM blends.

Year	P3HT provider	M_w (g mol^{-1})	Ratio to PCBM (weight)	Layer thickness (nm)	Solvent	Annealing time (min)	Annealing temperature ($^{\circ}\text{C}$)	Max EQE (%)	V_{oc} (V)	FF	J_{sc} (mA cm^{-2})	Eff (%)	Light intensity (mW cm^{-2})
2002	—	—	1:3	350	—	—	—	76	0.58	0.55	8.7	2.8	100
2003	—	—	—	110	DCB	4	75	70	0.55	0.6	8.5	3.5	80
2004	Rieke	—	5:2	350	CB	4	75	65	0.54	0.37	15.2	3.1	100
2005	Rieke	100,000	1:1	70	DCB	60	120	58	0.615	0.61	7.2	2.7	100
2005	Merck	11,600	1:1	—	CB	15	140	58	0.61	0.53	9.4	3.0	100
2005	—	—	1:1	63	DCB	10	110	—	0.61	0.62	10.6	4.0	100
2005	Aldrich	87,000	1:0.8	—	CB	5	155	—	0.65	0.54	11.1	4.9	80
2005	Rieke	—	1:0.8	—	CB	30	150	—	0.63	0.68	9.5	5.0	80
2006	Merck	21,100	1:1	175	CB	120	140	70	0.6	0.52	12	4.4	85
2006	—	—	1:0.8	—	CB	10	150	88	0.61	0.66	11.1	5.0	90
2006	Rieke	—	1:1	320	DCB	10	110	82	0.56	0.48	11.2	3.0	100
2008	Rieke	—	1:1	220	DCB	10	120	87	0.64	0.69	11.3	5.0	100

Source: Reproduced from Ref. 80. © Wiley-VCH Verlag GmbH & Co. KGaA, 2009.

the highest molecular regioregularity of polymer could result in the highest device performance both for electronic³¹ and optoelectronic devices.⁷⁸ However, for P3HT-based solar cells, more recently, Sivula *et al.*⁷⁹ found that consciously decreasing the effective regioregularity of P3HT by incorporating a dihexylthiophene repeat unit in the backbone, poly(1-*co*-2), has not lowered the device efficiency but conferred more thermal stability with implication of long-term performance compared to the pristine P3HT-based solar cells, due to the obtainability of stable interpenetrating network of electron donor and acceptors in poly(1-*co*-2)/PCBM blend layer (as shown in Figure 12). Such discovery

that consciously decreasing the effective regioregularity of P3HT could not lower the device efficiency but confers more thermal stability breaks the traditional views that only pursuing high regioregularity in molecular design and sparks new ideals for designing new high performing even high thermal stable polymer materials.

Anyway, in the past decade, P3HT/fillerene system in BHJ solar cells has been the research focus and PCE of 5.0% has been achieved since 2005 (as shown in Table 2).^{77,81,82} However, in the long term, to realize the real commercial applications for PSCs, reaching the expected 10% efficiency is necessary.⁸³ Theoretical calculation

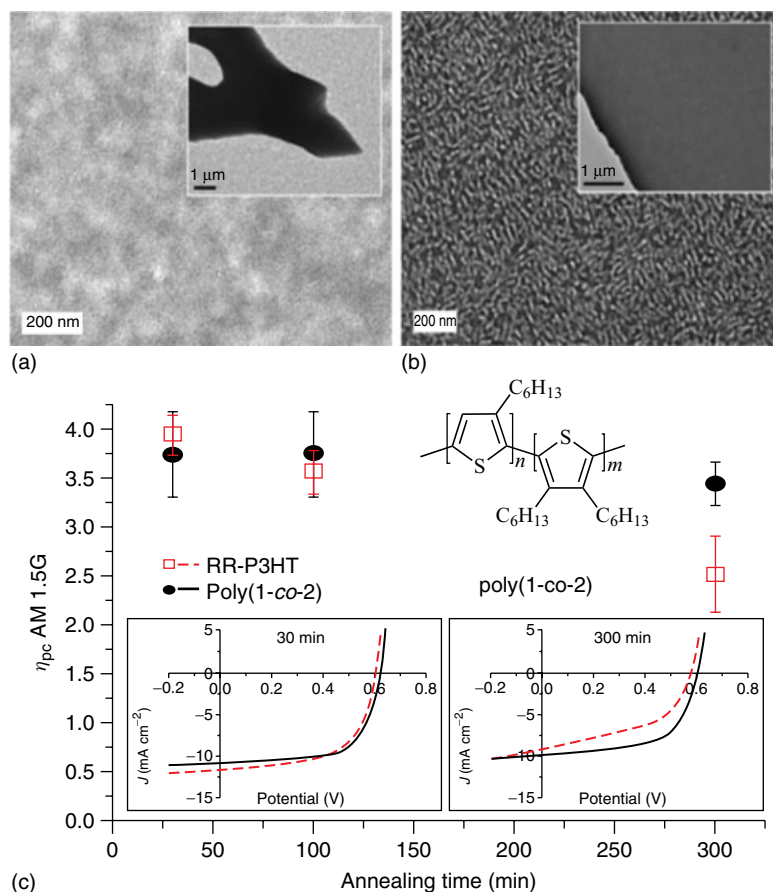


Figure 12 Transmission electron micrographs of annealed BHJ thin films containing 1:1 by weight RR P3HT:PCBM (a) and poly(1-*co*-2):PCBM (b). (c) Performance of photovoltaic devices fabricated with the control RR-P3HT or poly(1-*co*-2). The eight-device average PCE (η_{PC}) at standard conditions as a function of annealing time at 150 °C and typical *I-V* behavior (insets) observed after 30 and 300 min of annealing illustrate the difference between the materials. The error bars represent the 95% confidence interval of the average values. Inset is the molecular structure of poly(1-*co*-2). [Reprinted with permission from Ref. 79. Copyright 2006 American Chemical Society.]

demonstrated that assuming 100% external quantum efficiency for all photo energies above the 1.9 eV band gap of P3HT, the best possible P3HT-PCBM solar cell would produce roughly 17 mA cm^{-2} of photocurrent under AM 1.5 illumination, and combining the best open-circuit voltage (500 mV) and FF (0.6), the resultant highest power efficiency would be only 5.6%,⁸³ owing principally to the poor overlap between the P3HT absorption

and the solar emission spectrum (as shown in Figure 13).

3.3 Low-Band Gap Polymers

On the basis of the studies on 26 different polymer-PCBM BHJ solar cells, Scharber *et al.*⁶⁷ proposed a linear relationship between the V_{oc} and the used conjugated polymer oxidation potential,

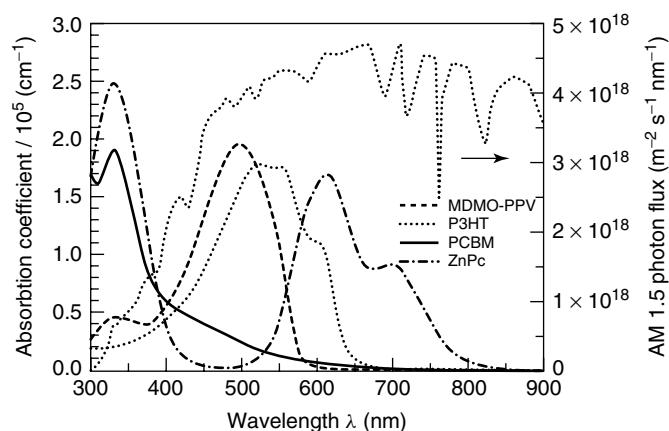


Figure 13 Absorption coefficients of films of commonly used materials are depicted in comparison with the standard AM 1.5 terrestrial solar spectrum. [Reprinted with permission from Ref. 84. Copyright 2007 American Chemical Society.]

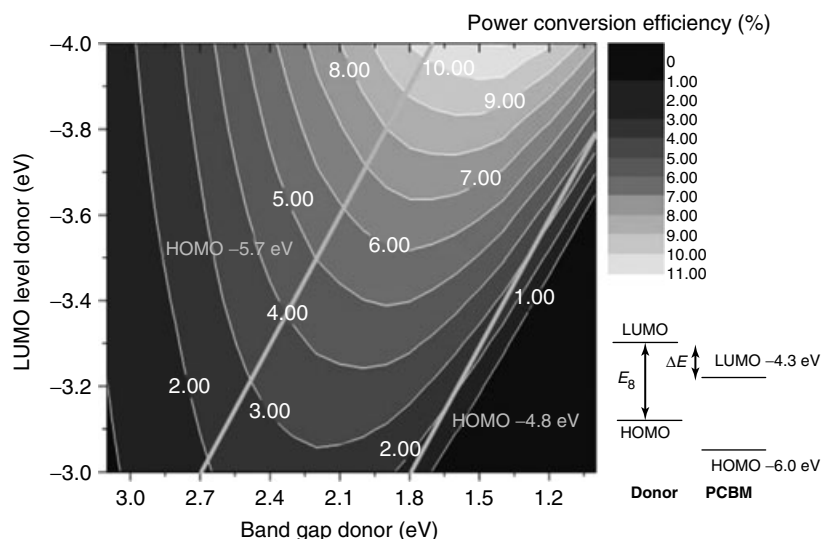


Figure 14 Contour plot showing the calculated energy-conversion efficiency (contour lines and colors) versus the band gap and the LUMO level of the donor polymer according to the model described above. Straight lines starting at 2.7 and 1.8 eV indicate HOMO levels of -5.7 and -4.8 eV, respectively. A schematic energy diagram of a donor PCBM system with the band gap energy (E_g) and the energy difference (ΔE) are also shown. [Reproduced from Ref. 67. © Wiley-VCH Verlag GmbH & Co. KGaA, 2006.]

which could be illustrated by (3). Where e is the elementary charge and using -4.3 eV for the PCBM LUMO energy and the value of 0.3 V is an empirical factor. Then, combining efficient equation (as shown in Figure 3b), the device efficiency can be predicted solely as a function of the band gap and LUMO level of the donor. On the basis of this important finding, and under the assumption of 65% FF and neglecting any contribution from photons absorbed by the fullerenes, they further calculated the expected efficiency as the function of the band gap and the LUMO level of the donor, which is clearly shown in Figure 14. It is clear that if improving the device efficiency of around 10%, the donor materials in BHJ solar cell must meet the requirements with a smaller band gap (<1.74 eV) and an appropriate LUMO level of <-3.92 eV, while this is impossible for the original P3HT just through device fabrication optimization.

$$V_{OC} = \left(\frac{1}{e}\right) (|E^{\text{donor}} \text{HOMO}| - |E^{\text{PCBM}} \text{LUMO}|) - 0.3 \text{ V} \quad (3)$$

The requirements for donor materials described above in polymer-fullerene in BHJ solar cells suggest that development of new polymer systems with low band gap as well as an appropriate LUMO energy level is recently the most promising strategy for the further improvement of device performance. Over the past several years, a large amount of effort has been devoted to this field research and remarkably important progresses have been made. And the highest PCE reported for PSCs is approaching 8%, representing a key breakthrough in PSCs. Figure 15 shows the molecular structures of some representative low-band gap donor materials with PEC $>5\%$ in combination with PCBM characterized in the BHJ solar cell structure.

Poly[2,6-(4,4-bis-(2-ethylhexyl)-4-cyclopenta[2,1-*b*;3,4-*b'*-dithiophene)-alt-4,7-(2,1,3-benzothiadiazole)] (PCPDTBT) is the first low-band gap material with an extremely low E_g of ~ 1.5 eV, corresponding to a wide spectra region to the near infrared spectra (850 nm) and is very suitable for efficient light harvesting charge carrier extraction in PSCs.^{51,85} In the early report, efficiency of up to 3.2% was roughly obtained for PCPDTBT/PC₇₁BM blend BHJ solar cells; however, the devices suffered from short carrier lifetimes and considerable

recombination probably due to the nonoptimized phase separation.⁵¹ With the ideal of incorporating a few volume of alkanedithiols in the blend to optimize the films morphology, Peet *et al.*⁸⁶ further significantly improved the device performance reaching an efficiency of up to 5.5% under 100 mW cm^{-2} together with V_{OC} of 0.62, FF of 0.55, and J_{sc} of 16.2 mA cm^{-2} for PCPDTBT-based solar cell, the values of which was further certified by Konarka by submitting a device to NREL with a return certification of $\sim 5.2\%$ efficiency.

Taking the use of the superior properties for carbazole-based copolymer⁸⁶ and the larger open-circuit characteristics for polyfluorene (PF)-based copolymers in solar cells,⁸⁷ recently many new copolymers based on PF and carbazole groups have been successfully developed.⁸⁸ Interestingly, with N or Si atom replacing the bridging C atom of PF core, not only the efficiency performance but also the thermal stability has been remarkably improved. PCDTBT (as shown in Figure 8) and PSiF-DBT are two of the most representative examples. Under standard measurement condition with AM 1.5 irradiation and light intensity of 100 mW cm^{-2} , the PCDTBT/PC₇₀BM solar cells exhibited high efficiency of approaching 6%, along with J_{sc} of 10.6 mA cm^{-2} , V_{OC} of 0.88 V, and FF of 0.66, this value of results has also been well certified by Konarka with a return back efficiency of 5.96%.⁵³ Similarly, very high efficiency of 5.4% with J_{sc} of 9.5 mA cm^{-2} , V_{OC} of 0.90 V, and FF of 0.51 was achieved for PSiF-DET/PC₆₀BM-based solar cells under AM 1.5 illumination with an irradiation intensity of 800 mW cm^{-2} .⁸⁸ In order to achieve a planar polymer conformation for better chain packing in films with expectation of a positive impact on the charge transport properties, Qin *et al.*⁶⁹ developed another new such kind of copolymer, poly(2-(5-(5,6-bis(octyloxy)-4-(thiophen-2-yl)benzo[*c*][1,2,5]thiadiazol-7-yl)thiophen-2-yl)-9-octyl-9H-carbazole) (HXS-1) just through cleverly tuning the positions of side chains, that is, with two octyloxy chains on the benzothiazole ring and an octyl chain on the carbazole ring. HXS-1 films exhibited highly crystalline nanostructure with a close π - π stacking, facilitating its efficient charge transport with hole mobility of around $0.06 \text{ cm}^2 \text{ V s}^{-1}$ estimated by PFETs.⁸⁹ Relative low band gap as well as excellent charge transport properties together contributed to the high efficiency of up to 5.4% for BHJ solar cells based on HXS-1/PC₇₁BM blend.

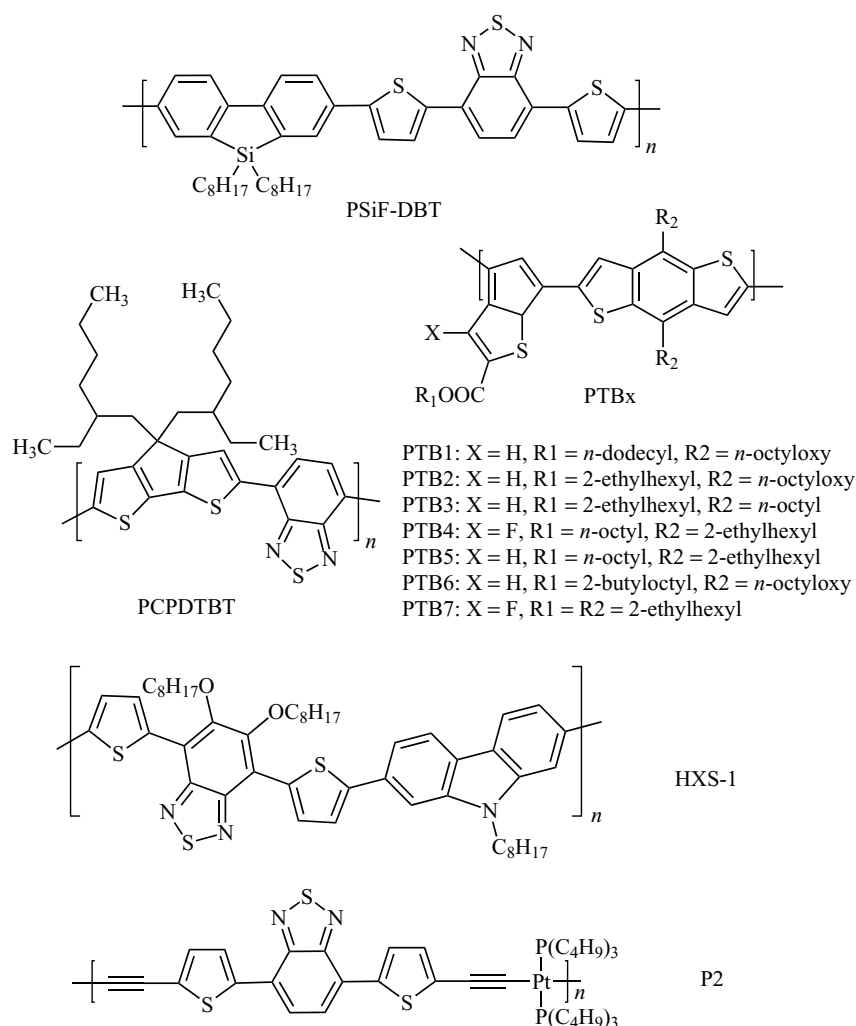


Figure 15 Molecular structures of some representative low-band gap donor materials with PCE > 5% in combination with PCBM characterized in the BHJ solar cell structure.

More recently, Liang and Yu⁶² developed a new class of excellent low-band gap polymers based on thieno[3,4-*b*]thiophene and benzodithiophene alternating units, named as PTBx. These materials have relatively low band gaps (from 1.70 to 1.85 eV) and exhibit efficient absorption throughout the region of greatest photo flux in the solar spectrum (around 700 nm) due to the stabilization of quinoidal structure in the backbone. Additionally, good self-assembly properties for high hole mobility, proper side chains for good solubility and miscibility with fullerene components, and flexible

structure tuning properties for the availability of relatively low-lying HOMO energy levels make this series of materials well fulfill the requirements for high efficient solar cells. Among them, BHJ solar cells based on the blend of PTB7 with PC₇₁BM exhibited unprecedented efficiency of 7.4%, which is also the highest PCE for PSCs reported so far and represents a big breakthrough in developing high-performance PSCs.

Additionally, with the organometallic as the donor materials in photovoltaic devices has also intrigued people's attention in the last decade;

Table 3 Electronic energy levels and the highest photovoltaic performance reported so far for above-discussed low-band gap polymers.

Polymer	E_g^a (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	V_{oc} (V)	J_{sc} (mA cm ⁻²)	FF	PCE ^b (%)	Reference
PSiF-DBT	1.82	-5.39	-3.57	0.90	9.50	0.51	5.4	88
PCPDTBT	1.46	-5.01	-3.55	0.62	16.2	0.55	5.5	86
PCDTBT	1.90	-5.5	-3.6	0.88	10.6	0.66	6.1	53
HXS-1	1.95	-5.21	-3.35	0.81	9.60	0.69	5.4	69
PTB7	1.82	-5.15	-3.31	0.74	14.5	0.69	7.4	22
P2	1.85	-5.37	-3.14	0.80 ± 0.02	15.1 ± 2.2	0.40 ± 0.04	4.8 ± 0.4	92

^aThe optical band gap deduced from their corresponding absorption edges.^bThe device properties were tested with BHJ solar cells based on polymer/fullerene blend system.

however, in the early report, the PCE is absolutely low probably due to the larger band gap and unoptimized device structure.^{90,91} On the basis of the previous studies, Wong *et al.*⁹² recently created a new platinum(II) polyyne polymer based on 4,7-di-2'-thienyl-2,1,3-benzothiadiazole as a core component (P2). By optimizing the fabrication process, the BHJ solar cells containing P1/PCBM blend exhibited the best PCE of approaching 5%, an open-circuit voltage of 0.8 V, and a FF of 0.40, indicating a new concept to apply low-band gap metallated conjugated polymers as the donor materials for high-performance solar cells. The molecular structures of low-band donor materials are shown in Figure 15. A brief summary of electronic energy levels and the highest photovoltaic performance reported so far for the above-discussed low-band gap polymers is presented in Table 3.

4 PROSPECTIVE DEVICE APPLICATIONS

The most attractive advantage for conducting and semiconducting polymers is their feasible solution processing, which makes them offer promising opportunities for a vast array of flexible, low-cost and large-area electronic, and photonic applications, such as organic complementary circuits, display drivers, solar cells, and photodetectors.^{5,9,93} As mentioned above, over the past years, tremendous progress has been made in the development both of PFET and PSC performance, and as high as 1.4 cm² Vs⁻¹ for PFETs or approaching 8% efficiency for PSCs has been achieved, the values of which have already been comparable to that of amorphous silicon devices. However, because of many problems relating to the device stability, device fabrication techniques, and so on, there is

still a large space for PFETs and PSCs to fully realize their commercialization. So, in parallel research of developing high-performing functional polymer materials, many studies from the laboratories and well-known big companies have already started to focus on exploiting their prospective applications in electronics and photonics, especially in terms of optimizing device fabrication processing and lowering the cost. Here, the prospective electronic and photovoltaic applications are presented, representing a promising development in these fields.

4.1 Low-Cost Polymeric Complementary Circuit

OFETs offer potential to form low-cost building blocks for large-area electronic devices, especially on flexible substrate.⁹⁴ Till date, various organic complementary circuits based on small organic molecules have been fabricated through vacuum deposition technique or metal electrodes.⁹⁵ However, from the viewpoint of low-cost, high-performing semiconducting polymers with good solubility are preferable for large-area electronics, even though the mobilities are generally one order lower than their small molecular counterparts.^{5,9,93} Actually, the early all-polymer transistor has come out in 1994, through laying down the semiconducting molecules and electrodes using the disruptive and simple printing technique.⁹⁶ Since, a large amount of effort has been made in integrating the individual all-polymer transistor into fully integrated functional circuits.^{94,97} However, low carrier mobility for polymer semiconductors has significantly hindered switching rate of the complementary logic products. The availability of

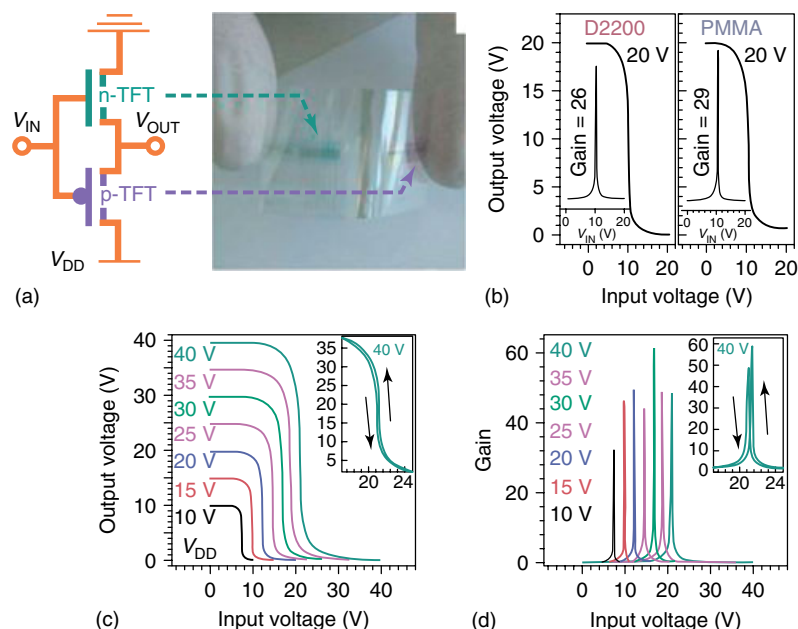


Figure 16 P3HT (p-channel)-P(NDI2OD-T2) (n-channel) complementary inverters. (a) Schematic electrical connections of the inverters, and optical image of the gravure-printed device before common gate deposition. (b) Static switching characteristics of the inverter where both the semiconductors and the indicated dielectrics are gravure-printed (insets, gain of the corresponding device). Red (forward) and black (reverse) scans. (c) Static switching characteristics of a spin-coated inverter based on poly(methyl methacrylate) (PMMA). (d) Gains of the corresponding spin-coated devices. Insets in (c) and (d) are expanded views with the same axes as the main plots. [Reproduced from Ref. 58. © Nature Publishing Group, 2009.]

high-performing n-type polymer semiconductor, P(NDI2OD-T2) provides the potential to form high-performance complementary all-polymer inverters. Additionally, P(NDI2OD-T2) also exhibits a very good chemical stability, large solubility in common organic solvents as well as feasible processing with versatile inexpensive techniques, such as gravure, flexographic, and inkjet printing. Figure 16 shows the static switching characteristics of all-polymer P3HT (p-channel)-P(NDI2OD-T2) (n-channel) complementary inverters through different fabrication processing and as high as 25–60 voltage gains were demonstrated, providing promising opportunities for high-performing flexible, large-area plastic electronics.⁵⁸

4.2 Roll-to-Roll Technique for Plastic Solar Cells

In another parallel research, much efforts have also been made in driving PSCs to their commercialization, especially in terms of the

operation stability in a large-scale, cost analysis for whole fabrication process as well as versatility of techniques, and so on. In this field, Krebs and his colleagues have made important contributions to the development of feasible, effective solution-processing methods.^{98,99} More recently, Krebs has developed a roll-to-roll process technique for monolithic large-area PSCs, which is free from the indium-tin-oxide electrode and significantly reduces (lowers) the processing costs compared to other fabrication techniques (as shown in Figure 17). In this process, a commercially available kapton foil with an overlayer of copper was used as the substrate. First, by sputtering of titanium metal onto the kapton/copper in an R2R vacuum process gave the monolithic substrate and back electrode for the devices. Then, the active layer was slot-die coated onto the kapton/Cu/Ti foil followed by slot-die coating of a layer of PEDOT:PSS. Importantly, no patterning of the first four layers was necessary and only the final front electrode required a pattern. The front electrode was applied by screen printing a protective layer in the areas

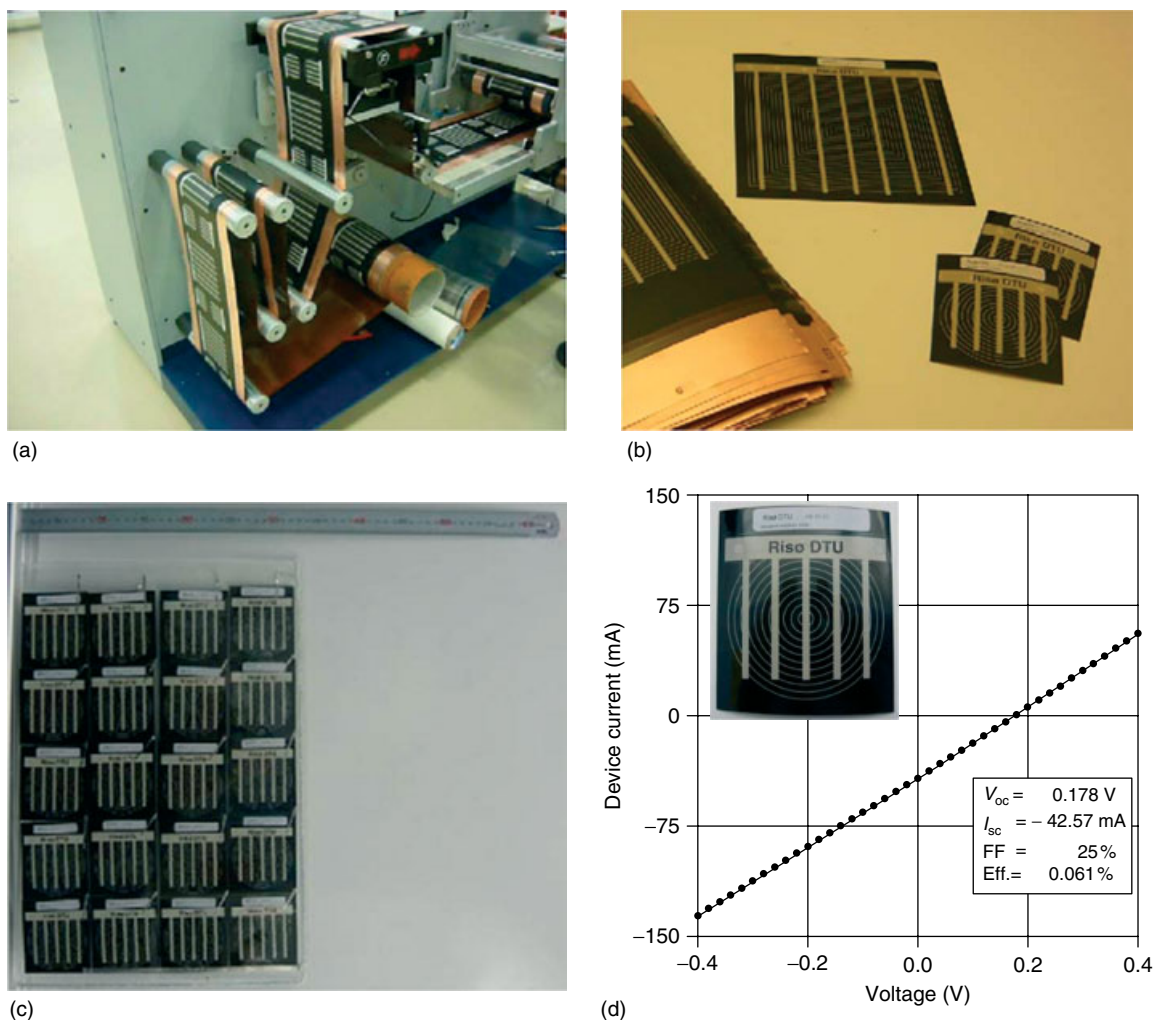


Figure 17 (a) R2R lamination of the modules and (b) a picture of the modules when cutting into sheets and final cells. (a) The large cell has nominal outside dimensions of 150×150 mm and the small cells have nominal outside dimensions of 70×70 mm. (c) A 4×5 array of the 70×70 mm² cells (the scale bar is 64-cm long with divisions every 10 cm). (d) Typical I - V curves for one of the 7×7 cm cells when illuminated through a 7×7 cm mask. [Reproduced from Ref. 99. © Elsevier, 2009.]

for front electrode contacts and a firetec silver grid was applied by screen printing. The topology of the device and the choice of fin grid electrode geometry allowed for serial connection of the individual cells into modules. The individual cells were as large as 150×150 mm. Through this method, as high as 74% FFs was achieved for the produced PSCs, which is much higher than that is readily achieved using serially connected cells on the same substrate, indicating its promising applications after further improvement in terms of volume and speed, device efficiency, supporting

temperature, as well as limitation. Anyway, it is a breakthrough in technology for PSCs.

5 CONCLUSION

In conclusion, with the significant effort, the performance of PFETs and PSCs has received great progress and has already been comparable to amorphous silicon in laboratory experiment and the small prototype device. However, to realize

their real commercialization, further development in both high-performing functional materials and optimization of various flexible and effective techniques is needed. Especially, in technology, significant effort to effectively integrate the discrete device to complex circuit is required. The device's operational stability and lifetime need to be improved and the fabrication costs have to be lowered. Anyway, polymeric electronics and photovoltaics are beginning to show us their significant potential and the bright future in low-cost, large-area, especially on flexible substrate applications.

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Silicon Radical Surface Chemistry

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1 INTRODUCTION

Radical chemistry is the method of choice for the preparation of numerous organic molecules and polymers, as well as inorganic complexes. It has also found its way into the area of surface science. In particular, the radical chemistry of silicon surfaces has attracted much attention because of the relative ease of application, that is, mild reaction conditions, high chemo- and regioselectivity, and the absence of metal catalysts, with no formation of by-products.^{1–4} This article reviews the different aspects of the radical chemistry involved in making organic monolayers on silicon surfaces, specifically Si–C-linked monolayers.

Ever since the development of the first integrated circuit in 1958, the demand for novel semiconductor-based electronic devices with ever-smaller dimensions has been continuously increasing. Silicon and germanium are the preferred metalloids because of their semiconductor properties and tunable electron mobility, and current state-of-the-art devices have reached feature sizes below 30 nm. As a consequence, the impact of surface effects is becoming increasingly important.^{2,3,5} The surface chemistry associated with these semiconductors, silicon in particular, has been explored as a potential means toward the fabrication of molecular electronic devices.^{6,7} For many sensitive electronic applications, however, it is also important that the silicon surface remains oxide-free.^{8–10} Silicon oxide acts as an insulator, and a thin layer of oxide on top of

a silicon-based electronic device prevents direct electronic contact between the organic functionality and the substrate, thereby reducing the signal intensity. Controlling the nature of the surface can be achieved in a number of ways, of which the attachment of self-assembled monolayers (SAMs) may be considered the most sophisticated.^{11–15} Such monolayers allow for the precise attachment of (bio)molecules and the subsequent detection of their counterparts. Moreover, high-quality SAMs may also prevent oxygen and water from reaching the surface, thereby improving the lifetime and robustness of such sensing devices.

Whereas the familiar SAMs on gold¹⁶ are mostly based on the reversible gold–thiol bond, SAMs on silicon are covalently attached to the surface.^{2,3,5} In effect, obtaining high-quality monolayers is not trivial. Siloxane-based SAMs are commonly applied in order to attach functional molecules onto silicon substrates in a rapid way, but these bonds are prone to hydrolysis and do not provide for oxide-free silicon substrates.^{17–20} The use of monolayers based on silicon–carbon bonds offers an exciting alternative. Si–C bonds are known to be both thermally and chemically robust because of the low polarity of this strong bond. This is essential for the formation of well-defined, highly stable, and robust organic monolayers on silicon.^{2,21}

In this article, various methods for the preparation of organic Si–C monolayers, including relevant issues concerning oxidation of the silicon surface, are presented. The radical mechanisms at the silicon surface based on experimental and

theoretical studies are discussed. In addition, the importance of high-quality oxide-free monolayers on silicon surfaces, as well as the introduction of functional groups to the monolayer, is addressed. Finally, applications and future research are presented, describing the main remaining challenges.

1.1 Silicon Surfaces

Two types of silicon are most commonly used: flat (single crystal) and porous silicon surfaces. The most widely employed type is flat silicon because of the variety of orientations possible, the possibility of adding dopants in a controlled manner, and commercial availability.^{1,22,23} The most common surface orientations are Si(100) and Si(111). Freshly cut surfaces are rapidly coated with a thin native oxide layer upon exposure to air.

The initial step in the formation of organic monolayers on silicon involves what may be called an *activating passivation of the silicon surface*, which opens up the surface reactivity to only a selected series of desirable reactions. In general, hydrogen is the most commonly employed passivating agent²⁴; however, halogens such as iodine and chlorine have also been investigated.^{25,26} Oxide-free, hydrogen-terminated silicon surfaces may be obtained via the adsorption of atomic hydrogen under ultrahigh vacuum (UHV) conditions at elevated temperatures ($>1100^{\circ}\text{C}$).²⁷ Alternatively, wet-chemical reactions using fluoride-containing solutions yield hydrogen-terminated silicon surfaces under rather mild conditions (i.e., ambient temperature and pressure). Important features of these hydrogen-terminated silicon surfaces include their high chemical homogeneity ($>99\%$ H-termination), their relative stability in air and water during brief rinsing procedures, and their low reactivity toward several organic solvents.^{21, 28–31} Treatment of Si(100) surfaces with dilute aqueous HF (1–3%) yields predominantly dihydride-terminated Si(100) surfaces that display nanometer-scale roughness (Figure 1).²⁹ However, mono- and trihydride orientations are also present. The preparation of mono- and dihydrated atomically flat surfaces is possible only by employing UHV techniques. Recently, Hines and coworkers used scanning tunneling microscopy (STM) and Fourier transform infrared spectroscopy (FTIR) to demonstrate that

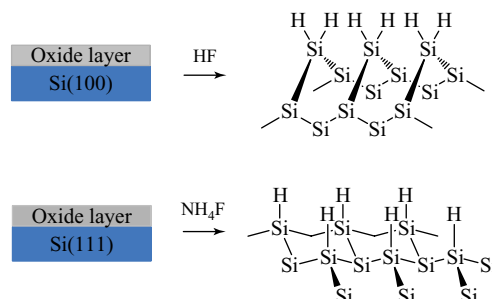


Figure 1 Preparation of hydrogen-terminated Si(100) and Si(111) surfaces by chemical etching in fluoride-containing solutions.^{28,29,32,33}

an aqueous solution of NH₄F (40%) selectively passivates Si(100) surfaces, eventually producing a hydrogen-terminated surface of near-atomic flatness.³²

Conversely, after only a brief immersion of the Si(111) surfaces in degassed aqueous NH₄F solution (40%), atomically flat surfaces, nearly exclusively occupied by Si–H groups, are readily obtained (Figure 1).^{28,29} The roughness of the surface has been studied by STM and FTIR spectroscopy. The attenuated total reflection-FTIR (ATR-FTIR) spectra of the hydrogen-terminated Si(111) surface show a very sharp and narrow silicon–hydrogen stretching vibration $\nu(\text{Si–H})$ at 2083.7 cm^{-1} , indicating a high degree of chemical homogeneity, while the STM image of the silicon surface shows atomically flat terraces with monoatomic steps (Figure 2).

In addition, the etching mechanism has been resolved on the basis of *in situ* STM and electrochemical measurements. Etching involves two components: one chemical and the other electrochemical; both are highly dependent on pH.^{34,35} Other passivating agents can be employed, such as HF and NaOH; however, these treatments lead to increased surface roughness, as well as the formation of mono-, di-, and trihydride-terminated Si(111) surfaces.^{36,37}

Other silicon surfaces, such as porous silicon, are also of great interest owing to their luminescent properties and high surface area.³⁸ These surfaces are prepared from crystalline silicon substrates (mainly Si(100)) using chemical or electrochemical methods. Surfaces typically consist of $-\text{SiH}_3$, $=\text{SiH}_2$, and $-\text{SiH}$ groups in different orientations and environments. Over the last few years, porous silicon has attracted much attention as a

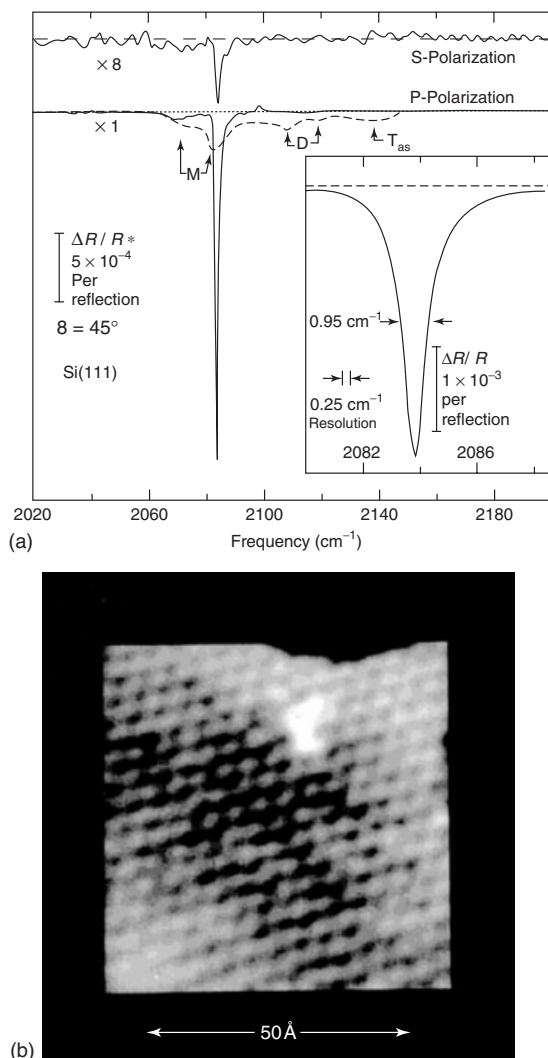


Figure 2 (a) ATR-FTIR spectra of the hydrogen-terminated Si(111) surface, prepared through the 40% NH_4F (aq) etching procedure, taken with both s- and p-polarized IR light. (b) STM image of the flat Si(111)-H surface, prepared through etching with 40% NH_4F (aq). The gray scale represents a height change of 0.5 Å. [Reprinted with permission from G. S. Higashi, R. S. Becker, Y. J. Chabal, A. J. Becker, *Appl. Phys. Lett.*, **58**, 1656–1659, (1991). Copyright 1991, American Institute of Physics; and G. S. Higashi, Y. J. Chabal, G. W. Trucks, K. Raghavachari, *Appl. Phys. Lett.*, **56**, 656–659, (1990). Copyright 1990, American Institute of Physics.]

platform for biomolecules.³⁹ The refractive index can be tuned, turning the substrates into photonic devices,⁴⁰ which can be subsequently modified by the attachment of complex biomolecules.^{39–42}

1.2 Oxidation of Silicon Surfaces

The oxidation of hydrogen-terminated silicon surfaces has been studied in detail.⁴³ However, the mechanism has still not been completely unraveled. Currently, the most accepted mechanism involves a radical route, analogous to the auto-oxidation of tris(trimethylsilyl)silane $(\text{TMS})_3\text{SiH}$ or TTMSS (see **Silanes as Reducing Reagents in Radical Chemistry**).⁴⁴ In this mechanism, molecular oxygen reacts with a surface-centered radical (surface **1**) to form the peroxy radical **2** (Figure 3).

This radical either abstracts a neighboring hydrogen, leaving a dangling bond at the surface (**3**), which may either react again with oxygen, or splits up under insertion of oxygen into a silicon backbond inside the surface (**4**). In the latter case, the silyloxy radical may abstract a hydrogen atom, resulting in a silanol group (surface **5**). Alternatively, this oxygen may be inserted in an available silicon backbond, resulting in surface **6**, the analog of which has been observed when TTMSS was employed in a model study.²³ Both situations result in the formation of dangling bonds at the surface which are prone to attack by oxygen.

The radical mechanism of oxidation of silicon surfaces was further investigated by FTIR.⁴³ The H-Si(111) surfaces were exposed to air, either in the dark or under irradiation at specific wavelengths. The intensity of the Si-H stretching vibration did not decrease significantly in the dark, or upon irradiation using 450-nm light. This is in agreement with the energy required for homolytic cleavage of Si-H bonds, which was found to be 84 kcal mol⁻¹,⁴⁶ requiring irradiation at wavelengths below 350 nm. This was further confirmed by a small decrease in signal observed upon irradiation at this wavelength, which is as expected, because 350 nm is apparently just barely enough for photolysis. Dramatic loss of the Si-H signal was observed upon irradiation at 254 nm, indicating that oxidation of the surface involves such homolytic cleavage of the Si-H bond. Interestingly, oxidation of porous silicon initially leaves the Si-H bonds intact, which shows that oxygen directly attacks the Si-Si bonds. FTIR spectra taken after irradiation of a freshly etched porous Si sample in the presence of oxygen ($\lambda = 365$ nm, 60 minutes) show a large increase of the silicon oxide band ($\nu_{\text{Si-O}}$ between 1000 and 1200 cm⁻¹) and a correspondingly loss of the

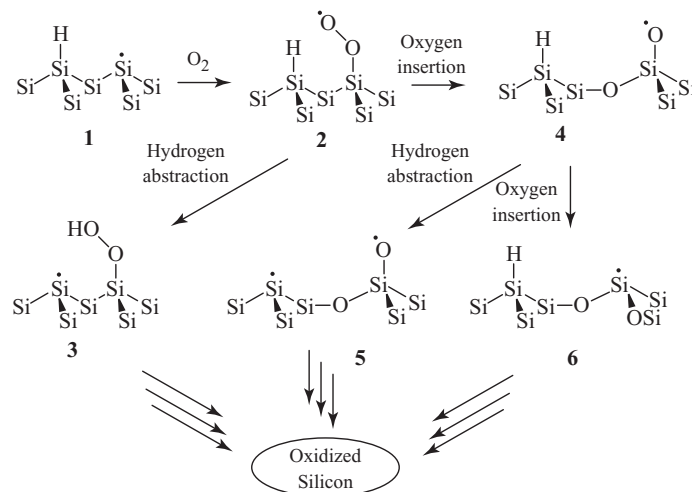


Figure 3 Oxidation of the hydrogen-terminated Si(111) surface.⁴⁵

SiH_2 signal ($\nu_{Si-H_2} = 2116\text{ cm}^{-1}$). However, the growth of the ν_{O-Si-H} band (2200 cm^{-1}) equals the loss of the SiH_2 signal, resulting in no net loss of the surface hydride species.⁴⁷ This difference in reactivity—which may be a reflection of slightly changed thermodynamics related to the surface structure of porous Si—also likely has consequences for the attachment of hydrocarbons to this substrate, via the occurrence of other reaction mechanisms.

2 RADICAL CHAIN PROPAGATION

Alkyl monolayers grown on appropriately prepared hydrogen-terminated Si(111) typically reflect the atomic flatness of the underlying silicon substrate. Several studies have focused on methods of chemical passivation of silicon through

formation of Si–C bonds.^{2,3,20,48} Hydrosilylation of alkenes or alkynes has been achieved via radical initiation,⁴⁹ thermally,^{49,50} or photochemically induced,^{43,51–53} or by utilizing Lewis acid catalysts.^{54,55} The first example of wet-chemical preparation of covalently attached organic monolayers on silicon surfaces, without an intermediate oxide layer, was reported in 1993 by Linford and Chidsey.⁵⁶ The carbon chains were bound to the hydrogen-terminated silicon surface via a radical reaction. Diacylperoxide is cleaved by pyrolysis (100°C) to form carbon-centered radicals (and CO_2), which abstract hydrogen from the surface, yielding surface-centered radicals (Figure 4). These silicon radicals in turn react with the abundantly present alkyl radicals to form stable Si–C bonds. As a result, densely packed monolayers were obtained, which showed good resistance to boiling chloroform, acids, bases, and even treatment with HF.

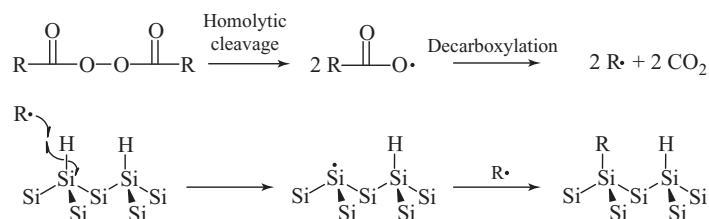


Figure 4 Formation of alkyl radicals from diacyl peroxide.

2.1 Attachment of Alkenes to Silicon Surfaces

Addition of alkenes and alkynes to silyl radicals was reported as early as 1947.^{57–59} This reaction proved very useful in the synthesis of organosilicon compounds (specifically from trichlorosilanes). Because of their reactivity toward silyl radicals,⁶⁰ alkenes and alkynes were used in a follow-up study on monolayer formation on silicon. Indeed, these compounds yielded high-quality monolayers in the absence and presence of various concentrations of diacyl peroxide. Deuterium labeling of the peroxide demonstrated that the attachment of unsaturated carbon chains is preferred over attachment of alkyl radicals stemming from diacyl peroxide. Moreover, at higher temperatures ($>150^{\circ}\text{C}$), dense monolayers were also obtained from alkenes in the absence of diacyl peroxide.⁴⁹ Formation of surface radicals was explained by either homolytic cleavage of the Si–H bonds or reaction with adventitious oxygen. As is known from the literature, radical addition to a double or triple carbon–carbon bond results in the formation of a β -carbon radical.⁶¹ This radical subsequently abstracts a hydrogen atom, either from unreacted olefin in solution or from an adjacent Si–H site. However, the latter is preferred, owing to the lower bond dissociation energy of 84 kcal mol^{-1} for Si–H⁶² in comparison to the terminal C–H bond in alkenes and alkynes (101 and 111 kcal mol^{-1} , respectively⁶³); this finally results once more in a surface-centered radical. Chidsey and coworkers proposed a radical chain reaction, which is depicted in Figure 5.⁴⁹ The feasibility of hydrogen transfer from the surface to the alkyl chain was later demonstrated on porous silicon by the group of Buriak.⁶⁴ After attachment of perdeuterated styrene to a hydrogen-terminated surface, they observed methylene vibrations at 2917 and 2846 cm^{-1} according to FTIR corresponding to consumption of Si–H sites.

Additional evidence for the radical propagation reaction was obtained from STM studies performed

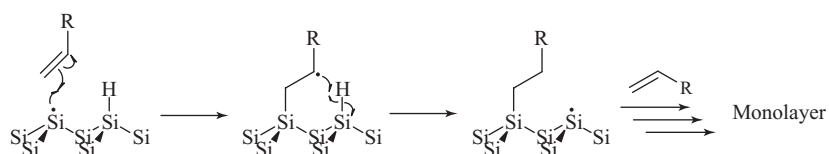


Figure 5 Reaction mechanism of the addition of 1-alkenes to hydrogen-terminated Si(111), as proposed by Chidsey and coworkers.^{49,65}

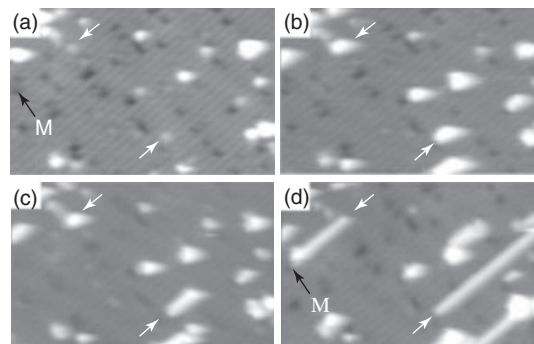


Figure 6 Growth of styrene lines on a hydrogen-terminated Si(100) surface with a small number of single Si dangling bonds. A sequence of STM images is shown for prolonged exposure to styrene: 3 L (a), 28 L (b), 50 L (c), and 105 L (d). White arrows denote two particular dangling-bond sites, leading to growth of long styrene lines. The missing dimer defect (marked M) terminates line growth in the top left-hand corner of the image. [Reprinted by permission from Macmillan Publishers Ltd: Nature (Ref. 66), copyright (2000).]

under UHV on Si(100). To this purpose, dangling bonds (basically surface-centered silyl radicals) were created at the surface with an STM tip, which subsequently were exposed to styrene. STM showed lines of attached styrene molecules growing from these dangling bonds (Figure 6).⁶⁶ Growth of these lines halted at surface defects, supporting the proposed hydrogen abstraction mechanism. The observed pattern originates from the geometry of the hydrogen-terminated Si(100) surface, which consists of parallel-aligned SiH₂ sites, as shown in Figure 7.

Further evidence for the radical propagation mechanism was provided by Wolkow and coworkers, who studied the attachment of styrene on Si(111) with STM (Figure 8).⁶⁵ In this case, the reaction of styrene with dangling bonds at the surface led to the formation of islands. This indicates unidirectional growth of the monolayer, dictated by the geometry of the surface. The

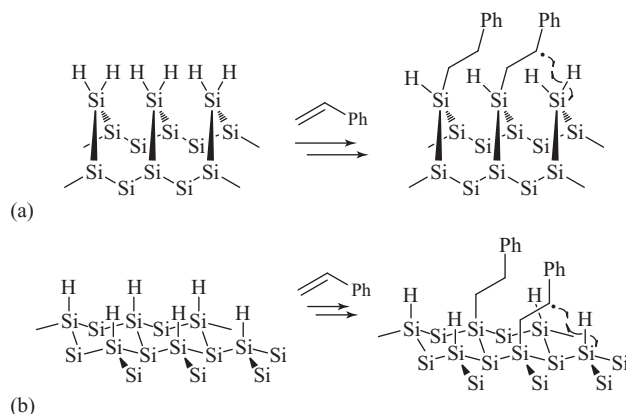


Figure 7 Styrene attachment onto hydrogen-terminated silicon surfaces: (a) Si(100); (b) Si(111).

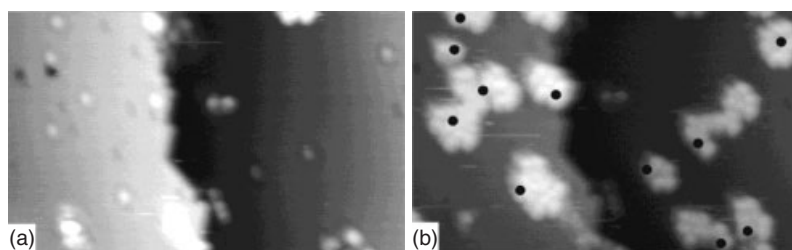


Figure 8 Occupied-state STM images of a hydrogen-terminated Si(111) surface with isolated dangling bonds created by desorption activated by STM tip: (a) before dosing with styrene and (b) after exposure to 12 langmuirs of styrene. The black dots in (b) mark the positions of the initial dangling bonds, showing that these sites serve to nucleate the growth of styrene islands. [Reproduced from Ref. 65. Copyright American Chemical Society, 2002.]

hexagonal array of Si–H sites on atomically flat terraces provides for six equivalent Si–H sites near any starting Si–H site at the surface. From a single alkylation site, the reaction thus propagates via one of these available Si–H sites, in six possible directions, as observed in Figure 7. This chain reaction was found to be self-limiting, and is proposed to terminate when no neighboring hydrogen atom is available for abstraction by the alkyl radical, for instance, because of the chain running into itself. Additional studies performed by Zuillhof and coworkers, based on alkyl monolayers fabricated from alkenes via white-light-induced reaction, showed that island formation on Si(111) is generic for this kind of reactions, and is thus neither specific for styrene nor requires the use of an STM tip to induce a radical reaction.⁶⁷ Monte Carlo simulations showed that, on average, 76 chains attached to the surface before the chain reaction terminated.⁴³

2.2 Surface Reactions of Vinyl Radicals

The attachment of alkyne moieties to the surface form a special case, since the resulting product, which is obtained after addition and subsequent hydrogen transfer, is an alkenyl group. This unsaturated carbon is able to react again with a neighboring silyl radical, forming bridged Si–C–Si or Si–C–C–Si structures.⁶⁸ This reaction competes with the hydrosilylation of alkyne molecules present near the surface; this would then leave alkenyl chains at the surface (Figure 9, reaction a). However, alkyne monolayers on Si(100) did not show the presence of double bonds (no absorption between 1500 and 1700 cm^{−1} according to ATR-FTIR studies), indicating saturation of the alkyl chains. There are two additional possibilities for double attachment of alkynes, as depicted in Figure 9 (routes b and c).⁶⁸ The first route involves the formation of a 1,2-bridged structure

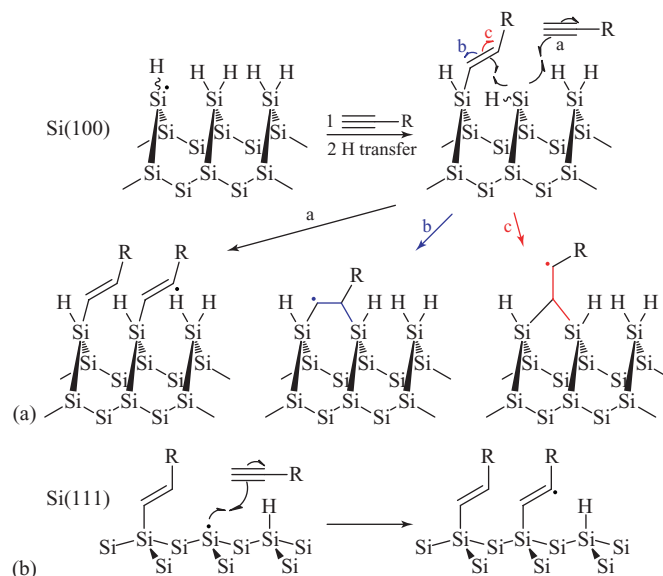


Figure 9 Reaction of alkynes with silicon surfaces: (a) Si(100); (b) Si(111).

obtained after reaction of the β -carbon in the double bond with the surface radical, resulting in a seven-membered ring (route b). Attachment via the α -carbon (route c), on the other hand, follows an anti-Markovnikov mechanism resulting in a six-membered ring. Route a is less favorable, since it does not follow for anti-Markovnikov type of addition, which is typically observed in reactions of silyl radicals.⁶¹ In addition, this route leads to the formation of a seven-membered ring, which is less favorable than a six-membered ring. The high strain is mainly located on the Si–C and C–C bonds, as the silicon atoms are constrained within the crystal lattice. Moreover, density functional theory (DFT) calculations confirmed that 1,1-bridged species are 5–7 kcal mol^{−1} lower in energy than 1,2 conformations.⁶⁸ It is important to note that both attachment modes are expected, since the energy differences are easily overcome at the high temperatures employed in these experiments. The characteristics of these alkyne-derived monolayers differ from those of alkene-derived monolayers prepared under these circumstances on H–Si(100) with respect to the tilt angles, which are on average higher for alkyne-derived monolayers (40°, 27°, and 33° for C12, C16, and C18-alkynes, as compared to 32°, 39°, and 18° for the alkene-analogs). For the more recently developed reactions that take place under milder conditions on H–Si(111),⁶⁹ precisely

the opposite is observed, pointing to the idea that attachment in those cases indeed only involves the terminal carbon atom, while here several bonding schemes are simultaneously operative (see Section 3.3.3).

On Si(111) surfaces, double α -attachment is unlikely, since the resulting bridged structure would form a highly strained four-membered ring. On the other hand, β -attachment would yield a five-membered ring, which is significantly lower in energy than the four-membered ring, though still too high in energy to form. Mono-attachment of alkynes as depicted in Figure 9b is therefore considered to be predominant. The presence of a C=C double bond in alkyne-derived monolayers on Si(111) was demonstrated by FTIR spectroscopy (C=C stretch at 1600.8 cm^{−1})⁴⁹ and by infrared reflection absorption spectroscopy (IRRAS) (C=C stretch at 1601 cm^{−1}).^{69,70}

2.3 Siloxyl Monolayers

Siloxyl monolayers are generally prepared by reacting chlorosilanes⁷¹ or trialkoxysilanes^{72–74} with an oxide-covered silicon surface. However, as a result of the poorly defined underlying silicon oxide surface, the resulting monolayers are less uniform than

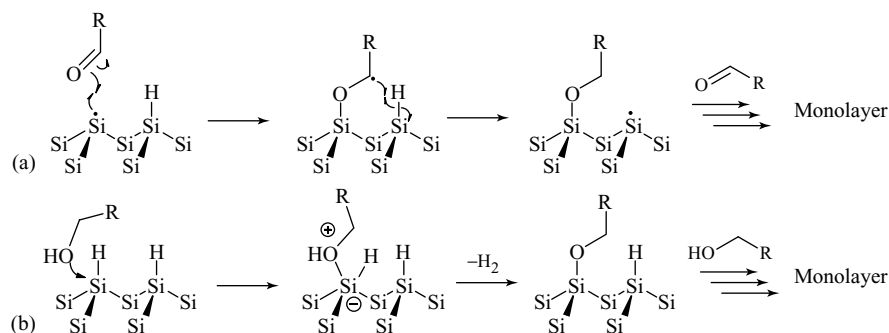


Figure 10 Formation of siloxyl monolayers from (a) aldehydes and (b) alcohols.

alkyl monolayers linked via Si–C bonds. Several groups have reported solutions to this problem by attaching α -alcohols^{75–77} or aldehydes directly onto oxide-free silicon.^{76–79} Although both moieties lead to the formation of Si–O–C linkages, the mechanisms of formation are entirely different. The attachment of a carbonyl moiety to the silicon surface is expected to proceed via a very efficient radical chain mechanism, similar to the reaction with unsaturated alkyl chains (Figure 10a). In the case of alcohols, attachment is likely to proceed via nucleophilic attack of the OH group to the silicon, leading to a pentavalent silicon intermediate. Subsequent release of di-hydrogen results in oxidative addition. Attachment via this pathway does not lead to the formation of a new reactive site, as is the case in the radical chain mechanism. This mechanism is consequently less efficient, resulting in an overall slower and incomplete monolayer fabrication, as elegantly shown for the attachment of methanol to Si(111) upon prolonged heating at elevated temperatures (65 °C, 12 hours), which leads to partial coverage of the surface (max. 33% of available Si–H sites).⁸⁰

2.4 Competing Reactions by Halogen Impurities

Neat alkenes and alkynes may easily contain traces of the starting material such as bromo or chloro alkanes. From the experiments performed by Chatgililoglu and coworkers, it is known that silyl radicals can react very fast with such halocarbons (see **Silanes as Reducing Reagents in Radical Chemistry**). The rate of reaction of a primary alkyl bromide toward the TTMSS radical

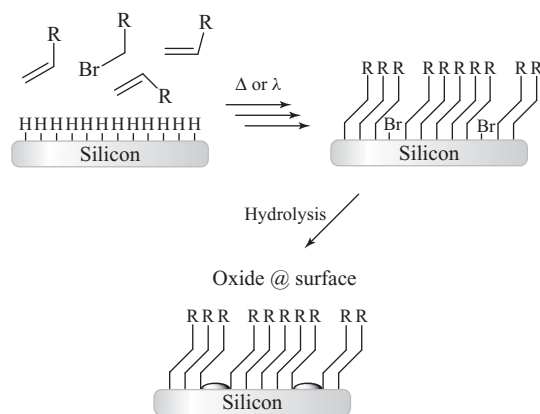


Figure 11 Bromine impurities in the reaction mixture lead to the formation of Si–Br, causing holes in the monolayer. Furthermore, the surface-bound bromine is susceptible to hydrolysis, leading to oxidation of the surface.

is in the order of 10^7 s^{-1} , whereas the chlorides react much slower (10^5 s^{-1}).⁸¹ The reactivity of bromine compounds easily overshadows that of aldehydes, alkenes, and alkynes, which are in the range of 10^4 – 10^6 s^{-1} . Traces of bromoalkanes present in the reaction mixture lead to holes in the monolayer (Figure 11). These Si–Br sites are susceptible to hydrolysis, resulting in oxygen bound to the silicon surface, which, for certain applications, is undesirable and decreases monolayer stability.

The reactivity of silyl radicals toward chlorocarbons is much lower (as described above), and lies within the range of those of aldehydes and alkenes. This may explain the fact that traces of chlorine compounds are typically not a big problem in monolayer formation. Even at a higher

concentration of such chlorine compounds present in the reaction mixture, no significant chlorination of the surface was observed.^{49,82} It is, in fact, quite possible to make chlorine-terminated carbon monolayers ($\text{Si}-(\text{CH}_2)_n-\text{Cl}$) from chlorine-containing compounds such as 1-chloroundecene, and such Cl termination was reported to be of good quality.² However, when high-quality oxide-free surfaces are required, chlorine traces still may cause undesired holes in the monolayer, which may facilitate oxidation.

3 FORMATION OF SURFACE-CENTERED SILYL RADICALS

3.1 Thermal Attachment

As previously mentioned, initial experiments demonstrated that monolayer formation also takes place at elevated temperatures ($>200^\circ\text{C}$) with linear alkenes C_nH_{n+2} ($n = 12\text{--}20$), and does not require the use of peroxides.⁴⁹ Zuilhof, Sudhölter, and coworkers showed the formation of high-quality alkene monolayers on silicon by employing a solution of alkene (2.5%) in toluene or mesitylene.³¹ The use of alkene solutions signifies a reduction of the amount of material required per wafer (40-fold), and allows the use of solid alkenes. This thermal method for monolayer formation on silicon is fast, yields high-quality monolayers, and is relatively easy to employ. However, owing to limitations in the thermal budget, the required temperatures limit the application of this method in ultrasmall integrated circuit (IC) manufacturing.² In addition, the direct attachment of functional alkenes and complex molecules may lead to the formation of side products, or (to a varying degree) result in the so-called upside-down attachment (Figure 12), drastically influencing monolayer quality (i.e., density and uniformity). Typically therefore, these complex molecules are attached to a prefunctionalized surface. These procedures will be explained in more detail later. Side reactions may slow down the monolayer formation, resulting in incomplete layers. The occurrence of bare patches on the surface has major consequences for the monolayer stability, since these patches are not protected against oxidation.

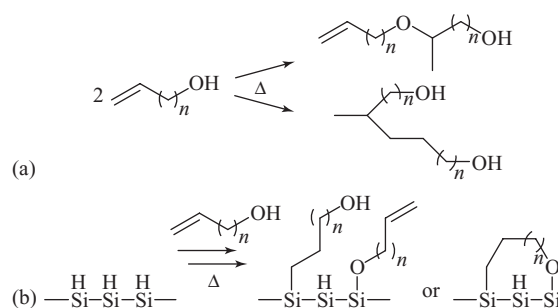


Figure 12 (a) Side reactions of functional molecules as a result of high reaction temperatures; (b) undesired reactions at the surface and upside-down attachment and bridge formation.

3.2 UV Attachment

In the search for milder reaction conditions for the attachment of alkenes and alkynes, the use of UV irradiation was considered. Early work of Chidsey and coworkers already showed that UV irradiation of Si(111) and Si(100) surfaces resulted in direct cleavage of the Si–H bond.⁴³ In their study, they found that the drastically enhanced formation of SiO_2 as observed by X-ray photoelectron spectroscopy (XPS) coincided with a decrease in Si–H signal at 2112 cm^{-1} in FTIR. A range of alkenes and alkynes was successfully attached to the surface, yielding monolayers of comparable quality as those obtained via thermal reaction. This UV method has several advantages over thermal attachment, such as significantly lower input of the thermal energy required, as these reactions are performed at room temperature without increase of reaction times. Considering the aforementioned thermal budget, this method is very suitable for the IC manufacturing industry.² Arguably, the most important advantage is the ability to direct photopattern the surface. The use of a mask allows local irradiation, and thus local monolayer formation, as shown in Figure 13. This was demonstrated by the selective functionalization of H–Si(111) with octadecanal using UV irradiation through a mask ($\lambda = 385\text{ nm}$).⁷⁸ The remaining unmodified patches were shown to still be reactive by attaching 1-octadecene in a following step. The different wettabilities of the monolayer-covered areas and the uncovered silicon areas were observed under a microscope.

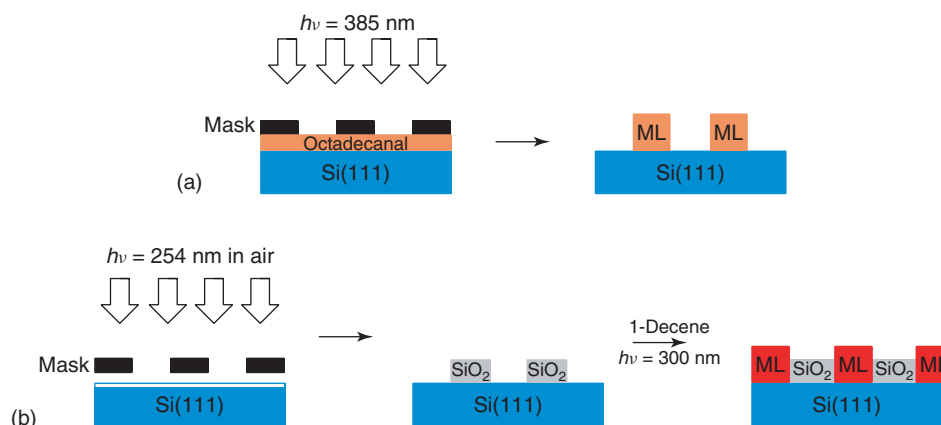


Figure 13 (a) Direct patterning via monolayer formation.⁷⁸ (b) patterning of oxide layer and subsequent filling of unmodified patches with a monolayer from 1-octadecene.⁸³

Interestingly, Wayner and coworkers successfully demonstrated the opposite approach by selectively oxidizing the silicon surface by irradiating through a mask under ambient atmosphere (Figure 13b). This resulted in oxidized, nonreactive patches, and nonirradiated reactive patches.⁸³ After growing a monolayer on the reactive patches, a pattern containing hydrophobic and hydrophilic domains was obtained, which was observed by scanning electron microscopy (SEM) and scanning auger electron microscopy (SAES), (Figure 14).

Side reactions also occur during UV-initiated monolayer formation. Photolysis of functional moieties may occur, and upside-down attachment has also been demonstrated, similar to the thermal methods.⁸⁴ Moreover, prolonged UV irradiation may cause cleavage of the Si–C bonds, resulting in degradation of the newly formed monolayers. This has also been observed for monolayers on porous silicon.^{55,85}

Bedzyk and coworkers have reported that, upon reaction with undecenoic acid bromoethyl ester, less than 10% of the ester was attached via the alkene moiety while retaining the bromine (Figure 15, A).⁸⁴ For the remaining sites, up to 50% reacted with bromine (B), 27% reacted with debrominated ester (C), and 13% showed upside-down attachment (D). Again the usefulness of these reactions depends on the application of the monolayer. When the function of the monolayer is simply to serve as a scaffold layer, and the resulting packing density and presence of surface oxides are not important, this method provides a fast and easy way to obtain such a layer.

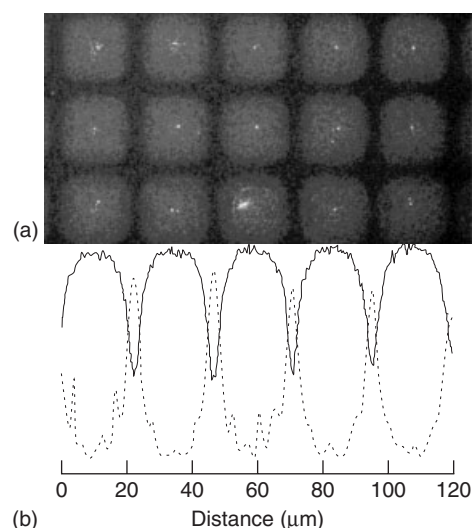


Figure 14 (a) SEM picture of a surface patterned by oxide and monolayer patches; (b) SAES line-scan of the modified surface depicting the relative abundance of carbon (dashed) and oxygen (solid) as a function of distance. [Reprinted with permission from Ref. 83. Copyright 2001 American Chemical Society.]

An alternative mechanism to the UV-induced cleavage of Si–H bonds was recently reported by Hamers and coworkers.⁵¹ They argue that UV irradiation leads to electron donation from the silicon surface into the acceptor levels of carbon–carbon double bonds present near the surface. This leaves a positive charge on the surface, in the form of a silyl cation, which is susceptible to nucleophilic attack (Figure 16). Attack of an alkene on this surface

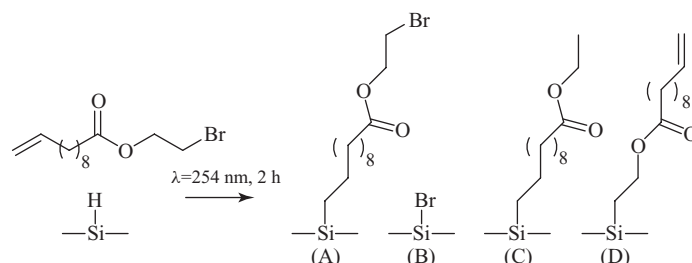


Figure 15 UV attachment of undecenoic acid bromoethyl ester to silicon, resulting in normal attachment (A), bromination of the surface (B), normal attachment of a debrominated alkene molecule (C), and upside-down attachment of a debrominated compound (D).⁸⁴

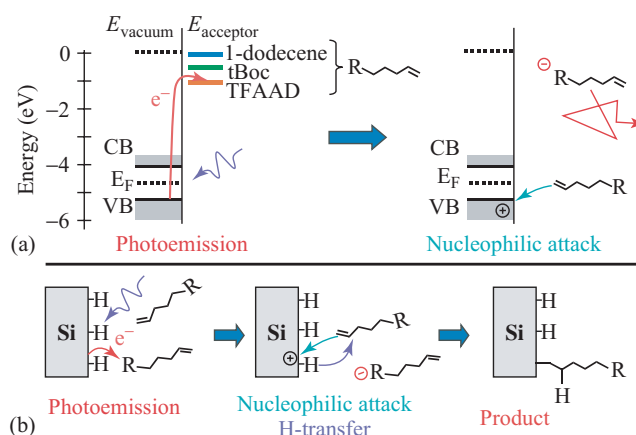


Figure 16 Photoemission mechanism for UV-initiated grafting of alkenes to hydrogen-terminated silicon surfaces: (a) photoemission to an acceptor level followed by nucleophilic attack of another alkene; (b) overall grafting mechanism. Acceptor levels in (a) are from Refs 86, 87. [Reprinted with permission from Ref. 51. Copyright 2010 American Chemical Society.]

cation and a (concerted or successive) hydride shift from the silicon surface to the carbon chain yield again a silyl cation, close to the alkylation center. This cation is available for a following nucleophilic attack. This proposed mechanism has, however, not yet been investigated in full detail.

3.3 Other Initiation Mechanisms

The need for more versatile and milder approaches toward obtaining functional monolayers on silicon still continues. Significant success has been achieved via the development of methods that make use of lower temperatures (<150 °C) or white light ($\lambda > 450$ nm),^{88–90} or even proceed without any significant external activation (i.e., at room temperature, in the dark),⁶⁹ frequently making these approaches, next to the toluene/mesitylene-based

method discussed before,³¹ the methods of first choice for Si–C based monolayer formation onto hydrogen-terminated Si. Since these conditions do not allow regular crossing of high activation barriers, direct cleavage of the Si–H bonds is not predominantly involved. Several mechanisms that have been proposed in order to explain mild attachment will be discussed in the following.

3.3.1 Initiation by Adventitious Oxide and Activation by Glass Reaction Vessels

The idea of adventitious oxide being able to create dangling bonds on the silicon surface dates back to the initial experiments performed by Linford and Chidsey.⁴⁹ In their experiments in the absence of radical initiator, they still observed efficient monolayer formation from alkenes and

alkynes. These reactions were attributed to the presence of traces of oxygen in the reaction mixture, which reacts with the silicon surface as previously described in Section 1.3. Although these reactions indeed result in the initiation of a radical chain reaction, recent studies show that the extensive exclusion of oxygen from the reaction mixture has no apparent influence on the reactivity.⁶⁹ In fact, the quality of the monolayers increases as oxidation of the surface is minimized. Therefore, still another initiation mechanism must be in operation that may coincide with oxygen initiation. On the basis of these findings, Miscki *et al.* proposed a mechanism that involves degradation of the unsaturated hydrocarbons by reaction with silanol groups of the glass reaction vessel at elevated temperature.⁹¹ This mechanism was supported by the observed drop in reaction rate and monolayer quality on employing PTFE reaction vessels.

3.3.2 Diazonium Salts

Aryldiazonium salts have been used for the direct grafting of aryl groups onto hydrogen-terminated silicon surfaces.^{92–94} These reactions form a special case, and show that solution reactions and surface reactions may have very different outcomes. Reactions with the silicon surface lead to hydrosilylation products, whereas solution reactions with silanes generally lead to substitution of a silicon-bound hydrogen with the counterion of the diazonium salt (Figure 17).⁹⁵ The reaction most likely proceeds via a one-electron reduction of the aryldiazonium cation, yielding an aryl radical and N₂. The

difference between surface reactions and reactions with silanes lies in nature and fate of the electron donor. In solution, electron donation by the silane leads to the formation of a silyl radical cation, which is attacked by the counterion of the diazonium salt. The dissociated hydrogen atom subsequently combines with the aryl radical (Figure 17a).

In contrast, electron donation from the surface leaves a hole that is highly delocalized and is able to migrate into the silicon bulk. The aryl radical picks up a hydrogen atom from the surface, leaving a surface-silicon-centered silyl radical, which reacts with an unreacted aryl radical to form a Si–C bond (Figure 18a). Although direct evidence of this reaction has not been demonstrated, formation of radicals at the surface has been evidenced, by trapping the radicals with alkenes and alkynes, leading to alkyl and alkenyl monolayers (Figure 18b).⁹⁶

Moreover, the electron injection from the silicon bulk into the accepting orbitals in solution is in good agreement with the findings of Hamers and coworkers described above.⁵¹ This is a very elegant example of fabrication of alkyl and alkenyl monolayers at room temperature via controlled radical initiation at the surface. When carboxylate and hydroxyl ω -functionalized alkenes are employed, mainly Si–C bonds are formed. This procedure allows the use of different functional groups without affecting the monolayer quality. Diazonium-initiated attachment occurs fast, as evidenced by the formation of a complete aryl monolayer in 3 hours,⁹⁶ where aryldiazonium salts act as both initiators and reagents (Figure 18b), making this an excellent approach to aryl monolayers. For high-quality alkyl monolayers, other methods may

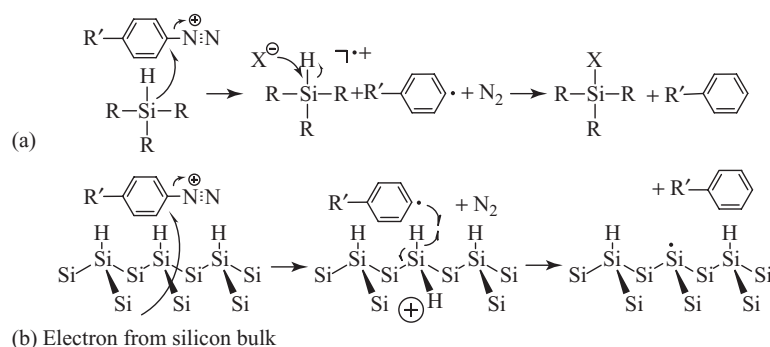


Figure 17 Reactions of diazonium salts with (a) silane molecules and (b) the silicon surface.

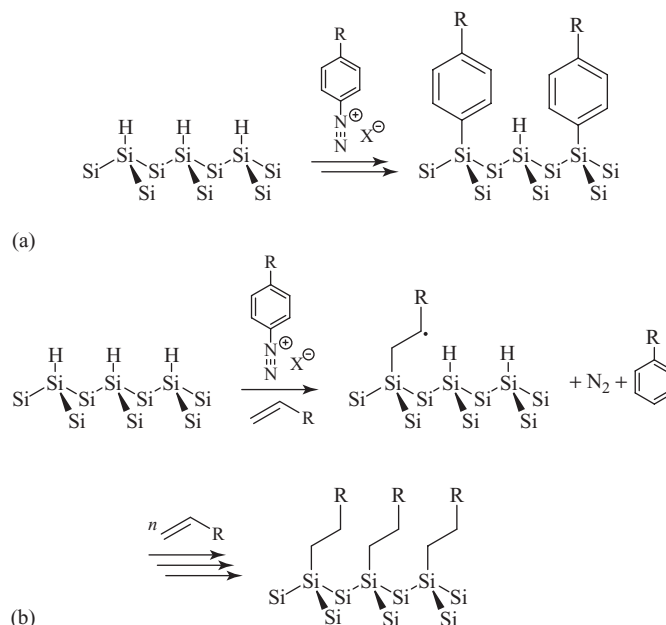


Figure 18 (a) Recombination of surface-centered radicals with abundant aryl radicals leading to the formation of aryl monolayers on silicon. (b) In small amounts, diazonium salts initiate formation of silicon-centered radicals that are trapped by alkenes, leading to the formation of an alkyl monolayer.

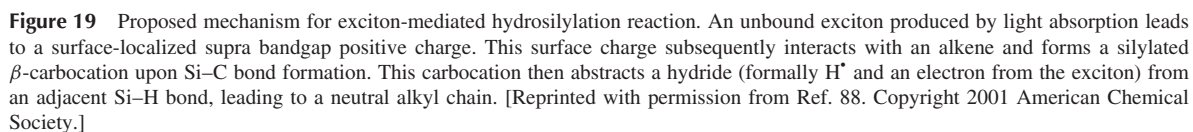
be more suited, given the instability of alkyl diazonium salts, which thus require the involvement of aryl salts that will themselves also show reactivity toward the H-Si surfaces and thus lead to distortions within the formed monolayer. In fact, a parallel can be drawn to the presence of halogen impurities discussed in Section 2.4. Though the aryl attachment is not susceptible to hydrolysis, the disruption of the layer will allow faster penetration of oxygen, resulting in oxidation.

3.3.3 Exciton-Mediated Initiation

Buriak and coworkers found that alkenes attach to porous silicon under irradiation at wavelengths higher than 450 nm.^{64,88} They proposed a mechanism involving excitons, in which electron/hole pairs form near the silicon surface (Figure 19), leading to positive charges on the surface. Nucleophilic attack on a positively charged silicon atom may then result in the formation of a β -carbocation on the attached alkyl chain. Transfer of a hydride from the surface to the β -carbocation yields a neutral alkyl chain. This mechanism, however, does not lead to

a chain reaction, as the attachment of a single chain does not lead to the formation of a new reactive site at the surface.

Zuilhof and coworkers also demonstrated the attachment of alkenes and alkynes onto Si(100)⁹⁰ and Si(111)⁸⁹ by irradiation at 658 nm (white-light reaction). This process is also based on exciton formation, though the charge separation was considered to take place both at the surface and deeper in the silicon bulk. The electronic band structure of silicon would then cause separation of the electron/hole pair, followed by migration of electrons to the silicon bulk. In contrast, the holes move toward the surface, resulting in delocalized radical cations at the silicon surface. Nucleophilic attack of alkenes on these radical cations results in cleavage of a silicon backbond and the formation of a Si-C bond and a β -carbon radical (Figure 20). Hydrogen transfer from the surface to this radical yields a surface-centered radical that propagates the radical chain mechanism.⁸⁹ A recent mechanistic study confirms the reactivity of alkenes and alkynes toward delocalized radical cations, and will be discussed in more detail in Section 4.3.⁹⁷ The studies on monolayer formation at room temperature in the dark



This mild technique, introduced by Zuilhof and coworkers, was shown to result in hexadecenyl monolayers of very high quality (water contact angles $\sim 111^\circ$, and CH_2 stretching vibrations at $\nu_{\text{C-H}} = 2919$ and 2850 cm^{-1}). In order to determine

the origin of this enhancement of the self-assembly process, the difference in reactivity between alkenes and alkynes, as well as the resulting quality of the monolayers, were studied in detail.^{70,98} To this aim, the rate of monolayer formation from both alkenes and alkynes was studied (Figure 21). A clear difference in reactivity of alkenes and alkynes is observed for samples prepared both under visible-light irradiation (Figure 21a) and in the dark (Figure 21b). Under irradiation, 1-hexadecyne monolayers came to completion after 8 hours, whereas the alkene layers were still far from completion (contact angles of $\sim 111^\circ$ and $\sim 100^\circ$).

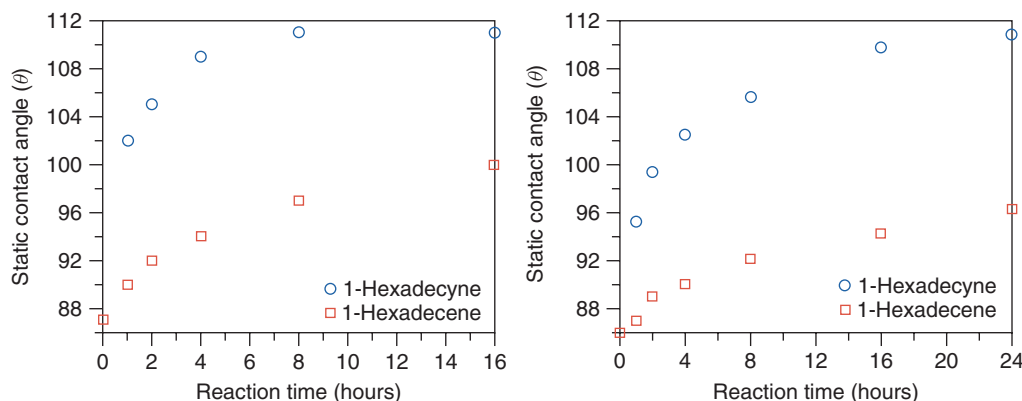


Figure 21 Static contact angles of 1-hexadecyne ($\circ$) and 1-hexadecene-derived ($\square$) monolayers on H-Si(111) at 20 °C (a) under ambient light, and (b) in the dark, as a function of reaction time. [Both pictures reprinted with permission from Ref. 70. Copyright 2010 American Chemical Society.]

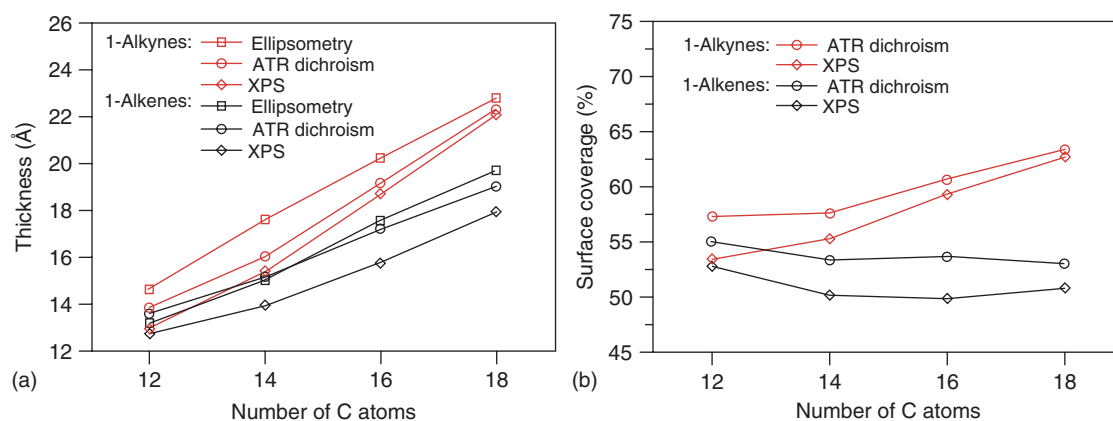


Figure 22 (a) Layer thickness and (b) surface coverages as a function of the number of carbons in alkyne-derived and alkene-derived monolayers, as determined by XPS, ATR, and ellipsometry. [Both pictures reprinted with permission from Ref. 70. Copyright 2010 American Chemical Society.]

respectively).⁷⁰ Comparison of these results to those from the experiments in the dark shows a clear effect of irradiation. Under dark conditions, alkyne-derived monolayers are fully formed (contact angle $\sim 111^\circ$) after 24 hours, whereas the contact angles of the alkene layers do not exceed 97° . These differences in reactivity of the alkenes and alkynes contribute to the differences in nucleophilicity and lower barriers in the hydrogen abstraction reaction at the surface, as will be discussed in more detail in Sections 4.2 and 4.3.

In addition, the structural differences between alkene-derived and alkyne-derived monolayers were studied in detail. A combination of surface analysis techniques (ATR-IR, XPS, ellipsometry, and water

contact angles) was used to determine accurate surface coverages of monolayers prepared from a series of alkenes and alkynes (C12 to C18).⁷⁰ Figure 22 shows the influence of the number of carbons in the chain on the thickness of the monolayer (Figure 22a), and the influence on the surface coverage (Figure 22b). Alkynes lead to thicker layers, indicating that the chains are in a more vertical position than the chains in the alkene layers (tilt angles $22\text{--}35^\circ$ and $37\text{--}40^\circ$ for alkynes and alkenes, respectively). This is in agreement with the observed surface coverages, which are significantly higher for alkynes (55–65% for C12 to C18) as compared to alkenes (50–55% for C12 to C18).

Supportive evidence was found in a modeling study performed by the same group.⁹⁸ Molecular mechanics simulations of the monolayers combined with quantum-chemical calculations showed that alkynes indeed should lead to a higher theoretical surface coverage than alkenes (up to 69% for alkynes vs 50–55% for alkenes) for a variety of reasons. First, the Van der Waals radius of a $\text{H-C}\equiv\text{CH-}$ group is smaller than that of a $\text{-CH}_2\text{-CH}_2\text{-}$. Second, the sp^2 hybridization of the carbon bound to the surface results in a more favorable angle (60° vs surface normal) over a sp^3 hybridized carbon (76° vs surface normal), which lowers the strain energy in the Si–C link. Third, as was shown by G3 calculation, the driving force for Si–C bond formation is $\sim 10 \text{ kcal mol}^{-1}$ higher for 1-alkynes than for 1-alkenes. These factors combined drive monolayer formation for 1-alkynes to a significantly higher degree of surface coverage and correspondingly improved surface properties.

3.3.4 Fluoride-Catalyzed and Neutral Attachment

Though Cerofolini and coworkers support the strong case of radical propagation, they argue that the Si–H bond is too strong for homolytic cleavage at 150°C .⁹⁹ Therefore, they investigated two alternatives: catalytic activity of trace fluoride, and a neutral concerted mechanism, which describe attachment to the silicon surface without initial cleavage of the Si–H bond.⁷⁹ Nucleophilic attack of F^- onto the silicon surface is suggested to result in the formation of pentavalent silicon. This intermediate then releases a hydride that attacks a carbon–carbon double bond, yielding an α -carbanion, which in turn attacks the silicon, substituting fluoride (Figure 23). The result is a neutral alkyl chain as well as a fluoride anion that is available for the next attachment. The proposed alternative mechanism, however, proceeds via a neutral transition state. In a concerted mechanism, the Si–C bond is formed, and the hydrogen is transferred to the alkyl chain. The two mechanisms were found to be indistinguishable in apolar media, whereas the activation energies may indeed be reached at these elevated temperatures.¹⁰⁰ However, both reactions result in a neutral product that does not lead to propagation of the reaction. Neutral attachment and

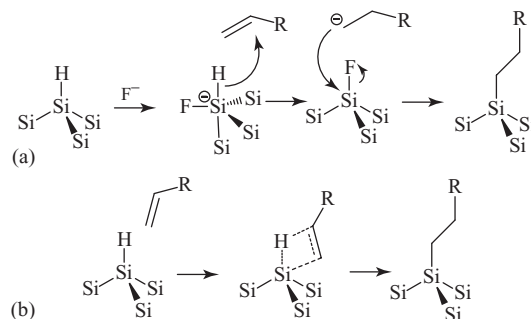


Figure 23 (a) Fluorine-catalyzed attachment of alkenes to silicon and (b) attachment and hydrogen transfer in a concerted reaction.

fluoride-catalyzed attachment can thus be not important in monolayer formation at ambient and slightly elevated temperatures, as under such conditions the formation of lines and islands of monolayers have been shown, for example, by the aforementioned STM results.⁶⁷ In the case of aldehydes, alkenes, and alkynes, the attachment therefore most likely proceeds mainly via the radical mechanism, as described in Section 3.2.^{89,101}

4 EXPERIMENTAL AND THEORETICAL MODELING STUDIES

In order to better understand the reactions taking place during monolayer formation, modeling studies were undertaken by several research groups. Most theoretical studies make use of a silicon slab or crystal to represent the silicon surface.^{99,102–104} An alternative suitable model is TTMSS, which may provide a good representation of the H–Si(111) surface. Moreover, the chemistry of the TTMSS radical has already been studied in detail,^{45,60,105–107} allowing a clear interpretation of novel reactivity patterns (see **Silanes as Reducing Reagents in Radical Chemistry**). Recently, Fouassier and coworkers extended these reactivity studies to a wide range of alkenes and combined them with density functional theory (DFT) calculations.^{108,109} The calculations of reaction barriers showed good correlation with experimental reaction rates. However, this study was not directed toward monolayer formation on silicon, and the used reagents are not representative of precursors commonly used in monolayer formation experiments. The

experimental setup, however, may be very useful in modeling the radical reaction at the silicon surface.

4.1 Quantum-Chemical Calculations on the Surface Radical Mechanism

While the methods for monolayer fabrication developed into milder and more efficient attachments, the actual kinetics of the reactions at the silicon surface remained until recently largely hidden. In order to gain a better understanding of the propagation mechanism at the silicon surface, Selloni and coworkers conducted a theoretical investigation of the radical chain reaction on silicon surfaces. With first-principles string molecular dynamics (FPSMD), the trajectory of acetylene and ethylene in the addition reaction with Si(111) was modeled, as well as the subsequent hydrogen transfer (Figure 24).^{103,110} A significantly higher addition barrier was found for acetylene than for ethylene (3.5 and 0.9 kcal mol⁻¹ respectively), which seemed to contrast the observed experimental reactivity of the surface, where alkynes display a ninefold higher reactivity.¹¹¹ However, the barrier for hydrogen transfer from the surface to the β -carbon radical is much higher for the attached ethylene (12.5 kcal mol⁻¹) than for acetylene (16.4 kcal mol⁻¹). In fact, the barrier of

hydrogen transfer to the ethylene moiety is even higher than the return barrier for dissociation from the surface (9.7 kcal mol⁻¹). Therefore the authors suggest that ethylene is more likely to desorb from the surface than to accept a hydrogen atom from a neighboring Si–H. This is in agreement with experimental findings of 1-hexene monolayers on silicon, which were shown to dissociate under UHV conditions (no heat or UV required) in an STM setup.¹¹² Although ethylene reacts faster with silyl radicals on the silicon surface, acetylene results in a faster overall reaction, as was also observed in the aforementioned monolayer experiments.¹¹¹ In a follow-up study, the barrier energies of formaldehyde addition (0.7 kcal mol⁻¹) and hydrogen transfer (8.1 kcal mol⁻¹) were calculated. These barriers are lower than those for ethylene or acetylene addition, indicating that reactions of aldehydes are likely to proceed even faster. However, a recent experimental study by Horrocks and coworkers revealed the contrary.¹¹³ Monolayer formation was studied by employing alkene and aldehyde moieties in equimolar amounts in the reaction mixture. The final attachment ratio reflects the rates of alkene and aldehydes addition. The addition of alkenes was found to proceed approximately nine times faster than aldehyde addition. Further modeling studies are therefore required to explain these differences in reactivity.

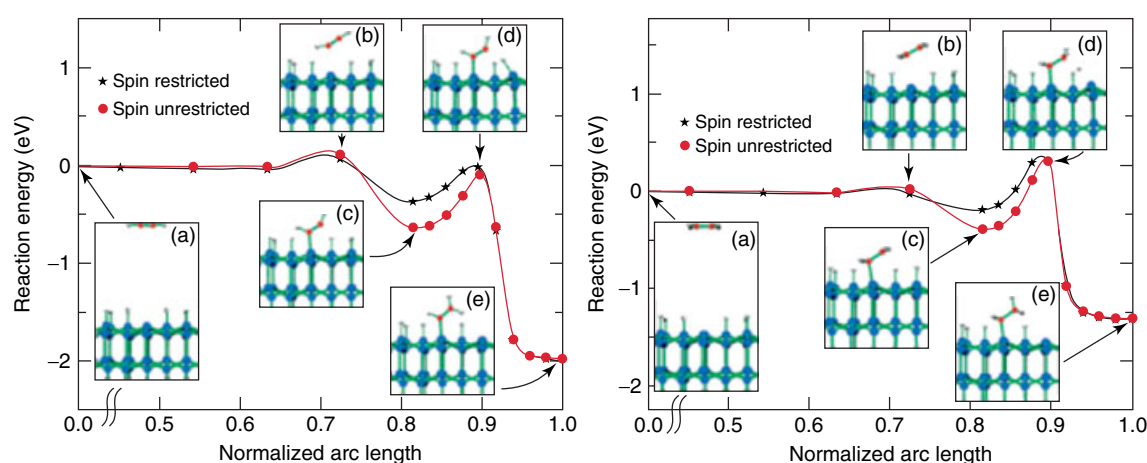


Figure 24 Potential energy profile along the minimum energy pathway for the reaction of (a) acetylene and (b) ethylene with the H-Si(111) surface. Black and red lines respectively correspond to spin-unpolarized and spin-polarized calculations. The zero-point energy corresponds to a noninteracting surface–molecule system. Blue: silicon atoms; red: carbon atoms; white: hydrogen atoms. [Reprinted with permission from Ref. 103. Copyright 2004 American Chemical Society.]

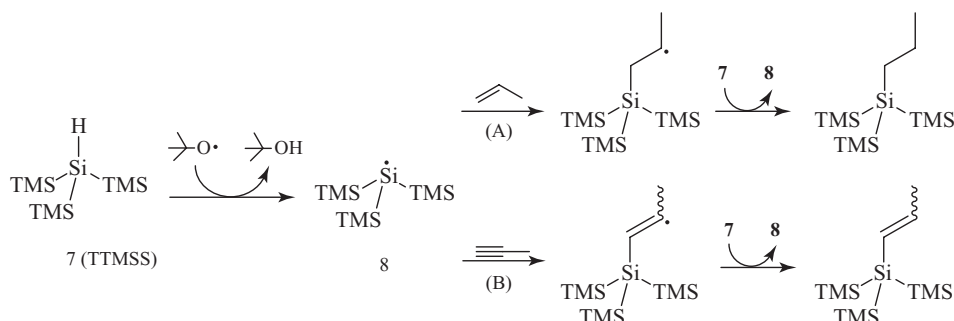


Figure 25 Competition experiments of TTMSS radical (**8**) with alkene and alkyne. The reactivity ratio is determined by the product ratio of reactions A and B.¹¹⁴

The group of Selloni further demonstrated that stabilization of the β -radical is key to increasing the reactivity of unsaturated carbon–carbon bonds toward silyl radicals.^{102,103} The reaction barriers for the addition of both styrene and phenylacetylene were shown to disappear as a result of the stabilization by the conjugated system. This indicates that addition will proceed rapidly. The barriers for hydrogen abstraction (6.9 and 5.8 kcal mol^{−1} for styrene and phenylacetylene, respectively) are also significantly lower than for the analogous nonconjugated compounds. Furthermore, the authors present the theoretically favorable reaction pathway as strong supportive evidence that the STM-observed styrene lines indeed are formed in a radical reaction. They show that hydrogen transfer between the β -carbon radical and the nearest Si–H site is very likely, and that addition of styrene to a dangling bond is also very favorable. As was discussed in the previous section, the direction of propagation on Si(100) is directed by the surface geometry, resulting in the formation of lines.

UV absorbance above 250 nm, its reactivity cannot be measured directly. Competition reactions involving the silyl radical and two monolayer precursor molecules (e.g., an alkene and an alkyne) resulted in relative reaction rates (Figure 25).

Since terminal alkenes are most commonly used in monolayer fabrication, the reactivity of 1-decene was used for reference (Table 1).^{2,3,50,86} The observed reactivity order of 1-decyne, 1-decene, and 1-undecanal is in good agreement with that obtained from monolayer experiments (aldehyde < alkene < alkyne).^{70,111,113} In addition, the introduction of conjugated bonds has a strong effect on the reactivity. A 10-fold increase in reactivity was observed for phenylacetylene as compared to 1-decene. The predictive potential of these reactivity experiments was demonstrated by the high reactivity of two novel potential precursors for monolayers, namely, hexadeca-3-ene-1-yne and 1,3-hexadecadiyne. The introduction of conjugated bonds leads to a dramatic increase of reactivity (200- and 1400-fold increase for the ene-yne and

4.2 TTMSS as a Model for the Si(111) Surface: Combining Experiment and Theory

Inspired by the mechanistic investigations into the chemistry of the (TMS)₃Si[•] radical (**8**), Zuilhof and coworkers combined the experimental and theoretical results of reactions of silyl radicals with precursors commonly used in monolayer formation¹¹⁴. The objective was to link observed reactivity to a theoretical model to explain and predict the experimental findings. Since the formed β -carbon radical in linear alkenes and alkynes does not display

Table 1 Experimental reactivity ratios (determined at 20 °C) and calculated reaction rates (calculated for 20 °C) for the addition of silyl radicals to monolayer precursors.

Reagent	Reactivity ratio vs 1-decene	Calculated rate (M ^{−1} s ^{−1})
1-Undecanal	0.03	4.2 × 10 ⁴
1-Decene	1.0	6.5 × 10 ⁵
1-Decyne	7.5	3.2 × 10 ⁶
Styrene	—	1.8 × 10 ⁷
Phenylacetylene	91	4.8 × 10 ⁷
Hexadeca-3-ene-1-yne	203	1.1 × 10 ⁸
1,3-Hexadecadiyne	1430	1.0 × 10 ⁹

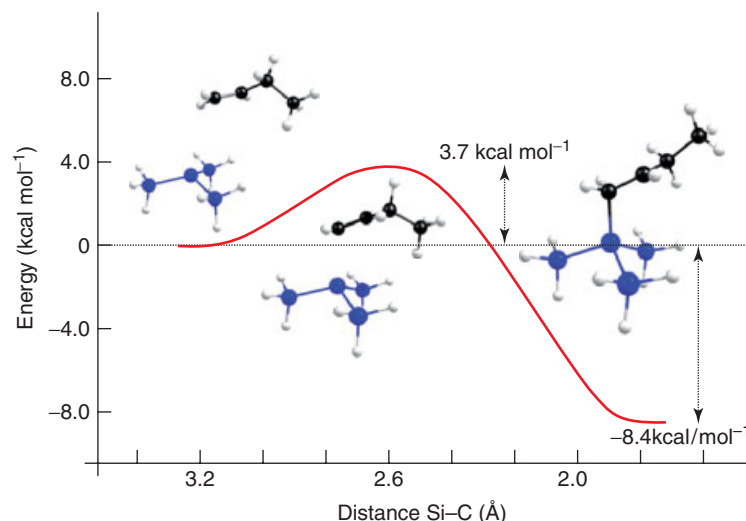


Figure 26 Si_4 model derived from TTMSS, which is used for calculating the reaction barrier for addition of unsaturated carbons to the silyl radical.

diyne, respectively), making these compounds very suitable for accelerated monolayer fabrication. Very recently, Rijksen *et al.* have indeed shown that this is the case.¹¹⁵

In order to investigate the rates for the addition reaction, DFT calculations were carried out on a simplified model of **8** (Figure 26). The study showed the importance of taking reaction entropy into account for calculation of the rates, as the rates calculated with inclusion of both enthalpic and entropic effects show a very good correlation with the reactivity ratios (Table 1), while calculations that only account for enthalpic effects do not yield a proper correlation with experimental results. Moreover, the theoretical rates closely resemble experimental rates from literature (8×10^4 , 1×10^5 , and $5 \times 10^7 \text{ s}^{-1}$ for addition of acetone, alkene, and styrene to **8**). The predictive power of the theoretical model was demonstrated by calculation of the rates for the diyne and yne-ene species. The employed models may prove useful in determining which functionalities are compatible, while avoiding undesired side reactions (upside-down attachment).

4.3 Experimental Modeling of Radical Cation Initiation

As discussed already in Section 3, early methods for monolayer formation were based on a substantial

input of energy in order to directly cleave Si–H bonds at the silicon surface. However, the success of new mild procedures shows that there must be another mechanism that coincides with direct cleavage of Si–H bonds. Section 3.3 gives a detailed overview of mechanisms proposed to explain mild attachment, which are supported by experimental findings. Recently, our group reported an experimental kinetics study on the reactivity of silyl radical cations, demonstrating the feasibility of radical cation initiation.⁹⁷ The molecules used in this study were designed to represent the top layer of the hydrogen-terminated silicon surface (Figure 27).

Silyl radical cations of **7**, **9**, and **10**, were efficiently generated by photoinduced electron transfer using *N*-methyl quinolinium salts (NMQ; 355 nm) and toluene as sensitizer and cosensitizer, respectively.¹¹⁶ These radical cations subsequently were shown to react readily with a variety of nucleophiles regularly used in monolayer fabrication. These experiments showed that alkenes and alkynes react with silyl radical cations with high rates ($k_2 \sim 10^6 \text{ M}^{-1} \text{ s}^{-1}$). This is in line with the initiation of monolayer formation by alkenes and alkynes onto hydrogen-terminated surfaces. However, the significantly higher reactivity of oxygen-centered nucleophiles ($k_2 > 10^7 \text{ M}^{-1} \text{ s}^{-1}$) contrasts with the difference in reactivity of aldehydes compared to alkenes that is observed in monolayer experiments (attachment via the alkene moieties was shown to be

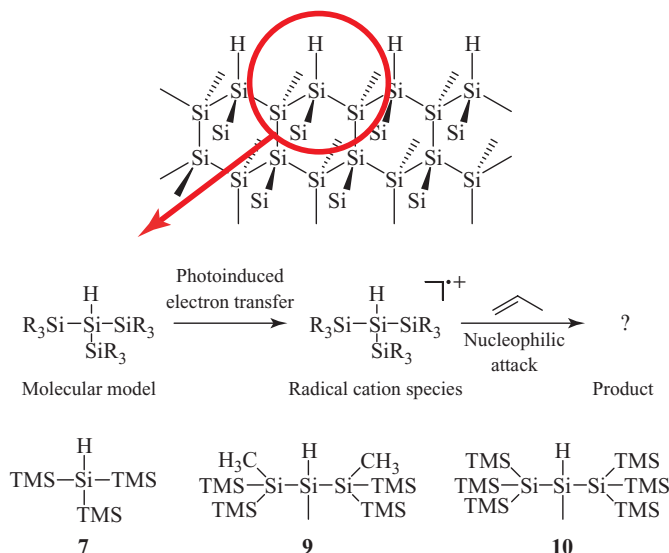


Figure 27 Selection of models used to represent the Si(111) surface (**7**, **9**, and **10**) and the subsequent study of the silyl radical cations. TMS = Si(CH₃)₃. [Reprinted with permission from Ref. 97. Copyright 2011 American Chemical Society.]

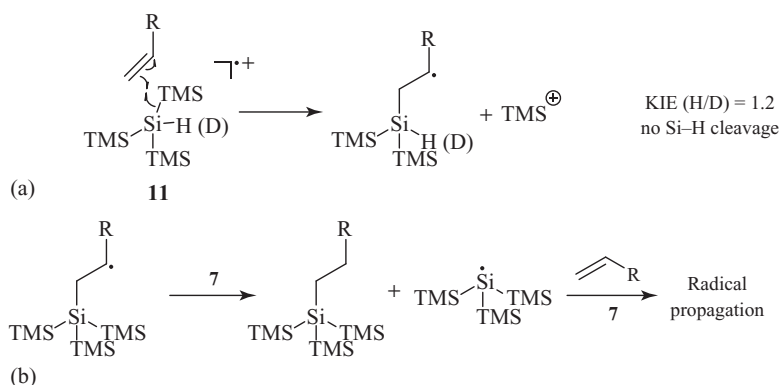


Figure 28 (a) Nucleophilic attack of alkene to the Si center of the TTMSS radical cation (**11**), resulting in the substitution of a TMS group and the formation of a β -carbon radical. The Si-H (or Si-D) bond remains intact, which is in line with the secondary KIE of 1.2; (b) β -carbon radical intermediates (like those obtainable via a) abstracting hydrogen from TTMSS (**7**), resulting in the formation of the TTMSS radical.

one order of magnitude more favorable than attachment of aldehydes,¹¹³ whereas carboxylic acids do not attach at all.¹¹⁷ Therefore, it can be concluded that, while the radical cation mechanism properly explains the initiation of the visible-light-induced reaction, the propagation step in the preparation of Si-C-linked monolayers does not involve radical cation but only surface-centered radicals. Furthermore, experiments with deuterium-labeled **9** and **10** (Si-D instead of Si-H) showed a (secondary) kinetic isotope effect (KIE) of 1.2, indicating that

cleavage of the Si-H (or Si-D) bonds does not occur in the rate-limiting step of the initiation, but that nucleophilic attack takes place close to the Si-H site. This was confirmed by analysis of the reaction mixtures of **7**, which showed products of substitution reactions (substitution of a TMS group, see Figure 28a). The presence of hydrosilylation products could contribute predominantly to radical formation by nucleophilic attack to the silyl radicals (Figure 28b) and only in a minor degree to spontaneous dissociation of **11**.

5 FUNCTIONALIZED MONOLAYERS ON SILICON SURFACES

The formation of functional monolayers on silicon surfaces has attracted significant attention over the past decades, since functional surfaces are essential in the development of new biosensors and molecular electronics.^{118–120} The presence of functional molecules on silicon surfaces allows selective binding and detection of target biomolecules.^{9, 121–123} In addition, these functional assemblies provide a way to gain control over surface properties such as wettability, friction, and adhesion.¹²⁴ Incorporation of functional moieties on the surface is, however, far from trivial and often relies on the use of protective groups or a reactive intermediate, to which the desired functional molecules are then coupled. Direct attachment of functionalities onto the silicon surface is not desirable, since side reactions readily take place resulting, for example, in upside-down attachment, drastically affecting packing of the alkyl chains in the monolayer, as discussed in the following sections.

5.1 C–H Bond Activation

The incorporation of functional groups into the silicon surface was initially studied by Chidsey and coworkers.^{125,126} Two strategies were studied, both involving C–H activation of terminal methyl groups in an octadecyl monolayer on Si(111). The first method entails illumination of the octadecyl monolayer at 350 nm for 15 minutes in the presence of 4'-[3-trifluoromethyl-3*H*-diazirin-3-yl]-benzoic acid *N*-hydroxysuccinimide ester (TDBA-OSu), (Figure 29). This aryl-diazirine cross-linker inserts into the carbon–hydrogen bonds of the terminal methyl groups of the octadecyl monolayer through a highly reactive singlet-state carbene intermediate.

This reaction was carried out using carbon tetrachloride as solvent and resulted in a surface with amino-reactive *N*-hydroxysuccinimidyl moieties. Although this method is fast, it leads to rather ill-defined structures on the surface. Moreover, only low surface coverages of amino-reactive groups are achieved (approximately 10%) and, as a result, the surfaces remain hydrophobic, affecting further functionalizations. However, this route allowed

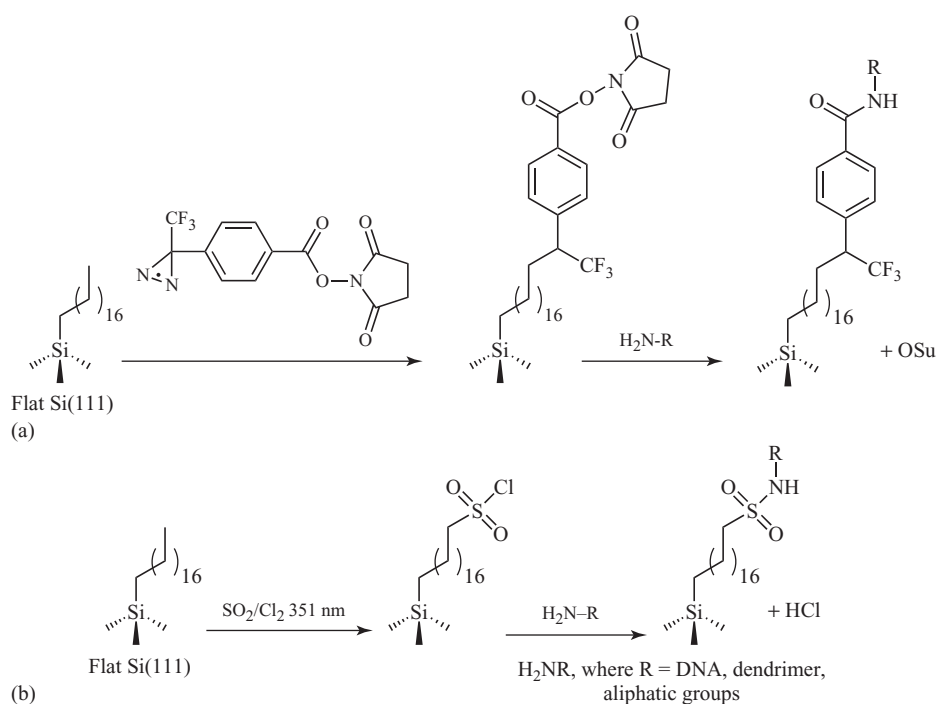


Figure 29 Functionalization of octadecyl monolayers on silicon through C–H bond activation, followed by (a) amide and (b) sulfonamide formation. [Reprinted with permission from Ref. 2. Copyright 2002 American Chemical Society.]

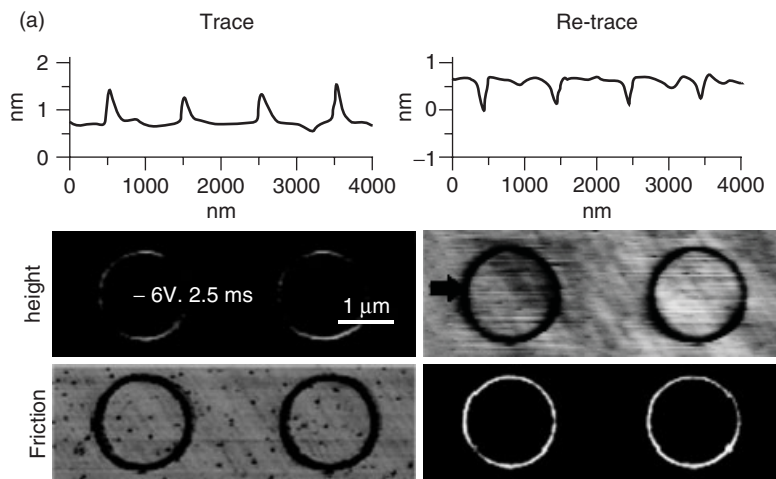


Figure 30 Contact-mode AFM height and friction images of a patterned hexadecylated silicon surface. Two circles show monolayer oxidation (-6 V bias at a pixel duration of 2.5 ms), and section profiles are along the arrow above the height images. All patterns were obtained with a resolution of ~ 205 pixels/ μm . [Reprinted with permission from Ref. 128. Copyright 2009 American Chemical Society.]

the successful immobilization of amino-functional biomolecules, such as amino-modified DNA, making these systems suitable for biological scanning probe microscopy (SPM)^{123,126,127}; further improvements on the coverage may be feasible.

Alternatively, a gas-phase free-radical chlorosulfonation reaction was employed to introduce *in situ* highly reactive sulfonylchloride groups onto the octadecyl monolayer by irradiating the surface with 350 nm UV light with chlorine gas in sulfur dioxide. Subsequent reaction with primary amines leads to sulfonamide formation, Figure 29b. This route also results in less disordered amino-modified monolayers than aminopropyltriethoxysilane-based organic films on silicon oxide surfaces. Another advantage of this approach is that the density of sulfonylchloride groups can be controlled by irradiation time, while the conjugation reaction depends on amine concentration and reaction time, allowing for ample control over the surface coverage. The amine-terminated alkyl monolayers obtained after reaction of the sulfonylchloride groups with ethylenediamine provide a facile route to a wide range of heterobifunctional cross-linkers such as benzoylbenzoic acid and *N*-hydroxysuccinimide or direct conjugation of amino-functional biomolecules. Oxidation of terminal methyl groups present on hexadecyl monolayers on Si(111) was recently studied by Zuilhof,

Schubert, and coworkers as a functionalization method.¹²⁸ Densely packed hexadecyl monolayers were locally oxidized using an electrically biased Pt-coated atomic force microscopy (AFM) probe in contact mode. The oxidation behavior was studied as a function of the applied voltage. At low voltages, these monolayers remained unchanged; however, upon increasing the bias voltage, oxidation of the terminal methyl groups occurred, resulting in carboxylic acid moieties. Depending on the voltage employed, as well as the length of the oxidation pulse, a highly controlled partial to complete degradation of the monolayer was achieved, with the concomitant control over the oxidation of the underlying silicon (partial monolayer degradation to yield (among others) carboxylic acid moieties does not lead to surface oxidation yet). Figure 30 shows the contact-mode height and friction images in both directions (trace and retrace) obtained after local probe oxidation of the hexadecyl monolayer.

This method allows even milder local probe oxidations using labile functional groups that are oxidized already at very low bias voltages (e.g., NHS moieties, discussed in the following section). While this process is carried out on the microscale, plasma treatment of alkyl monolayers on silicon gives access to functionality over much larger areas. Hexadecyl monolayers on Si(111) or Si(100)

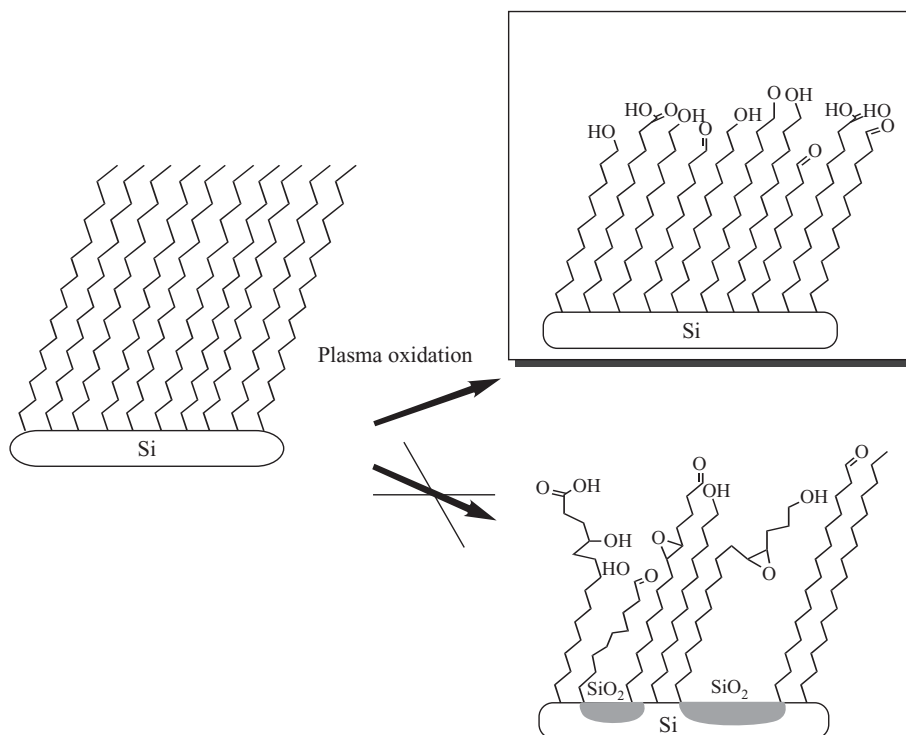


Figure 31 Schematic representation of the surface reactions during plasma treatment of alkyl monolayers on silicon. [Reprinted with permission from Ref. 129. Copyright 2010 American Chemical Society.]

underwent short plasma treatments (1–3 seconds), which resulted in oxidation of the terminal methyl groups into hydroxyl, aldehydes, and carboxylate functionalities, Figure 31.¹²⁹ Importantly, on Si(111) substrates this did not damage the underlying oxide-free silicon as evidenced by the C 1s and Si 2p signals in XPS narrow-scan analysis. After 1 second of oxidation, C=O bonds represent a significant part of the surface functionalities, in the form of aldehydes groups. Oxidation of the silicon substrate was indeed observed for Si(100) surfaces. After 3 seconds of plasma treatment, 5% of the total Si 2p signal corresponds to SiO₂. Carbon atoms with a single bond to oxygen (C–O) are mostly formed during plasma treatment. This was further evidenced by reacting these monolayers with *p*-trifluoromethylbenzylamine (TFBA), resulting in conjugation with 35–40% of the C=O groups introduced by plasma treatment.

Packing of the alkyl monolayers was not significantly affected by the plasma treatment, as observed by IRRAS. Initially, the symmetric and

antisymmetric C–H stretching vibrations of the CH₂ moieties are observed at 2851 and 2920 cm^{−1}, respectively. Upon plasma oxidation, the intensity of these vibrations gradually decreases, while the CH₃ vibration at 2965 cm^{−1} disappears entirely already after 3 seconds of plasma treatment. The underlying alkyl chains retain their initial packing as indicated by the symmetric CH₂ vibration at 2920 cm^{−1}. To demonstrate the reactivity of aldehyde-terminated monolayers (1 second plasma treatment), reaction with cysteamine was carried, resulting in thiol-terminated surfaces. These surfaces were successfully employed in the attachment of gold nanoparticles (Au NPs). In addition, the binding of Au NPs was used to demonstrate the ability of surface patterning using a plasma. To this purpose, a soft contact mask was employed during the plasma treatment, allowing the formation of patterns with micrometer-sized features, as observed by AFM in Figure 32. This novel and facile route gives access to patterning of high-quality functional silicon surfaces.

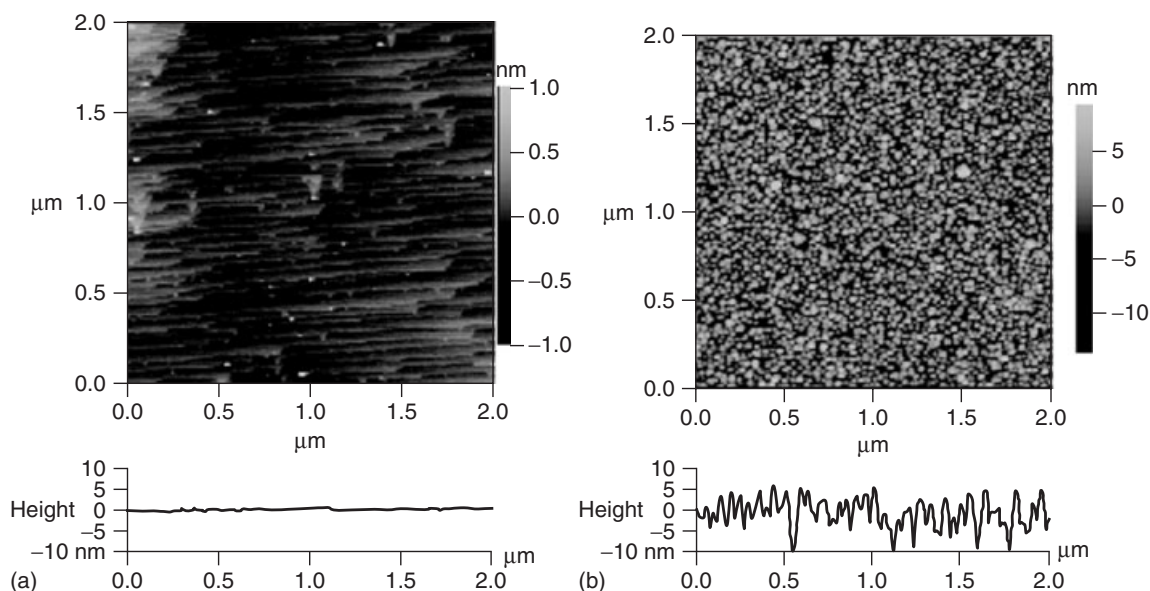


Figure 32 AFM images and sections measured on monolayer-coated silicon(111) surfaces, (a) after exposure to cysteamine and gold nanoparticles without plasma treatment and (b) after 1 second of air-based plasma followed by reaction with cysteamine and gold nanoparticles. [Reprinted with permission from Ref. 129. Copyright 2010 American Chemical Society.]

5.2 Carboxylic Acids

Carboxylic acid-terminated monolayers have proven to be a very useful scaffold for further functionalization of silicon surfaces.^{117,130,131} However, the quality of the corresponding monolayers depends largely on the method employed for their fabrication. Early investigations by Zuilhof, Sudhölter, and coworkers showed that thermal attachment (200 °C, 2 hours) resulted in significant upside-down attachment. According to FTIR studies, these monolayers display poor packing as compared to alkyl monolayers.⁵⁰ On the other hand, when employing photochemical methods ($\lambda = 300$ nm, 3 hours), high-quality monolayers were obtained without significant upside-down attachment.¹³⁰ This suggests that the acid moiety is able to react with surface Si–H at elevated temperatures, whereas it displays a highly diminished reactivity at room temperature. This compatibility of carboxylic acid moieties with the hydrosilylation reaction was further studied by Bowden and coworkers who functionalized the silicon surface with a mixture of 1-octadecene and a fluoro-capped carboxylic acid in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) (see **Nitroxides in Synthetic Radical Chemistry**)

(Figure 33).¹¹⁷ The thus obtained surfaces were characterized by XPS and IR spectroscopy. The silicon surface did not oxidize, since no signal was observed at the 101–104 eV region in the Si 2p narrow scan.¹³² In addition, the F 1s narrow scan did not display any signals in the 684–694 eV region, indicating the absence of fluorine atoms, which confirms the limited reactivity of acid moieties toward silyl radicals. Chazalviel and coworkers studied the preparation of mixed monolayers employing photochemical methods ($\lambda = 312$ nm) with 1-alkenes and acid-terminated 1-alkenes. A drawback of this method is the use of numerous rinsing steps with hot acetic acid to remove physisorbed carboxylic acid molecules from the silicon surface.¹³³

5.3 Esters: Hydrolysis, Reduction, and Cleavage

As discussed in the previous section, direct attachment of carboxylic acids during hydrosilylation of the silicon surface is problematic because of the formation of silyl esters on the silicon surface.^{50,56,134,135} Instead, the use of 1-alkenes bearing ester moieties such as methyl and propyl

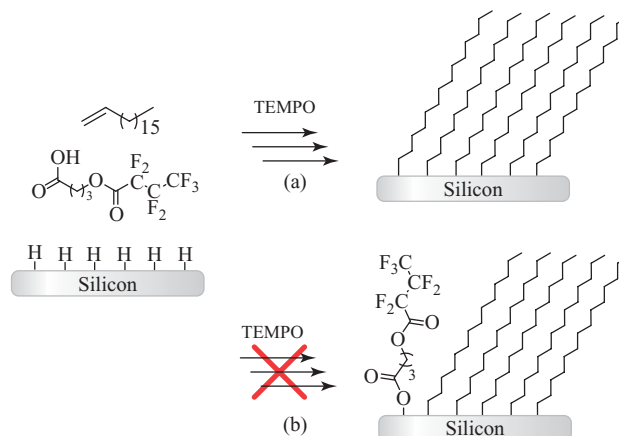


Figure 33 (a) TEMPO-initiated monolayer formation of 1-octadecene and fluorine-capped carboxylic acid resulting solely in the formation of octadecyl layers. (b) No attachment of the carboxylic acids was observed with STM (no fluorine signal in the 684–694 eV region).¹¹⁷

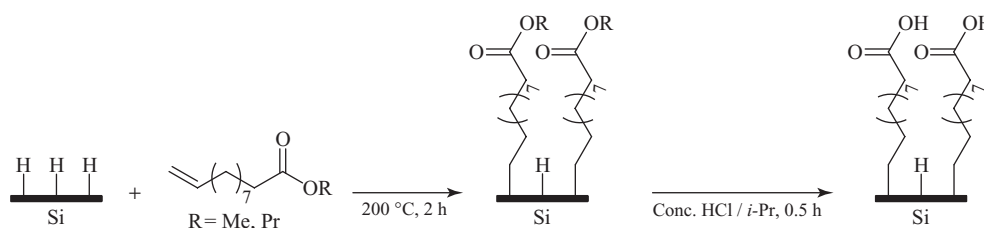


Figure 34 Attachment of 10-undecenyl ester on Si(100) surfaces and formation of acid-terminated monolayers on silicon after hydrolysis.⁵⁰

esters of 10-undecylenic acid has been successfully employed in the formation of monolayers on silicon; subsequent hydrolysis of the esters yielded carboxylic acid-functionalized silicon surfaces, Figure 34.⁵⁰

These ester-terminated monolayers on Si(100) were prepared under thermal conditions (200 °C). The resulting silicon monolayers are well ordered as demonstrated by the antisymmetric and symmetric methylene stretching vibrations in the FTIR spectra (for methyl ester-terminated monolayers: ν_a 2923 cm^{-1} , ν_s 2854 cm^{-1} , and for propyl ester-terminated monolayers: ν_a 2920 cm^{-1} , ν_s 2850 cm^{-1}). The ester moieties do not significantly affect packing of the monolayers. Subsequent hydrolysis of the ester groups led to the formation of acid-terminated monolayers (Figure 34). It may be desirable to use acidic conditions, since strongly alkaline solutions may damage the silicon surface. Acetate-functionalized monolayers on Si(100) have been studied as well. These monolayers were

prepared from 10-undecylenyl acetate employing thermal conditions (Figure 35).⁵⁰ A close packing of the alkyl chains in the monolayer was observed by FTIR spectroscopy. Hydrolysis of these surfaces was foreseen to provide a route to alcohol-terminated surfaces. However, under acidic conditions the acetate moieties were not hydrolyzed, most likely due to inaccessibility of the esters due to steric hindrance. Use of LiAlH_4 , however, conveniently yielded hydroxyl-terminated monolayers.

In addition to these studies, Boukherroub and Wayner investigated the modification of Si(111) surfaces with ethyl undecylenate employing UV irradiation.¹³⁶ Several reactions on the ester moieties using standard chemical and solid-phase chemical procedures were performed to generate functional silicon surfaces (Figure 36). For example, alcohol-terminated monolayers are obtained after reduction of the ester moieties with NaBH_4 , while reaction with an alkyl Grignard reagent gives a tertiary alcohol that can be acylated with acetyl

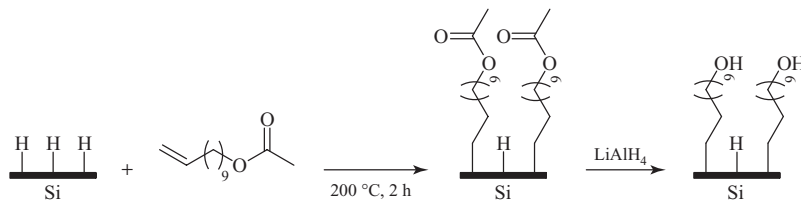


Figure 35 Attachment of 10-undecenyl acetate on Si(100) surfaces and subsequent reduction to provide alcohol-terminated silicon surfaces.⁵⁰

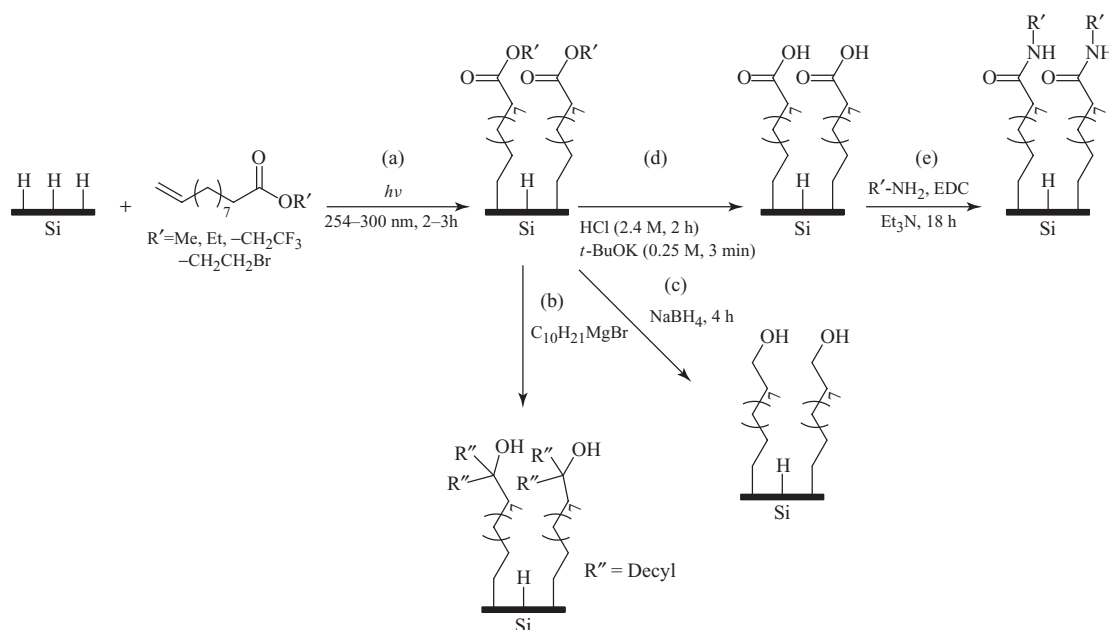


Figure 36 Modification and reactivity of 10-undecenyl ester-derived monolayers on Si(100) and Si(111) surfaces. Formation of alcohol (b, c) and acid-terminated monolayers (d) and subsequent immobilization of biomolecules (e) using conventional solid-phase amide coupling protocols.¹³⁶

chloride. Finally, hydrolysis of the ester leads to a carboxylic acid-terminated surface that could be coupled to a protected amino acid (glycine methyl ester) using a standard solid-phase amide coupling protocol. The surface density of the ester function can be controlled by dilution of the reacting ester with a long-chain alkene. This has the beneficial effects of minimizing the disruption of the alkyl chain packing in the monolayers and avoiding steric blocking of the ester group.

5.4 Active Esters

Ester and amide linkages are the most frequently employed groups for the conjugation of functional

molecules onto surfaces. As described previously, the ester groups present in an alkyl monolayer are easily hydrolyzed, giving access to alcohols and carboxylic acid functionalities. Carboxylic acid-terminated monolayers may further react with alcohols or amines to form esters or amides, respectively. These reactions are of great interest, because they facilitate the attachment of biomolecules such as proteins, peptides, antibodies, and DNA.^{137,138} However, activation of the carboxylic acid moieties is required. In general, acid-terminated surfaces are activated by carbodiimide reagents, such as 1-ethyl-3-(3-(dimethylaminopropyl)-carbodiimide (EDC) or *N,N'*-dicyclohexylcarbodiimide (DCC) to form a reactive *O*-acylurea intermediate. Upon reaction

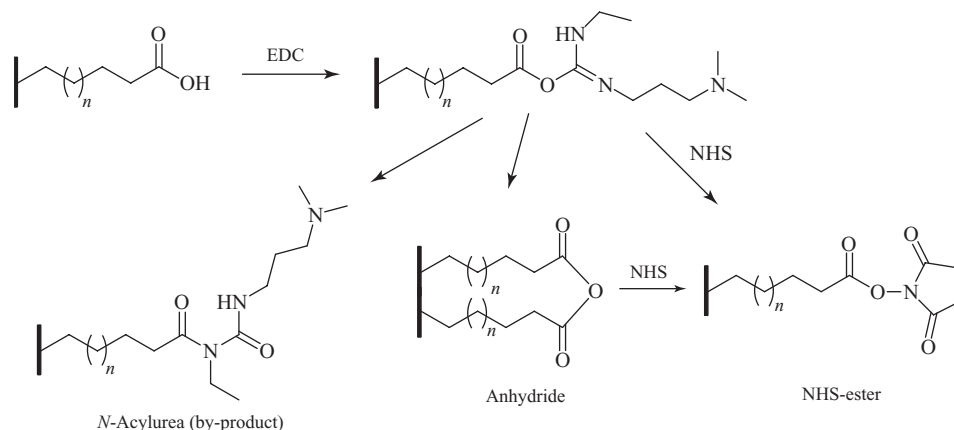


Figure 37 Activation of acid-terminated surfaces employing carbodiimide (EDC) reagents and alternative reaction pathways.

with amines, stable amide bonds are formed, Figure 37.^{139,140} These reactions are often carried out in organic solvents, but aqueous solutions are also suitable. Hydrolysis of the *O*-acylurea intermediate may, however, take place in water, limiting the efficiency of conjugation. Alternatively, *N*-hydroxysuccinimide (NHS) has been employed to activate acid moieties. In contrast to the *O*-acylurea intermediate resulting from carbodiimide activation, an NHS ester is formed. These NHS esters are very reactive toward amines and much less prone to hydrolysis than the carbodiimide esters.

The activation of acid-terminated monolayers using NHS/EDC chemistry on silicon, initially introduced by Boukherroub and coworkers,¹⁴¹ is widely employed as a common platform for the *in situ* attachment of amines, so as to obtain functional monolayers on silicon.^{131,142–144} Similarly, several approaches have been developed for the formation of NHS-activated silicon surfaces.^{50,145,146} Many of these procedures rely on the use of ω -ester or ω -acid-terminated 1-alkenes/1-alkynes, requiring several steps and rather harsh conditions that affect the monolayer quality, either after the hydrolysis step (for ester-terminated 1-alkene/1-alkyne monolayers) or due to upside-down attachments (in the case of acid-terminated 1-alkene/1-alkyne),^{142,147} although recently direct photochemical attachment of undecylenic acid was reported to proceed without upside-down attachment.¹³³ The use of photochemical methods enables the direct attachment of NHS esters onto silicon in a one-step reaction by irradiation of the silicon surface immersed in

ω -NHS-functionalized 1-alkene. Although irradiation with 254 nm^{138,148,149} leads to the formation of NHS-activated silicon surfaces, partial decomposition of the NHS-ester-terminated monolayer (30%) and formation of SiO₂ take place, linked to the photoreactivity of the NHS moiety under these circumstances. Recently, the mild and quantitative preparation of NHS-ester functionalized monolayers on silicon surfaces using mild photochemical methods (447 nm) was reported.¹⁵⁰ This method offers an alternative to prepare well-defined mixed monolayers from NHS-functionalized 1-alkene and 1-alkynes at room temperature. Under these conditions, no degradation of the NHS-ester moieties was detected. Further functionalization of the resulting surfaces with a variety of primary amines, as well as with biotin hydrazide, was investigated (Figure 38).

Apart from the attachment of small-molecule amines, NHS esters have been used for immobilization of substituted hydrazide derivatives and even in the covalent coupling of antibodies.¹⁵¹ This method is often applied to the immobilization of proteins, including native proteins, since no additional coupling reagents are required, and the conjugation proceeds in a single step. Achieving high conversion remains an issue however, due to hydrolysis of the NHS esters. Very recently, Sam *et al.*¹⁵² reported on the activation of acid-terminated monolayers via the NHS/EDC route on porous silicon (Figure 39). In these studies, infrared spectroscopy was used to investigate the formation of succinimidyl ester-terminated chains by varying the EDC and NHS concentrations in order to avoid by-products.

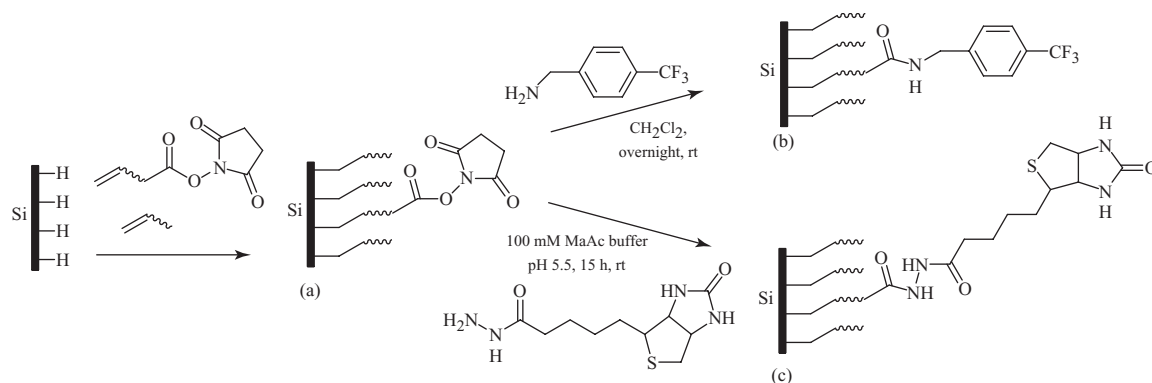


Figure 38 Schematic representation of (a) the formation of a mixed monolayer terminated with NHS-ester moieties, and the subsequent substitution of the NHS-ester moiety by (b) *p*-trifluoromethyl benzylamine (TFBA) or (c) biotin hydrazide. [Reprinted with permission from Ref. 150. Copyright 2008 American Chemical Society.]

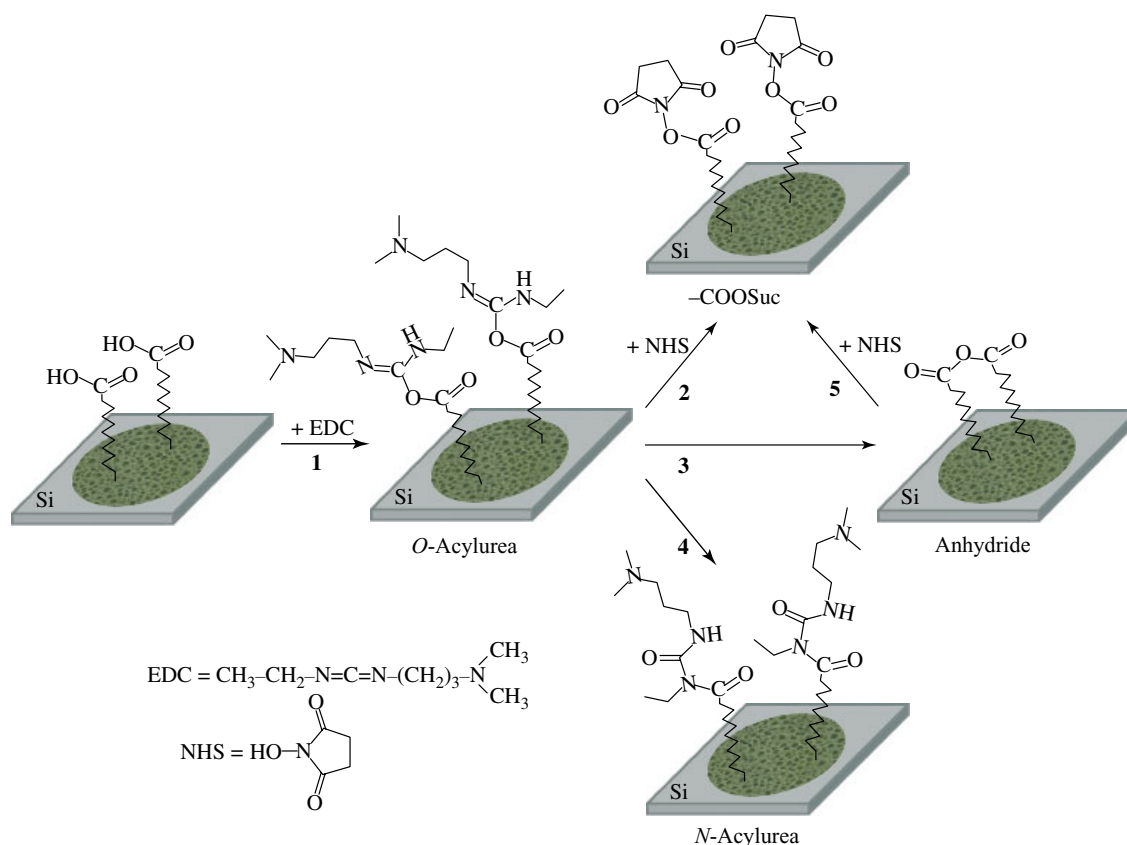


Figure 39 Schematic representation of activation reactions at the surface. Interaction between acid-terminated moieties and EDC, forming the *O*-acylurea intermediate (1) and subsequent reaction paths (2–5) for the experimentally detected products (succinimidyl ester, anhydride, urea). The kinetic competition between the various paths determines the final surface composition. [Reprinted with permission from Ref. 152. Copyright 2010 American Chemical Society.]

Equimolar mixing of EDC and NHS in a range of 5 mM was found to be optimal to achieve high conversions. These results are explained in terms of kinetic competition between different reaction pathways, taking into account that sites where NHS adsorbs at the surface become inactive. The applicability of these findings to flat hydrogenated silicon surfaces remains to be demonstrated.

Several alternative strategies have been reported toward activation of acid-terminated monolayers on silicon. For instance, an anhydride-terminated monolayer was obtained after reaction of the terminal acid moieties present in the monolayer with trifluoroacetic anhydride, in the presence of triethylamine.¹¹⁷ These surfaces were further reacted with allylamine in order to yield alkene moieties available for further reactions. Yet another approach relies on the covalent attachment of protected semicarbazide-functionalized alkenes on Si(111) surfaces via photochemical methods (254 nm, 2 hours), as depicted in Figure 40a.¹⁵³

Successful covalent binding of the organic layer onto the silicon surface was demonstrated by XPS and FTIR spectroscopy. However, the silicon surface did not remain oxide-free, especially after the acidic treatment to remove the protecting groups of the semicarbazide moieties. The deprotected semicarbazide-terminated monolayer was then further reacted with peptides bearing a glyoxylyl group for site-specific R-oxo semicarbazone ligation, Figure 40b. Successful peptide immobilization was confirmed by AFM and fluorescence experiments.

5.5 Acid Fluoride Monolayers

A highly useful functionalization of oxide-free silicon surfaces using acid fluoride-terminated alkynes was recently investigated.¹⁵⁴ The acid fluoride functionality is stable under ambient conditions, but reacts readily with strong nucleophiles (amines and anionic nucleophiles). In addition, acid fluoride-terminated monolayers do not form dimeric structures, since hydrogen-bonding interactions do not occur, which prevents extensive washing steps as required for carboxylic acid-containing alkenes/alkynes. These $\text{C}(=\text{O})\text{--F}$ terminated monolayers were prepared from 10-undecynoyl fluoride on oxide-free Si(111) under mild conditions (80 °C,

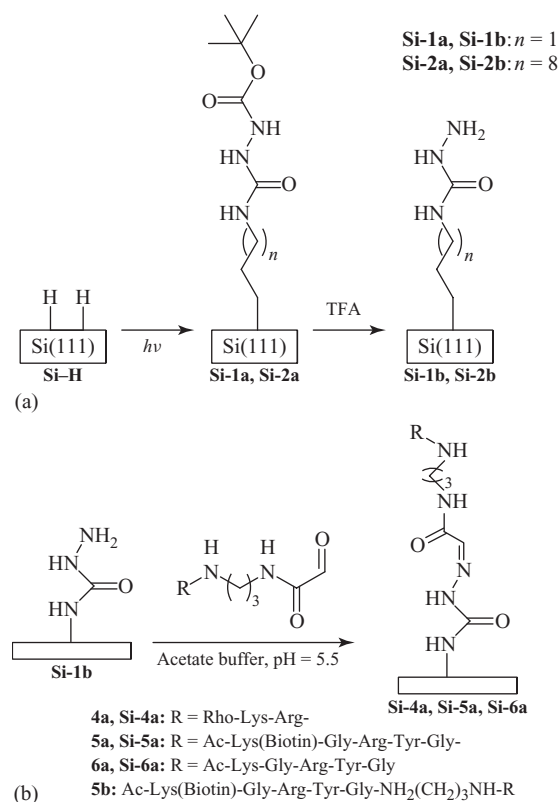


Figure 40 Schematic representation of (a) the functionalization of silicon surfaces with semicarbazide groups and (b) immobilization with different peptides. [Reprinted with permission from Ref. 153. Copyright 2005 American Chemical Society.]

16 hours; Figure 41). These surfaces remain oxide-free as indicated by the Si 2p narrow scan, in which no signals are observed in the 101–104 eV region. The terminal alkyne functionality of 10-undecynoyl fluoride reacts with H-Si under mild conditions and yields stable $\text{Si-C}\equiv\text{C}$ bonds on Si(111) that are known to inhibit the oxidation of the underlying Si substrate.^{43,69} The ellipsometric layer thickness of 12 Å is consistent with the length of the molecule, and the expected tilt angle of 30–35° with respect to the surface normal confirms the formation of the monolayer. Upside-down attachment are excluded as indicated by ATR-IR, which showed the double-bond stretching vibration of the $\text{Si-C}\equiv\text{C}$ moiety ($\nu_{\text{C}\equiv\text{C}}$ 1603 cm^{-1}) and CH_2 stretching vibrations, which indicate a high-quality packing that is rare for functionalized surfaces, whereas the more easily visible alkyne C-H stretch (expected around $\nu_{\text{C-H}}$ = 3309 cm^{-1}) remained

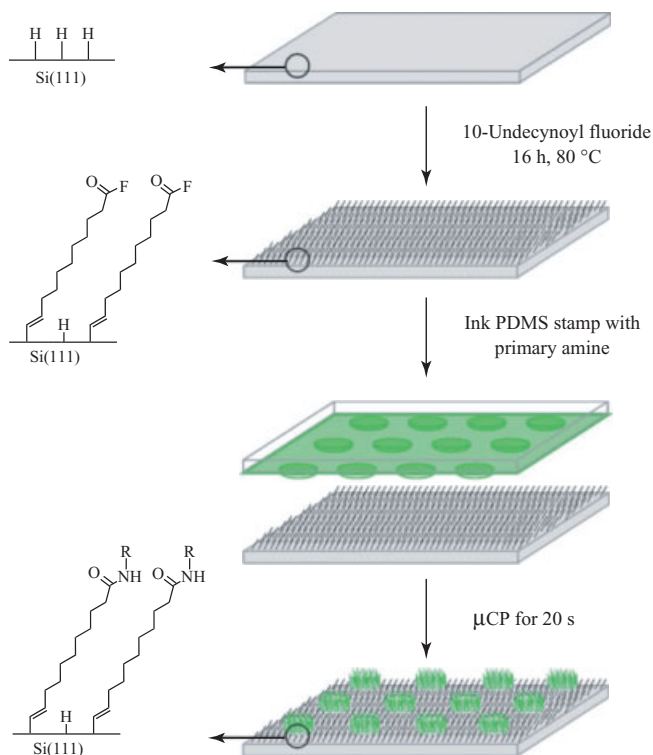


Figure 41 Schematic representation of the procedure used for μ CP on oxide-free silicon via highly reactive acid fluoride-functionalized monolayers. [L. Scheres, B. Klingebiel, J. ter Maat, M. Giesbers, H. de Jong, N. Hartmann, H. Zuilhof: Micro- and Nanopatterning of Functional Organic Monolayers on Oxide-Free Silicon by Laser-Induced Photothermal Desorption. *Small*. 2010, **6**, 1918–1926. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.]

absent. These acid fluoride-terminated monolayers were also employed as a reactive platform for further functionalization and patterning with primary amines. The high efficiency of amide formation was shown by quantitative amide formation upon application of reactive microcontact printing (μ CP) with a flat poly(dimethoxy silane) (PDMS) stamp (20 seconds) that is indistinguishable from surfaces that were immersed in a solution of *N*-decylamine (1 hours). Both surfaces showed an increase of water contact angle from 83° (acid fluoride layer) to 104°, which is indicative of a methyl-terminated layer. Furthermore, the layer thickness increased in both cases from 12 to 26 Å. ATR-IR showed complete conversion of acid fluorides (complete disappearance of acid fluoride absorption at 1843 cm⁻¹ and the appearance of the amide N–H stretch at 3313 cm⁻¹). The stability of the resulting *N*-hexadecylamide-terminated monolayers in water was investigated by XPS, which displays as most

characteristic feature the lack of oxide formation, even after amide formation (no traces of SiO₂ at the surface around 102 eV). The high reactivity toward amines makes acid fluoride-terminated monolayers excellent platforms for reactive μ CP, while the high selectivity of the amide formation makes them excellent intermediates for introducing a broad range of functionalities on oxide-free silicon surfaces, including complex biomolecules, such as fluorescently labeled oligo-DNA on oxide-free silicon, which is still accessible for hybridization.¹⁵⁴

For more information regarding μ CP, the reader is directed to the work of Zhu and coworkers (μ CP of alcohols on Si–Cl surfaces),¹⁵⁵ that of Mizuno and Buriak (μ CP of 1-octadecyne directly on Si(111) and Si(100) by use of catalyst-impregnated stamps),¹⁵⁶ and the work of Toone and coworkers (catalytic conversion of terminal groups on the monolayer by chemically modified stamps).^{53,157}

5.6 Click Chemistry

Owing to the relatively sensitive nature of silicon surfaces, the wide range of desirable functionalizations requires versatile reactions that proceed under mild conditions. Hence, in addition to, for example, the amide-forming reactions from NHS esters or acid fluorides (see above), click reactions have attracted considerable attention for orthogonal and site-selective immobilization of functional moieties.¹⁵⁸ Click reactions are identified by the mild reaction conditions needed, their high chemo- and regioselectivity, and their efficiency.^{158,159} Gooding and coworkers prepared alkyne-terminated monolayers on Si(100) through thermal addition of 1,9-nonadiyne. Subsequently, the Cu-catalyzed azide-alkyne cycloaddition was employed to attach a variety of functional azides onto these monolayers.^{160,161} Very robust oxide-free modified silicon surfaces were produced via the hydrosilylation reaction. Moreover, these surfaces are stable to allow the preparation of redox assemblies for aqueous environments and antifouling surfaces.^{161,162}

The radical addition reaction of thiols to alkenes or alkynes has recently emerged as an elegant and appealing alternative coupling reaction (see **Radical Thiol-X Click Chemistry**). Very mild reaction conditions, the absence of a metal catalyst, and the ready availability of thiol-functional (bio)molecules are distinctive features of this coupling chemistry.^{159,163,164} In addition, these radical reactions have been used as an efficient strategy toward immobilization and patterning of biomolecules on inorganic substrates such as gold, glass, and silicon.^{159,162,165} For example, Bertin and Schlaad used thiol-ene chemistry as a method to rapidly functionalize glass substrates with polymers.¹⁶⁶ Dendrimeric and polymeric approaches have been reported, demonstrating both thiol-ene and thiol-yne chemistry. Waldmann and coworkers, for example, used polyamidoamine dendrimers attached covalently to silicon oxide surfaces to develop a new method for the site-specific immobilization and patterning of proteins.^{167,168} Patton and coworkers used silicon substrates functionalized with silanes to generate a library of polyfunctional, patterned, and multicomponent polymer brush surfaces.¹⁶⁹ Recently, Ravoo and coworkers reported the immobilization of functional thiols on

alkene- and alkyne-terminated SAMs on silicon oxide substrates by photochemical μ CP.¹⁷⁰ Although these strategies are not specific for oxide-free silicon surfaces, the versatility of the employed coupling strategies allows their easy extension to these surfaces. This was shown, for example, by Buriak and coworkers who used thiol-ene chemistry for the layer-by-layer assembly of α,ω -dithiols and α,ω -diene molecules on oxide-free silicon, silicon oxide, and germanium surfaces.¹⁷⁰ The Si(100) surfaces were modified using photochemical methods (254 nm, 3 hours) by reacting the hydrogen-terminated silicon surface with the desired α,ω -diene (i.e., 1,7-octadiene, 1,11-dodecadiene). The alkene-terminated monolayers thus obtained were immersed in neat α,ω -dithiols, and after UV irradiation for 0.5 hours, thiol-terminated monolayers were generated. Subsequent reaction of these silicon surfaces with α,ω -dienes led to the formation of alkene-terminated monolayers, and this procedure was continued until the desired number of layers was reached, Figure 42. This layer-by-layer approach provides an interesting platform for growing covalently bound films of controlled thickness onto oxide-free silicon.

Recently, Zuilhof and coworkers reported on a versatile approach employing thiol-ene click chemistry as a versatile, efficient, and patternable route to functionalize silicon surfaces under ambient atmosphere without the introduction of silicon oxide.¹⁷¹ In these studies, alkene-terminated monolayers on oxide-free Si(111) were obtained after reaction of hydrogen-terminated Si(111) with neat 1,13-tetradecadiene under thermal conditions (80 °C, 16 hours). The alkene-terminated monolayers were further exposed to 365 nm light in the presence of different functional thiols and 2,2-dimethoxy-2-phenylacetophenone (DMPA), which acted as a photoinitiator (Figure 43). This led to a wide range of functionalized surfaces, which in all cases displayed a high surface coverage (45–75%; typically limited by the steric bulk of the functional group with respect to the alkene chains), while the silicon surfaces did not undergo any discernable oxidation.

In addition, μ CP of thioglycolic acid onto an alkene-terminated monolayer was investigated. A PDMS stamp with 10- μ m pillar-like features was covered with a mixture of thioglycolic acid and

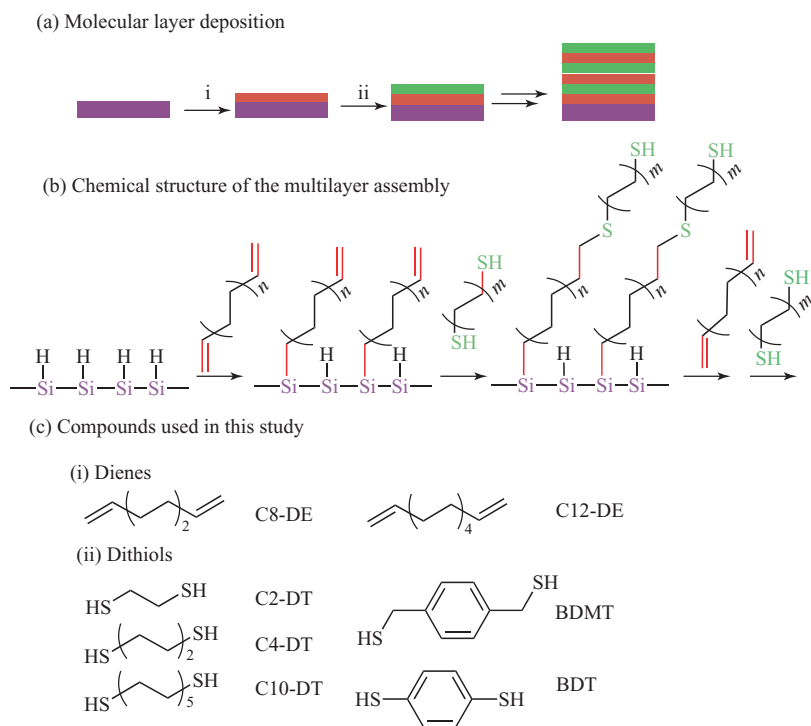


Figure 42 (a) Schematic representation of the covalent molecular layer deposition assembly of a thiol-ene multilayer, (b) chemical structure of the multilayer assembly, and (c) dienes and dithiols employed in this study. [Reprinted with permission from Ref. 170. Copyright 2009 American Chemical Society.]

DMPA in ethanol, subsequently brought into contact with the alkene-functional silicon substrate, and next the surface was irradiated through the stamp for 5 minutes. After thorough cleaning of the substrate, the surface displayed a 10- μm sphere pattern in the AFM phase image, confirming successful transfer of the pattern, as shown in Figure 43c.¹⁷¹ This further demonstrates that thiol-ene chemistry provides an efficient method for metal-free light-induced patterning onto silicon.(c)

6 PERSPECTIVES

The rapidly development of novel approaches to form covalently attached monolayers on silicon surfaces parallels the deepening insights into silyl radical chemistry. The high stability of Si-C bonds, in combination with the versatile chemistry available for the functionalization of monolayers, makes these systems ideal platforms for electronic

and sensory devices. This section outlines the currently unresolved “hot” topics in this area.

Since the pioneering research in the early 1990s, monolayer fabrication has seen major developments. Starting from experiments using relatively harsh reaction conditions (temperatures $>200^\circ\text{C}$),^{49,56} methods progressed into much milder methods for the generation of surface-centered silyl radicals. Si-H bonds were also shown to cleave under UV irradiation,^{43,78,83} and eventually monolayer formation was demonstrated to occur without the direct cleavage of these bonds (white-light method and attachment in the dark).^{64,69,88–90} These increasingly milder methods have resulted in the direct attachment of sensitive molecules, such as complex sugars and peptides, that would otherwise degrade.¹⁷² At this moment, experimentalists have a repertoire of mild methods and techniques available.^{2–4} Depending on the desired properties, ease of use, and availability of precursors, several options exist for the fabrication of monolayers on silicon.

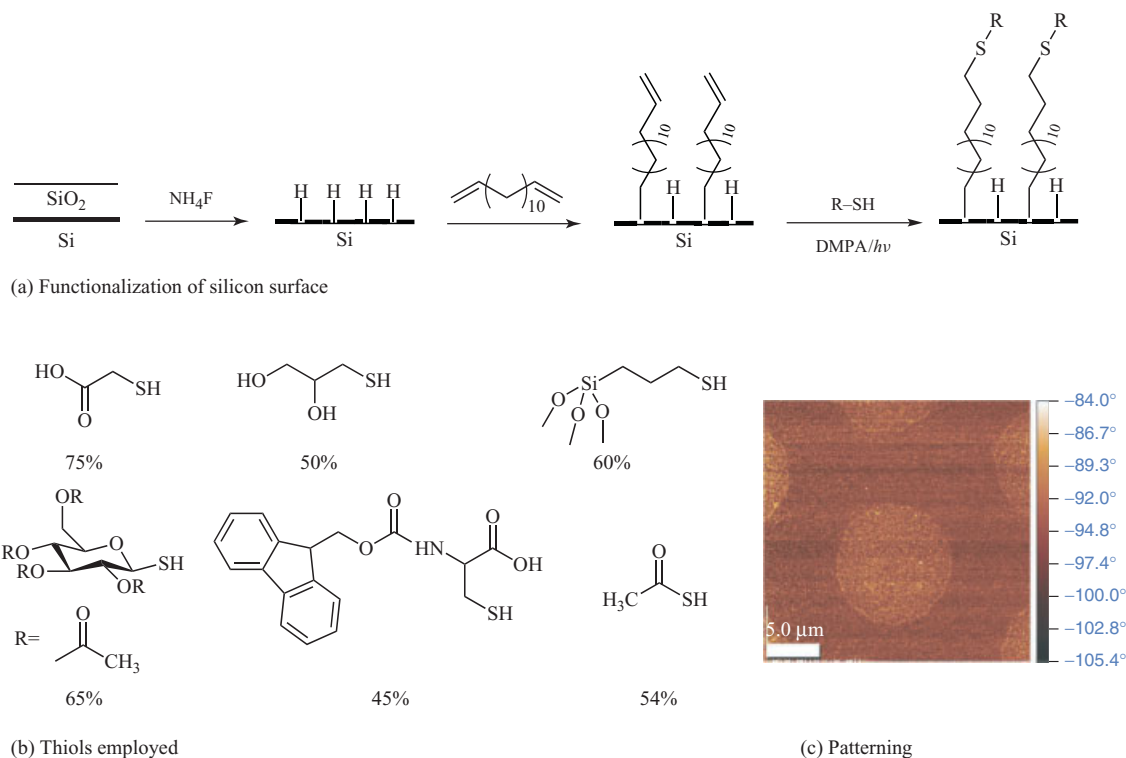


Figure 43 (a) Schematic representation of functionalization of silicon surfaces using thiol–ene chemistry; (b) Thiols employed in surface functionalization, with corresponding surface coverages; (c) AFM phase image of the patterned silicon monolayer with thioglycolic acid. [M. A. Caipa Campos, J. M. J. Paulusse, H. Zuilhof, *Chem. Commun.* 2010, **46**, 5512–5514—Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/C0CC01264E>.]

A major challenge, however, still lies in speeding up monolayer formation. Where typical formation of SAMs from thiols on gold using stamps takes minutes,¹⁷³ attachment onto silicon is still takes hours. Experiments have shown that up to 90% of the layer is formed within minutes; yet filling up the remaining holes (and thus completing the layer) is a slow process.^{67,174} Looking from a radical chemistry perspective, basically there are two approaches to achieve this speedup. The first approach is to change reaction conditions in order to initiate more dangling bonds at the silicon surface. Radical addition and the subsequent hydrogen transfer have been shown to be efficient reactions for covalent attachment of precursors. In this respect, addition of radical initiators and/or catalysts may prove valuable in increasing the reaction rates, as long as no undesirable side reactions take place. Additionally, irradiation (UV or visible light) possibly assisted by electronic modification of the surface properties

(bias voltages) may also catalyze the formation of surface-centered radicals.

A promising second approach to the speedup may lie in the modification of the precursors. An enhanced reactivity in both the addition and hydrogen-transfer steps may lead to larger islands and longer lines, depending on the surface (Si(111) and Si(100), respectively).^{114,115} Moreover, recent studies show that modification of these precursors—in order to reduce the number of close contacts near the surface—also contributes to higher surface coverages and increased packing of the monolayers.⁹⁸

Another “hot” topic is the functionalization of monolayers. With the advent of efficient coupling chemistry, also new moieties are readily introduced in the monolayers. Functionality of these layers has progressed from aldehydes and acids to azides and alkenes, which can be used in “click” chemistry (alkyne–azide, thiol–ene, etc.) for the attachment of more complex molecules. However,

the ever-increasing demand for high-quality monolayers on oxide-free silicon requires side reactions of functional moieties to be reduced to an absolute minimum, as indicated, for example, by the attachment of ω -aldehyde functionalized alkenes to Si(111).¹¹³ Since aldehydes are also reactive toward silyl radicals, up to 10% of the precursors attaches via this moiety instead of the desired attachment via the alkene. For aldehyde-functionalized alkynes, however, this ratio is expected to further shift in favor of the alkyne attachment. In general, alkyne-derived Si–C-linked monolayers display superior linking properties as compared to alkene-based monolayers in terms of packing density,^{70,98} rate of formation,^{69,70,97,114} and stability toward oxidation,¹²³ and alkyne precursors are thus expected to be the basis of novel functional monolayers on silicon surfaces.

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Persistent and Stable Silyl Radicals

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1 INTRODUCTION

Silyl radicals are reactive intermediates that play an important role in many fields of chemistry. For recent reviews see Refs 1–7. For example, silyl radicals efficiently abstract halogen atoms from organic halides, and thus serve as reducing agents in organic synthesis (Scheme 1a)^{3,4,7}; they are also efficient photoinitiators of polymerization (see **Overview of Radical Initiation**)⁸ and are used as catalysts in cyclotrimerization of acetylenes.⁹ Silyl radicals are also intermediates in the synthesis and photodegradation of polysilanes, an important class of polymers^{10,11} (Scheme 1b).

Silyl radicals are often generated on silicon surfaces¹²—one of the technologically most important materials in the electronic industry. For example, significant recent attention is directed toward the synthesis of organic monolayers on silicon surfaces which can be modified for specific technological requirements,^{12,13} as demonstrated in Scheme 2 for H–Si(111) surfaces (see **Silicon Radical Surface Chemistry**). Such surfaces undergo radical-activated reactions involving silyl radicals with a variety of terminal olefins to yield densely packed monolayers, which can be modified for specific requirements (Scheme 2).¹³

In view of this broad interest and the numerous applications of silyl radicals in general and of polysilyl radicals in particular, knowledge of their fundamental properties and ways to control their reactivity is very important.

Simple aliphatic carbon-centered¹⁴ and silicon-centered radicals^{15,16} are in general highly reactive intermediates and have very short lifetimes. For example, $\text{MeH}_2\text{Si}^\bullet$, $\text{Me}_2\text{HSi}^\bullet$, and $\text{Me}_3\text{Si}^\bullet$ were observed by electron paramagnetic resonance (EPR) spectroscopy in solution only at low temperature (150–200 K) and their half-lifetimes ($\tau_{1/2}$) are at an estimated range of 0.005–0.01 s.^{15,16} Bulky alkyl, aryl, and silyl substituents reduce the reactivity of simple C-centered radicals prolonging their lifetimes, making them relatively long-lived.^{17,18} Several stable carbon-centered radicals stabilized by conjugation, for example, triarylmethyl, have been isolated.^{19,20} One case of a stable aliphatic silyl-substituted carbon-centered radical lacking resonance stabilization has also been reported.²¹ A stable triarylgermyl radical was recently isolated.²² In contrast, triarylsilyl radicals are not stable enough to be isolated; their half-life times are estimated to be 0.1–1 s (Figure 1).²³

The properties, chemistry, and stability of reactive short-lived silyl radicals have been reviewed.^{3–5} In this review, we concentrate on persistent and stable silyl radicals. The synthesis and isolation of stable silyl radicals and their heavy congeners is fundamentally interesting and opens up many new opportunities. For example, stable radicals can serve as “building blocks” for new materials which may possess a unique combination of magnetic, electrochemical, and photochemical properties. Stable aromatic organic radicals, such as dendritic and polymeric radicals of the triphenylmethyl type, have

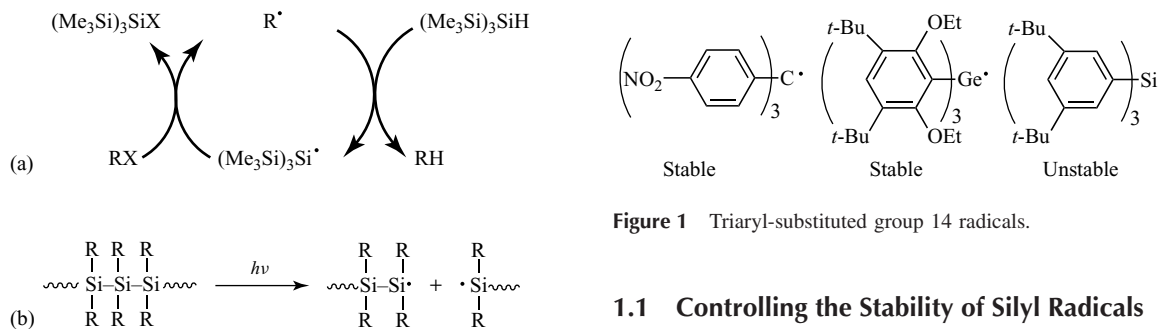


Figure 1 Triaryl-substituted group 14 radicals.

1.1 Controlling the Stability of Silyl Radicals

The thermodynamic and kinetic stability of radicals can be controlled by the electronic and steric effects of their substituents.

1.1.1 Thermodynamic Stabilization—Electronic Effects

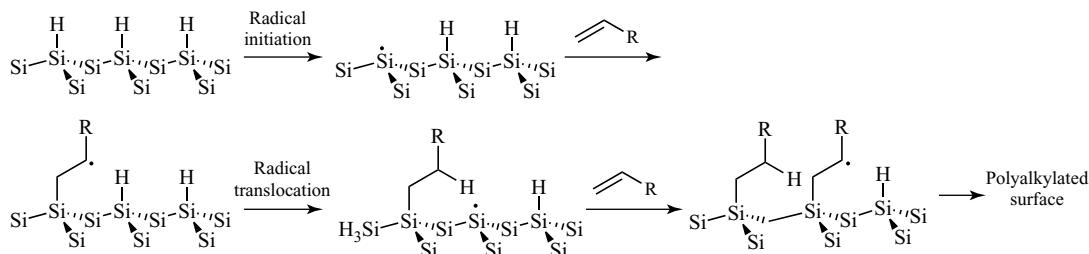
There is little data, either experimental or theoretical, on the effect of substituents on the stability of silyl radicals. The experimental and theoretical data presented here were gathered from different sources. For experimental data, two main sources were used: (i) the comprehensive NIST database³³ and (ii) *Handbook of Bond Dissociation Energies in Organic Compounds*.³⁴ We have also used experimental data reported in the references that are cited in Table 1. The reported theoretical values are at different levels of calculation, and the reader is referred to the cited original papers given in Table 1 for details.

A measure of the thermodynamic stability of a substituted radical $\text{RH}_2\text{E}^\bullet$ is provided by the E–H bond dissociation energy (BDE) of RH_3E . Substituents that reduce the BDE stabilize the radical, and vice versa. The stabilization energy of $\text{RH}_2\text{E}^\bullet$ relative to $\text{H}_3\text{E}^\bullet$, reflecting the effect of

already found applications as organic magnets²⁴ and as new paramagnetic materials,²⁵ and nitroxyl type radicals have been applied in organic radical polymer batteries (see **Tin Hydrides and Functional Group Transformations**).²⁶ Fullerene-based stable radicals can potentially be used in electron-spin quantum computing,²⁷ and stable silyl radicals can in principle play a similar role.

In this review, the major focus is on persistent and stable silyl radicals, and in particular on stable polysilyl radicals which are the majority in this group. We define a stable radical as one that can be isolated and handled as a pure compound. Radicals that are relatively long-lived and can be observed using conventional spectroscopic methods, but cannot be isolated, are classified as “persistent.”¹⁷ The term “persistent” is of course subjective and we use it for radicals that have a lifetime of several hours or longer.

Readers who are interested in radicals of the heavier congeners of silicon, Ge, Sn, and Pb are referred to Refs 2, 6, and 28–32.



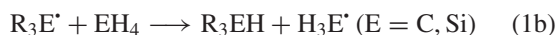
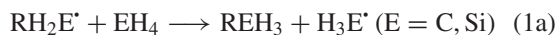
Scheme 2 Silyl radical activated olefination of a H-Si(111) surface.

Table 1 Experimental^a and calculated^b energies ΔE (kcal mol⁻¹) for isodesmic equations (1a), (1b), and (2).

ΔE of equations (1a) and (1b) ^c				
Radical	E = Si		E = C	
	Experiment	Theory	Experiment	Theory
(H ₃ C)H ₂ E [•]	-1.0 ^d	-1.0 ^e	4.0 ^f ; 4.5 ^{d,e}	3.8 ^f ; 3.9 ^e
(H ₃ C) ₃ E [•]	-2.9 ^g	-2.0(-1.4) ^h	9.5 ⁱ	6.8 ^j
PhH ₂ E [•]	-0.4 ^{d,e}	0.4 ^{d,e}	14.6 ^f ; 16.5 ^{d,e}	14.1 ^f ; 13.7 ^e ; 14.6 ^j
Ph ₃ E [•]	3.2 ^g	3.1 ^k	24.1 ^l	24.7 ^m
LiH ₂ E [•]	—	12.0 ⁿ	—	9.4 ⁿ
(H ₃ Si)H ₂ E [•]	2.9 ^o	2.8 ^{k,o}	—	2.8 ^p
(H ₃ Si) ₃ E [•]	—	7.6 (6.3) ^h	—	—
(Me ₃ Si)H ₂ E [•]	—	2.6 ^e	5.0 ^e	2.9 ^q ; 3.0 ^e
(Me ₃ Si) ₃ E [•]	8.1 ^g ; 8.0 ^k	7.2 ^h ; 8.8 ^k	—	7.4 ^q
FH ₂ E [•]	—	-2.6 ^e	3.7 ^e ; 3.5 ^f	3.8 ^e ; 3.5 ^f ; 3.1 ^j
F ₃ E [•]	-11.5 ^{g,k}	-6.5(-7.7) ^h ; -7.6 ^k	-2.4 ^d	-1.0 ^m
ClH ₂ E [•]	-1.3 ⁱ	-0.2 ^e	5.5 ^f ; 5.7 ^e	5.0 ^f ; 4.9 ^e
Cl ₃ E [•]	-2.6 ^g ; 0.4 ^k	0.8 ^k	11.2 ^d	10.1 ^m
BrH ₂ E [•]	—	1.9 ^h	3.4 ^d	3.4 ^f
Br ₃ E [•]	12.0 ^d	6.3 ^h	9.6 ^d	—
(H ₂ N)H ₂ E [•]	—	1.0 ^e (2.7 ^r) ^e	11.1 ^e (14.0 ^r) ^e	12.0 ^e (12.3 ^r) ^e ; 10.7 ^j
(H ₂ N) ₃ E [•]	—	-2.9 ^k	—	11.2 ^q
ΔE of equation (2) ^s				
Radical	Experiment ^t		Theory	
H ₃ E [•]	-13.2 ^u		-12.6 ^u	
(H ₃ C) ₃ E [•]	-0.8		0.5 ^v	
Ph ₃ E [•]	7.7		—	
(H ₃ Si) ₃ E [•]	—		-15.3 ^w	
(Me ₃ Si) ₃ E [•]	—		-16.1 ^w	
F ₃ E [•]	-4.5		—	
Cl ₃ E [•]	-1.2		—	

^aThe experimental energies were derived from E–H bond dissociation energies or from the relevant standard heats of formation.^bFor the level of calculations see the cited references.^cPositive values indicate stabilization by R.^dReference 34.^eReference 35.^fReference 36.^gReference 37.^hReference 38.ⁱReference 33.^jReference 39.^kReference 40.^lReference 41.^mReference 42.ⁿReference 43.^o ΔE derived from data in Ref. 37 (exp.) and Ref. 38 (calc.).^pReference 39, see also Ref. 43.^qFrom calculated bond dissociation free energies, Ref. 44.^rFor ((H₃C)₂N)H₂Si[•].^sNegative values imply that R₃Si[•] is more stable than R₃C[•].^tDerived from the experimental values given above for (1b).^uReference 45.^vOur unpublished results at B3LYP/6-31G(d).^wReference 46.

substituent R, is given by the difference between the E–H BDE in EH_4 and in H_3ER . This value is referred to as the *radical stabilization energy* (RSE) and is determined by isodesmic hydrogen transfer equations (1a) [(1b) for $\text{R}_3\text{E}'$]. The thermodynamic effect of the substituents is attributed to their ability to delocalize the unpaired electron.^{36,38,43,45} The energies of isodesmic equations (1a) and (1b) for $\text{E} = \text{Si}$ and C and $\text{R} = \text{Me}$, Ph (phenyl), Li , SiH_3 , SiMe_3 , F , Cl , Br , and NH_2 are collected in Table 1. Isodesmic equation (2) (Table 1) compares the RSEs of $\text{R}_3\text{Si}'$ relative to those of $\text{R}_3\text{C}'$. The experimental energies of (1) and (2) were derived from E–H BDEs or from relevant heats of formation. A positive value indicates that R is stabilizing, that is, (1), or that $\text{R}_3\text{C}'$ is more stable than $\text{R}_3\text{Si}'$, that is, (2).



Substitution of $\text{H}_3\text{Si}'$ with one methyl group has a small destabilizing effect of 1 kcal mol^{-1} (1a). Three methyl groups destabilize it by $2.9 \text{ kcal mol}^{-1}$.³⁷ A single phenyl substituent does not affect the stability of $\text{H}_3\text{Si}'$, and $\text{Ph}_3\text{Si}'$ is stabilized by circa 3 kcal mol^{-1} relative to $\text{H}_3\text{Si}'$. The electropositive silyl substituent has a significantly larger stabilizing effect, and $(\text{R}_3\text{Si})_3\text{Si}'$ ($\text{R} = \text{H}$, Me) is stabilized by circa $\sim 7\text{--}9 \text{ kcal mol}^{-1}$ relative to $\text{H}_3\text{Si}'$. A β -silyl substitution is calculated to have no effect on the thermodynamic stability of silyl radicals.⁴⁷ The electropositive Li substituent has a large calculated stabilizing effect of 12 kcal mol^{-1} .⁴³ On the other hand, the electronegative fluorine destabilizes the silyl radical and $\text{F}_3\text{Si}'$ is by 11 kcal mol^{-1} (experimental, calculated $6.5\text{--}7.5 \text{ kcal mol}^{-1}$) less stable than $\text{H}_3\text{Si}'$ (Table 1). Chlorine substitution has a small effect on the stability of $\text{H}_3\text{Si}'$, while three bromine substituents stabilize the silyl radical by as much as 6 kcal mol^{-1} (calculated) or 12 kcal mol^{-1} (experiment) (Table 1). The π -donating amino group is slightly destabilizing (Table 1). In summary, the substituent stabilizing effect follows the order [(1a) and (1b), Table 1] Li (strongly stabilizing) $\gg \text{Br} \approx \text{SiR}_3 > \text{phenyl} > \text{Cl} \approx \text{Me} \approx \text{NH}_2 > \text{F}$ (strongly destabilizing).

A comparison of the thermodynamic stability of silyl radicals and the corresponding alkyl radicals (2) is of interest. The parent $\text{H}_3\text{Si}'$ radical is thermodynamically more stable than $\text{H}_3\text{C}'$ by $\sim 13 \text{ kcal mol}^{-1}$ ⁴⁵ (Table 1). However, as the effect of substituents on $\text{H}_3\text{C}'$ and $\text{H}_3\text{Si}'$ is very different (compare (1a) and (1b) for $\text{E} = \text{C}$ and $\text{E} = \text{Si}$, Table 1), the relative stabilities of substituted silyl and methyl radicals change significantly depending on R. For example, three methyl groups stabilize the methyl radical by as much as $9.5 \text{ kcal mol}^{-1}$ ³³ (exp., $6.8 \text{ kcal mol}^{-1}$ calc.,³⁹ Table 1), in contrast to a destabilization of $2\text{--}3 \text{ kcal mol}^{-1}$ of the silyl radical. These opposing substituent effects place $\text{Me}_3\text{C}'$ and $\text{Me}_3\text{Si}'$ at nearly the same thermodynamic stability ((2) for $\text{R} = \text{Me}$ is nearly thermoneutral). Similarly, the π -conjugating phenyl substituents have a significant stabilizing effect of 24 kcal mol^{-1} on the methyl radical and thus $\text{Ph}_3\text{C}'$ is $\sim 8 \text{ kcal mol}^{-1}$ more stable than $\text{Ph}_3\text{Si}'$. The electropositive silyl substituent has a similar stabilizing effect on both silyl and methyl radicals and therefore $(\text{R}_3\text{Si})_3\text{Si}'$ is more stable than $(\text{R}_3\text{Si})_3\text{C}'$ ($\text{R} = \text{H}$, Me) by $\sim 15\text{--}16 \text{ kcal mol}^{-1}$ (Table 1). An amino group has a significant stabilizing effect on a methyl radical but a small destabilizing effect on the analogous silyl radical, and thus $(\text{H}_2\text{N})_3\text{Si}'$ and $(\text{H}_2\text{N})_3\text{C}'$ have similar stability.

1.1.2 Kinetic Stabilization—Steric Effects

Kinetic stabilization of silyl radicals is effectively achieved by the introduction of bulky substituents. For example, $(\text{Me}_3\text{Si})_3\text{Si}'$ has a half-life of $0.1\text{--}1 \text{ s}$, and $(i\text{-Pr}_3\text{Si})_3\text{Si}'$ has a half-life of 3 days.⁴⁸ The use of even larger substituents, such as $t\text{-Bu}_2\text{MeSi}$, has led recently to the isolation and structural characterization of stable silyl radicals and other group-14-centered radicals.^{1,2,28–31,49,50} These large silyl substituents sterically protect the radical center from undergoing typical radical reactions, such as dimerization, hydrogen abstraction, and disproportionation, and prolong their lifetime. For example, $(t\text{-Bu}_2\text{MeSi})_3\text{Si}'$ is stable at room temperature for several years in an inert medium.^{49,50}

Another important factor controlling the lifetime of $\text{R}_3\text{E}'$ is the central atom E.^{5,14–18,23,32,51} The heavier the E atom, the longer is the E–E bond

in the dimer formed by recombination of two R_3E radicals and consequently the larger the substituents required to create sufficient steric repulsion which would inhibit dimerization and thus stabilize kinetically the radical. In R_3C-CR_3 , the C–C distance is 1.5–1.6 Å⁵² and six $R = Me_3Si$ substituents cause steric repulsion, which is large enough to hinder dimerization, making $(Me_3Si)_3C^\bullet$ persistent with a lifetime of several days at 298 K.^{17,18} In sharp contrast, the analogous Si-centered radical $(Me_3Si)_3Si^\bullet$, which is thermodynamically more stable than $(Me_3Si)_3C^\bullet$ (see Table 1, Section 1.1.1), is highly reactive ($\tau_{1/2}$ of 0.1–1 s at 298 K).^{5,16} This large difference in the lifetimes between $(Me_3Si)_3C^\bullet$ and $(Me_3Si)_3Si^\bullet$ is due primarily to the fact that the Si–Si bond distance in the corresponding dimer (2.4 Å),⁵³ is much longer than that of a C–C bond and therefore the Me_3Si substituents are not large enough to suppress the dimerization of $(Me_3Si)_3Si^\bullet$. Thus, the high kinetic stability of $(Me_3Si)_3C^\bullet$ imposed by the substituents' steric effects overrides its lower inherent thermodynamic stability compared with that of $(Me_3Si)_3Si^\bullet$, as well as the fact that the C–C bond is much stronger than a Si–Si bond (90.2 kcal mol^{−1} for H_3C-CH_3 vs 76.7 kcal mol^{−1} for $H_3Si-SiH_3$ ⁵²). The relationship between the dissociation energy of the central Si–Si bond in $R_3Si-SiR_3$ and the kinetic stability of the corresponding $R_3Si^\bullet$ radicals is discussed in more detail in Section 2.4.1.

1.2 Structure

The methyl radical, $H_3C^\bullet$, is planar.⁵⁴ In contrast, $H_3Si^\bullet$ has a pyramidal C_{3v} structure (where the sum of the bond angles around the radical center ($\Sigma\theta$) is 332.6°) and the inversion barrier is 5.3 kcal mol^{−1}.^{55,56} $Me_3Si^\bullet$ is slightly more pyramidal than $H_3Si^\bullet$ ($\Sigma\theta = 331.1^\circ$), but its inversion barrier is significantly higher, 12.1 kcal mol^{−1} (Y. Apeloig, *et al.*, unpublished results). Calculations predict that α -trisubstituted silyl radicals $R_3Si^\bullet$ ($R = H_3C, H_2N, OH, F, H_3Si, H_2P, HS, Cl$) are all pyramidal at the silicon radical center (Figure 2) (Y. Apeloig, *et al.*, unpublished results).⁵⁷ The degree of pyramidality is larger for substituents that possess lone-pair electrons ($\Sigma\theta$ of 321–327°) (Y. Apeloig, *et al.*, unpublished results see also Ref. 57). On the other hand, silyl substituents decrease the degree of pyramidality; for example, in $(H_3Si)_3Si^\bullet$ $\Sigma\theta = 348^\circ$

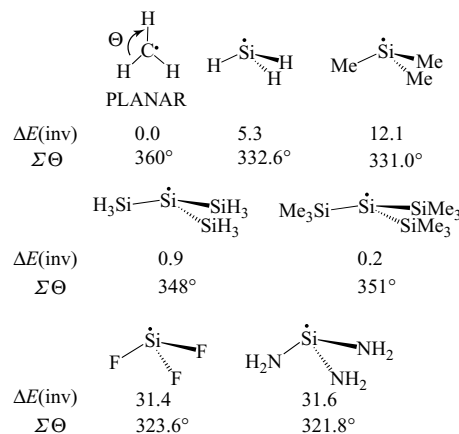


Figure 2 Calculated (UB3LYP/6-31+G(d)) degree of pyramidality $\Sigma\theta$ and inversion barriers (kcal mol^{−1}) of several silyl radicals (Y. Apeloig, *et al.*, unpublished results).

and the inversion barrier is 0.9 kcal mol^{−1} and it decreases to only 0.2 kcal mol^{−1} in $(Me_3Si)_3Si^\bullet$ (Figure 2) (Y. Apeloig, *et al.*, unpublished results). Larger silyl substituents decrease the degree of pyramidality and the inversion barrier even further, and X-ray analysis shows that $(t-Bu_2Me)_3Si^\bullet$ is planar (*vide infra*).⁴⁹

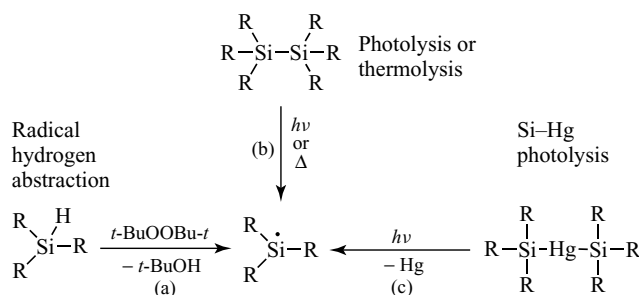
More calculations on the structures and magnetic properties of various silyl radicals are available, and the interested reader is referred to these papers.^{51,57–59} Accurate quantum mechanical calculations of structural and EPR parameters of other free radicals can be found in Refs 60–62.

2 TRIS(SILYL)-SUBSTITUTED SILYL RADICALS

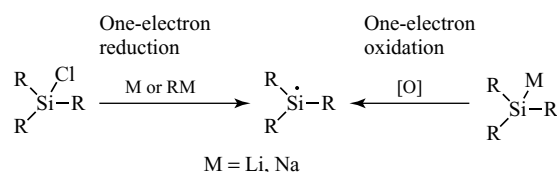
This group of radicals deserves a separate section because they comprise most of the known persistent and stable silyl radicals.

2.1 Methods of Generation

The methods used to generate silyl radicals in general and tris(silyl)silyl radicals in particular, can be divided into three major groups: (i) Methods involving hydrogen abstraction from Si–H bonds (Scheme 3, path (a)); (ii) Si–Si or Si–Hg bond cleavage by photolysis or thermolysis (Scheme 3,



Scheme 3 Generation of silyl radicals by bond cleavage.



Scheme 4 Generation of silyl radicals by one-electron reduction of silylhalides and by one-electron oxidation of metallosilanes.

path (b) and (c), respectively). These methods are usually used to generate reactive or persistent radicals within the cavity of the EPR spectrometer; (iii) Methods involving one-electron reduction of silylhalides or one-electron oxidation of metallosilanes (Scheme 4). These methods allow obtaining radicals in high concentrations, making it possible in some cases to isolate them.

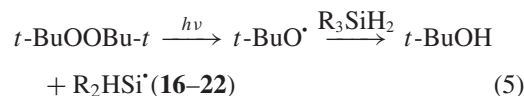
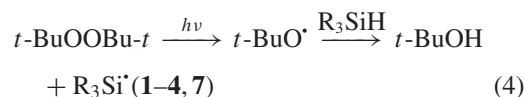
2.1.1 Hydrogen Abstraction

Hydrogen abstraction is the most widely used method for generating silyl radicals. It involves the reaction of silicon hydrides with atoms, radicals, or excited molecules (3).^{3,15,16,50,51}



For example, the reaction of photolytically generated $t\text{-BuO}^\bullet$ with tris- or bis(silyl) substituted silanes was extensively used to produce silyl radicals for organic synthesis and for their study by EPR spectroscopy ((4) and (5), respectively; radical numbers

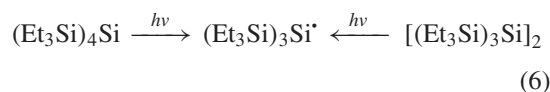
refer to the radicals given in Tables 2–4).^{3,15,51}



A variety of silyl radicals, shown in Tables 2 and 4, ranging from the short-lived $\text{Me}_3\text{Si}^\bullet$,¹⁵ **1–4**,^{5,16,63} and **16–22**⁵¹ to the persistent ($i\text{-Pr}_3\text{Si}$)₃Si[•] (**7**) radical,⁴⁸ were generated using this method. The main disadvantage of this method is its low yield and therefore in general it cannot be used for the preparative synthesis of stable silyl radicals.

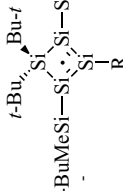
2.1.2 Si–Si Bond Cleavage

A variety of silyl radicals were generated by photolysis or thermolysis of polysilanes.^{47,63,64} For example, the tris(silyl)silyl radicals ($\text{Et}_n\text{Me}_{3-n}\text{Si}$)₃Si[•] ($n = 1–3$) were generated by photolysis of tetrakis(silyl) silanes ($\text{Et}_n\text{Me}_{3-n}\text{Si}$)₄Si and hexakis(silyl) disilanes [($\text{Et}_n\text{Me}_{3-n}\text{Si}$)₃Si]₂ (**6**).⁶³

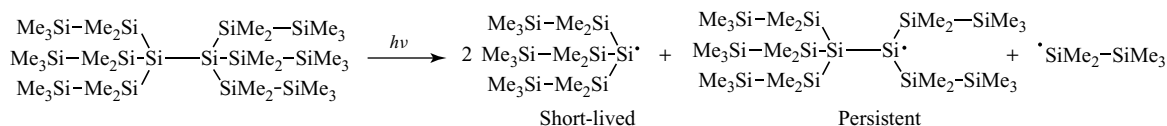


Photolytic generation of polysilyl radicals from the corresponding dimers is not always a selective processes and it can produce several radicals from a single precursor. For example, photolysis of the polysilane shown in Scheme 5 leads to the formation

Table 2 EPR parameters, stability (at 298 K), and calculated degree of pyramidality of tris(silyl)silyl radicals.

No.	Radical	$a_{\text{Si}}(^{29}\text{Si})$, G	$a_{\text{X}}(\text{X})$, ^a G	g	$\Sigma\theta$ (Si) ^b	Stability	References
1	(Me ₃ Si) ₃ Si [•]	63.8	7.1 (²⁹ Si _β), 0.43 (¹ H _γ)	2.0053	351	$\tau_{1/2} \sim 1$ s	5, 16
2	(EtMe ₂ Si) ₃ Si [•]	62.8	7.1 (²⁹ Si _β), 0.37 (Me ¹ H _γ), 0.14 (Et ¹ H _γ)	2.0060	—	$\tau_{1/2} \sim 1$ s	63
3	(Et ₂ MeSi) ₃ Si [•]	60.3	7.3 (²⁹ Si _β), 3.2 (¹³ C _γ), 0.27 (Et ¹ H _γ), 0.15 (Me ¹ H _γ)	2.0060	—	$\tau_{1/2} \sim 1$ s	63
4	(Et ₃ Si) ₃ Si [•]	57.2	7.9 (²⁹ Si _β), 3.0 (¹³ C _γ), 0.12 (¹ H _γ)	2.0063	—	$\tau_{1/2} \sim 1$ s	63
5	(Me ₃ SiMe ₂ Si) ₃ Si [•]	57.2	7.4 (²⁹ Si _β), 4.0 (¹³ C _γ), 0.1 (¹ H _γ)	2.0060	—	$\tau_{1/2} \sim 1$ s	47, 64
6	(<i>t</i> -Bu ₂ HSi)(Me ₃ Si) ₂ Si [•]	61.6	7.9 (²⁹ Si _β)	2.0056	—	$\tau_{1/2} \sim 1$ s	65
7	(<i>i</i> -Pr ₃ Si) ₃ Si [•]	55.5	8.1 (²⁹ Si _β), 2.2 (¹³ C _γ)	2.0061	360	Persistent	48
8	(<i>t</i> -BuMe ₂ Si) ₃ Si [•]	56.8	8.0 (²⁹ Si _β), 0.1 (<i>t</i> -Bu ¹ H), 0.3 (Me ¹ H)	2.0060	358.3	$\tau_{1/2} \sim 1$ s	65, 66
9	(<i>t</i> -Bu ₂ MeSi) ₃ Si [•]	58.0	8.0 (²⁹ Si _β), 0.14 (<i>t</i> -Bu ¹ H), 0.21 (Me ¹ H), 2.8 (¹³ C _γ)	2.0056	360	Stable	49, 50
10	[(Me ₃ Si) ₃ Si] ₂ (<i>t</i> -Bu ₂ MeSi)Si [•]	63.9	8.0 (²⁹ Si _β)	2.0053	360	Persistent	Y. Apeloig, <i>et al.</i> , unpublished results.
11	(<i>t</i> -Bu ₃ Si)(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	60.5	8.0 (²⁹ Si _β)	2.0053	360	Stable	Y. Apeloig, <i>et al.</i> , unpublished results.
12	(<i>t</i> -Bu ₂ MeSi) ₂ HSi(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	59.3	7.3 (²⁹ Si _β), 10.4 (²⁹ Si _γ)	2.0051	359.8	Stable	50
13	(<i>i</i> -Pr ₃ Si) ₂ HSi(<i>t</i> -Pr ₃ Si) ₂ Si [•]	57.1	7.5 (²⁹ Si _β), 10.0 (²⁹ Si _γ), 1.1 (¹ H _β)	2.0054	360	Persistent	50
14	(<i>i</i> -Pr ₃ Si) ₂ HSi(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	58.3	7.3 (²⁹ Si _β), 10.5 (²⁹ Si _γ), 0.65 (¹ H _β)	2.0051	—	Persistent	Y. Apeloig, <i>et al.</i> , unpublished results.
15		39.0 (²⁹ Si)	15.5 (²⁹ Si _β)	2.0058	—	Stable	67, 68

^a Atoms X responsible for the quoted h_{fcc} are given in parentheses.^b Calculated sum of the bond angles around the radical center (in degree).⁶⁹

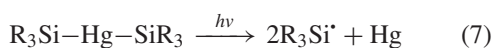


Scheme 5 Nonselective formation of silyl radicals by photolytic Si–Si bond cleavage of branched polysilanes.

of two radicals: a short-lived radical ($\tau_{1/2} \sim 1$ s) formed by cleavage of the central Si–Si bond and a longer lived persistent radical ($\tau_{1/2} \sim 50$ min) obtained by cleavage of one of the $\text{Me}_3\text{SiMe}_2\text{Si}$ groups (Scheme 5).⁶⁴

2.1.3 Si–Hg Bond Cleavage

Photolysis of silyl-mercury compounds produces silyl radicals with high *selectivity* because only the silicon–mercury bond is cleaved (7).^{47,70,71} This is a major advantage over the photolysis of polysilanes where several fragmentation pathways are competing. Furthermore, the concentration of the silyl radical produced by this method is usually high, producing good quality EPR spectra. Additional advantages are that there is no need to use initiators and the only side-product is metallic mercury which is easily removed. Examples of radicals produced by this method are: **5**, **8**, **25**, and **26** (see Tables 2 and 4).^{65,69,70}



2.1.4 Oxidations and Reductions

One-electron oxidations and reductions are powerful methods for generating persistent and stable radicals in high yield.^{1,6,66,71} The first two silicon-centered radicals that were isolated and characterized by X-ray crystallography **9**⁴⁹ (Figure 3) and **12**⁵⁰ (Table 2) were produced by one-electron oxidation reactions. Sekiguchi and coworkers prepared in 2002 (*t*-Bu₂MeSi)₃Si[•] (**9**) by oxidation of (*t*-Bu₂MeSi)₃SiNa (**8**) and isolated it as air-sensitive yellow needles.⁴⁹ More recently Apeloig and coworkers synthesized by a single-pot

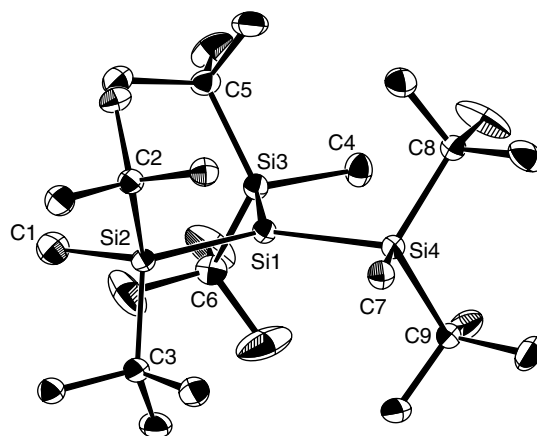
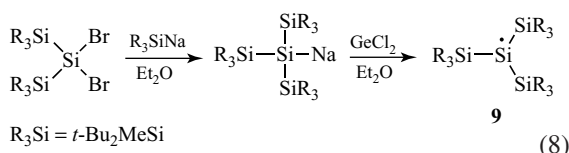


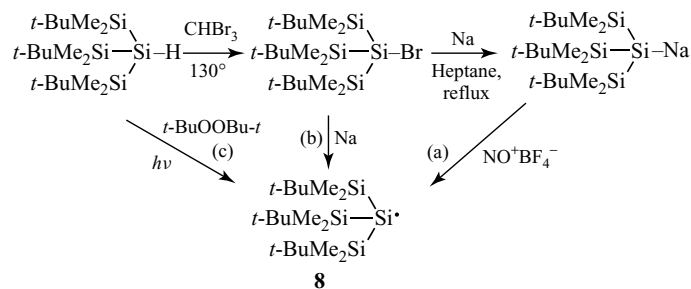
Figure 3 ORTEP diagram of the X-ray molecular structure of (*t*-Bu₂MeSi)₃Si[•] (**9**). [Adapted with permission from Ref. 49. Copyright 2002 American Chemical Society.]

substitution-oxidation reaction the new stable radical **12** (see below).

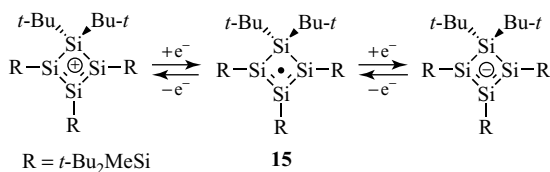


The persistent (*t*-BuMe₂Si)₃Si[•] (**8**) (Table 2) was generated by Kira and coworkers in 1998 by the oxidation of (*t*-BuMe₂Si)₃SiNa (Scheme 6, path a) with NO⁺BF₄[−] and by the reduction of (*t*-BuMe₂Si)₃SiBr (Scheme 6, path b), as well as by hydrogen abstraction from (*t*-BuMe₂Si)₃SiH (Scheme 6, path c).⁶⁶

An interesting example of the use of one-electron oxidation and reduction reactions to produce the unique cyclotetrasilanyl silyl radical **15** is shown in Scheme 7.^{67,68} Radical **15** was generated from the corresponding cyclotetrasilanylium cation⁷² by reduction with sodium metal or KC₈ in ether and it was isolated as red-purple crystals. Cyclotetrasilanyl radical **15** is the first stable polysilyl



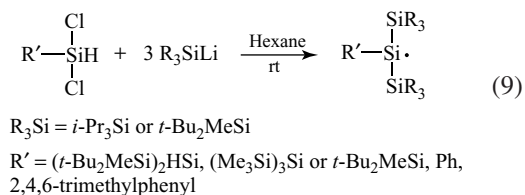
Scheme 6 Synthesis of radical **8** by several methods.



Scheme 7 Synthesis of cyclotetrasilanyl silyl radical **15**.

radical with allylic conjugation as is also clear from its spin-density distribution (Table 2).⁶⁷ Radical **15** can be reduced further by alkali metals to the corresponding silyl anion.⁶⁷ Remarkably, all the reduction–oxidation processes shown in Scheme 7 are reversible.

More recently, a new efficient one-pot method for preparing stable silyl radicals in high yield was developed by Apeloig's group.⁵⁰ Reaction of trichlorosilanes or dichlorosilanes with aggregated nonsolvated bulky trialkylsilyllithiums produces in high yield stable or persistent silyl radicals (**9**).⁵⁰ For example, reaction of trichlorosilane with 3 mole equiv of (*t*-Bu)₂MeSiLi in hexane yields the stable (*t*-Bu₂MeSi)₃Si[•] radical (**9**) in 85% yield after recrystallization.⁵⁰ The previous method, which uses a one-electron oxidation to produce **9** (**8**), consists of four steps and produces radical **9** in a lower yield of 44%.⁴⁹



Several new persistent and stable silyl radicals, such as **10–14** (Table 2) as well as

Ph(*t*-Bu₂MeSi)₂Si[•] (**23**) and Mes(*t*-Bu₂MeSi)₂Si[•] (**24**) (Table 4), were recently synthesized by Apeloig *et al.* using the method in (9) (Y. Apeloig, *et al.*, unpublished results.).⁵⁰

2.2 X-Ray Crystallography of Silyl Radicals

Currently, the X-ray structures of four stable radicals, namely, **9**, **11**, **12**, and the cyclotetrasilanyl silyl radical **15**, have been solved. Radical **9**, whose X-ray molecular structure is shown in Figure 3,⁴⁹ has a trigonal-planar geometry around the Si radical center ($\Sigma\theta = 360^\circ$). Steric effects dictate or contribute to many of the structural details, such as the planarity of the radical center and the clockwise arrangement in the Si1–Si2–Si3–Si4 plane of all methyl substituents at the peripheral Si atoms, thus minimizing the steric repulsion of the bulky *t*-Bu groups. The Si–Si bond length (average 2.42 Å) are slightly longer than the normal values of 2.30–2.40 Å.⁷³

The X-ray molecular structures of radicals **11** and **12** (Y. Apeloig, *et al.*, unpublished results⁵⁰), which also have a planar radical center, are similar to those of radical **9**.

The cyclotetrasilanyl radical **15** (Figure 4) has an almost planar array of four silicon atoms, of which three (Si1, Si2, Si3) are trigonally coordinated.⁶⁷ The sum of bond angles around each of these silicon atoms (Si1–Si3) is 360.0°, 359.1°, and 356.2°, respectively. Si1 and Si2 have a planar geometry, but Si3 is slightly pyramidalized. The Si–Si bond lengths of 2.26 Å are intermediate between those of the Si=Si double bond (2.174 Å) and the Si–Si single bond (2.349–2.450 Å)⁷³ in the four-membered ring of

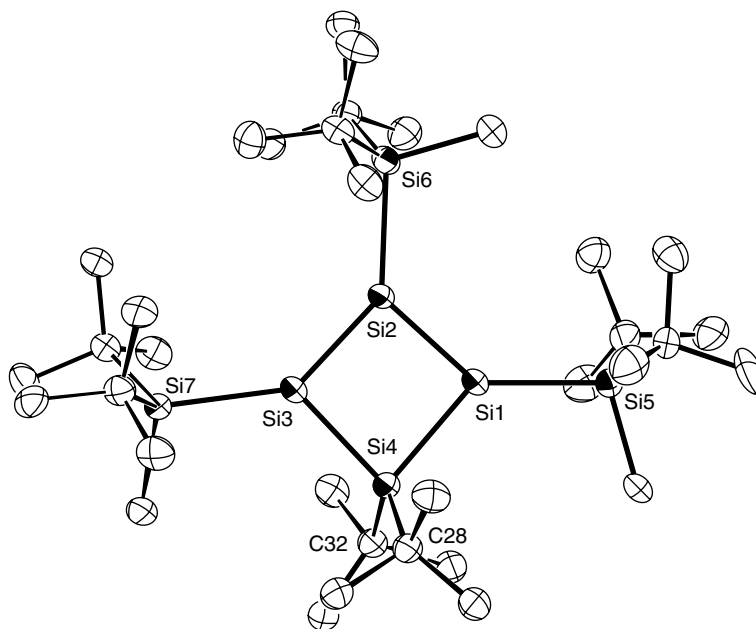


Figure 4 ORTEP diagram of the X-ray molecular structure of cyclotetrasilanyl radical **15**. [Adapted with permission from Ref. 67. Copyright 2001 American Chemical Society.]

hexakis-(*tert*-butyldimethylsilyl)cyclotetrasilene,^{67,74} supporting the occurrence of allylic delocalization of the unpaired electron.⁶⁷

2.3 EPR Parameters of Silyl Radicals

EPR spectroscopy is the most important spectroscopic tool for studying radicals (see **Analysis of Radicals by EPR**) and therefore a few general comments regarding the EPR parameters of silyl radicals are called for.

The EPR spectrum of silyl radicals consists of a central singlet signal characterized by its *g*-factor which results from the unpaired electron residing on the nonmagnetic ²⁸Si nuclei (95.33% natural abundance). This central signal is split by the central ²⁹Si nuclei (*I* = 1/2, 4.67% abundance) and by other magnetic elements present in the substituents. Substituents bonded directly to the silicon carrying the unpaired electron (α -position) affect significantly the EPR parameters of silyl radicals; the $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ hyperfine coupling constants (*hfccs*) vary from 55.5 G for (*i*-Pr₃Si)₃Si⁴⁸ to 416 G for Cl₃Si⁷⁵ and to 498 G for F₃Si⁷⁶. These large

variations in $a(^{29}\text{Si}_\alpha)$ *hfccs* are attributed to changes in the geometry of the radical center, affecting its hybridization, and to the electronic effects of the α -substituents. Based on theoretical calculations, it was suggested that a higher electronegativity of the α -substituents and an increase in the degree of pyramidalization at the radical center lead to a larger contribution of the 3s orbital to the singly occupied molecular orbital (SOMO) and therefore to a larger $a_{\text{Si}}(^{29}\text{Si})$.^{51,57} Electronegative substituents (e.g., F, Cl) increase the degree of pyramidalization at the radical center and thus increase $a_{\text{Si}}(^{29}\text{Si})$,⁷⁶ while electropositive substituents (e.g., silyl groups, metals) lower the degree of pyramidalization, decreasing $a_{\text{Si}}(^{29}\text{Si})$.^{51,57} Bulky substituents reduce the degree of pyramidalization at the radical center, as the steric repulsion is minimal in a planar geometry, and therefore the larger the substituents the smaller the $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ values. These effects are clearly evident in the EPR data presented in Tables 2 and 4.

Theoretical quantum mechanical calculations are very helpful in characterizing and studying silyl radicals. Thus, the calculated geometry and EPR spectrum are crucial for the correct assignment of a measured EPR spectrum to a specific radical and thus for its identification. In addition, the

calculations allow the evaluation of the role of the different effects that determine the magnetic properties of a given free radical. The importance of theory to radical research led in recent years to numerous computational studies using a variety of theoretical approaches and levels of sophistication.^{50,51,57–62, 69}

2.3.1 EPR Parameters of Tris(silyl)silyl Radicals

The EPR parameters, the degree of pyramidality, and the half-life of several persistent and stable tris(silyl) substituted silyl radicals are presented in Table 2. The g -factor values that are presented in the tables are given at the highest available measurement accuracy. The EPR parameters of a variety of alkyl, alkoxy, phenyl, halogen, and other short-lived α -substituted silyl radicals are summarized in Ref. 5 and are not repeated here.

The EPR spectra of tris(silyl) substituted silyl radicals are characterized by a central signal at g in the range of 2.0053–2.0065 which is split by hyperfine interactions. The $hfcc$ of the central silicon α - ^{29}Si , of 55–64 G, is much larger than the $hfcc$ with the β - ^{29}Si or the γ - ^{29}Si nuclei of the substituents (6–10 G). Additional splitting from the substituents' protons is generally very small (0.4 G) (Table 2). The g -factor is not sensitive to the substitution pattern.

A typical EPR spectrum of a stable silyl radical [$(t\text{-Bu}_2\text{MeSi})_3\text{Si}^\bullet$] (**9**) is shown in Figure 5. It consists of a central singlet signal at $g = 2.0056$ that results from the unpaired electron residing on

the nonmagnetic ^{28}Si nuclei, a doublet splitting with $hfcc$ of 58.0 G assigned to the coupling of the unpaired electron with the $^{29}\text{Si}_\alpha$ nucleus, and a doublet splitting having a higher intensity and a smaller $hfcc$ value (8.0 G) assigned to the $hfcc$ with three $^{29}\text{Si}_\beta$ nuclei (Figure 5a). Coupling with the methyl and t -butyl protons is also observed (the number of interacting nuclei is also given): $a_{\text{H}}(54^1\text{H}) = 0.14$ G; $a_{\text{H}}(9^1\text{H}) = 0.21$ G (Figure 5b).⁵⁰ An important observation is that $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ is linearly dependent on the temperature in the range of 180–340 K, so that raising the temperature increases $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ by 1.73 G/100 K (Y. Apeloig, *et al.*, unpublished results).⁶⁹ This temperature dependence is due to the out-of-plane vibrations of the substituents and is similar to that observed in planar alkyl radicals.⁷⁷ This temperature dependence must be taken into consideration when assigning EPR signals to new silyl radicals.

2.4 Reactions and Structure

2.4.1 Dimerization

The two major decay routes of silyl radicals are (i) dimerization to the corresponding disilane and (ii) hydrogen abstraction from the solvent or from the substituents of another silyl radical molecule. In the absence of scavengers, trapping reagents, or efficient H-donors, dimerization is the major decay route of silyl radicals and thus determines their lifetime. The rate of dimerization depends

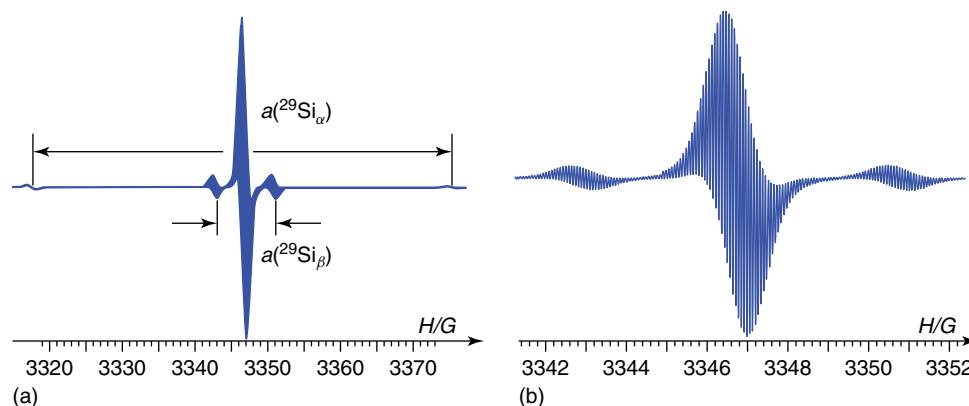


Figure 5 (a) High-resolution EPR spectrum of $(t\text{-Bu}_2\text{MeSi})_3\text{Si}^\bullet$ in pentane; (b) Expanded central multiplet. [Adapted with permission from Ref. 50. Copyright 2009 American Chemical Society.]

Table 3 Kinetic data for dimerization of silyl radicals **1**, **5**, **6**, and **8**.

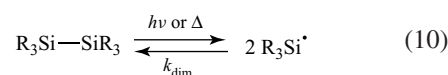
Radical	k_{dim}^a	Relative k_{dim}	$r(\text{Si-Si})$ in dimer ($\text{\AA}$)
1	$\sim 1 \times 10^8$	5×10^5	2.405
5	5×10^3	25	2.409
6	2×10^3	10	2.480
8	2×10^2	1	2.630

^aSecond order rate constant in $\text{M}^{-1} \text{s}^{-1}$.

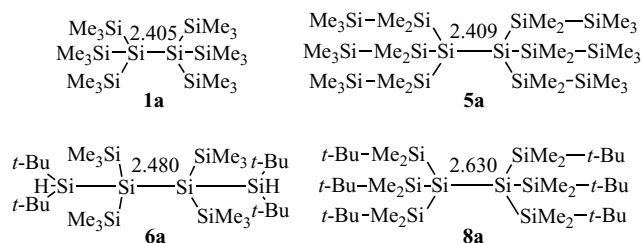
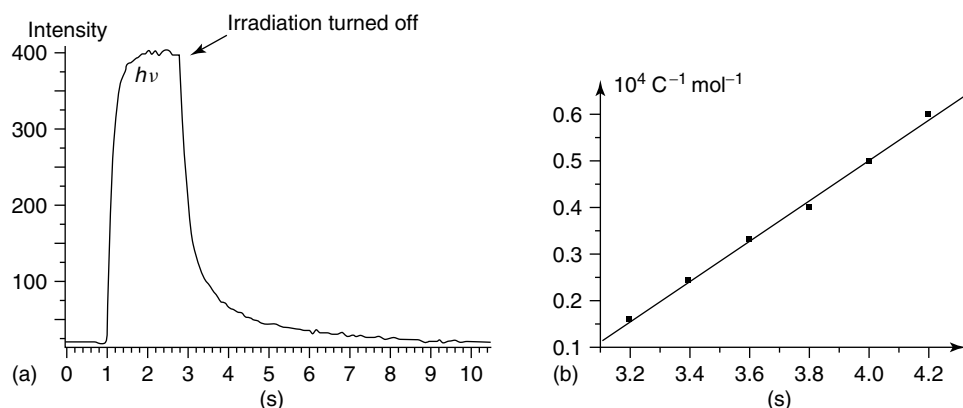
on the dissociation energy of the central Si-Si bond (a thermodynamic factor) and on the size of the substituents and the steric effects which they exert (a kinetic factor). To demonstrate these effects, we discuss below the kinetic stability of several very reactive ($\tau_{1/2} \sim 0.1\text{--}1 \text{ s}$) $\text{R}_3\text{Si}^\bullet$ radicals (**1**, **5**, **6**, **8**, Table 3) toward dimerization to the corresponding oligosilanes $\text{R}_3\text{Si-SiR}_3$ (**1a**, **5a**, **6a**, and **8a**, respectively, Scheme 8).⁶⁵

The rate constants for the dimerization of radicals **5**, **6**, and **8** to produce the corresponding disilanes, shown as the backward reaction of (10), were

measured using EPR spectroscopy.⁶⁵ These radicals were generated photolytically ($\lambda \geq 300 \text{ nm}$), **5** from disilane **5a** (10) and radicals **6** and **8** from the corresponding silylmercury compounds (see Section 2.1.3). In the kinetic measurements, the light was turned off after a few seconds and the decrease in radical concentration $[C]$ as a function of time was measured by following the decrease in the intensity of the radical's EPR signal, as shown in Figure 6a for radical **6**. Good linear curves of $1/[C]$ versus time were obtained in all cases (e.g., Figure 6b). The resulting second-order reaction rate constants (k_{dim}) at 290 K are given in Table 3.⁶⁵



The dimerization rates in Table 3 cover a range of 500 000 and they are strongly dependent on the radical's substituents. The most reactive radical is **1** because the Me_3Si substituents are too small to effectively slow down its dimerization. The

**Scheme 8** Si-Si bond lengths ($\text{\AA}$) in **1a**, **5a**, **6a**, and **8a**.**Figure 6** EPR measurements of k_{dim} of radical **6**: (a) decay curve of the EPR signal at 290 K; (b) Plot of $1/[C]$ versus time. [Reproduced by permission from Ref. 65. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA.]

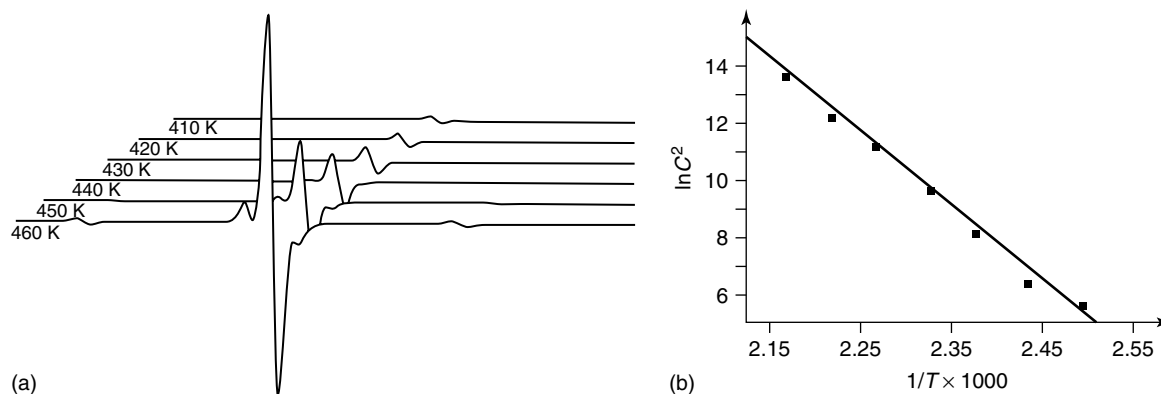


Figure 7 (a) Temperature dependence of the intensity of the EPR signal of radical **6**; (b) Plot of $\ln C^2$ versus $1/T$ for radical **6**. [Reproduced by permission from Ref. 65. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA.]

small steric repulsions in dimer **1a** are reflected in its relatively short Si–Si bond of 2.405 Å.⁵³ Substitution of the three Me₃Si substituents in **1** by three Me₃SiMe₂Si groups (**5**) has a significant effect on k_{dim} which is reduced by a factor of 20 000 relative to **1** (Table 3), but has only a minor effect on the central Si–Si distance which is 2.409 Å in **5a** (Scheme 8). When one of the Me₃Si groups in **1** is substituted by the bulkier *t*-Bu₂HSi substituent (i.e., **6**), the rate of dimerization decreases further and is slower by a factor of 5×10^4 relative to **1**. In this case, the central $r(\text{Si}–\text{Si})$ distance in its dimer **6a** is elongated considerably to 2.480 Å. Radical **8** with three *t*-BuMe₂Si substituents is the least reactive and its dimerization rate is by a factor of 25 slower than that of **5** and 5×10^5 times slower than that of **1**. In **8a** (which was not yet isolated) the calculated (ONIOM, MP2/6-31G(d):B3LYP/6-31G(d):HF/3-21G) central Si–Si distance is 2.630 Å,⁶⁵ significantly longer than that of **1a**. Density functional theory (DFT) calculations show that β -alkyl or β -silyl substitution have a negligible thermodynamic effect on the stability of silyl radicals^{47,55} and therefore the thermodynamic stabilities of **8** and **1** are expected to be nearly the same. The reason that **8** reacts 5×10^5 times more slowly than (Me₃Si)₃Si[•] is therefore kinetic in origin and is due to the effective steric protection of the radical center of **8** by the three *t*-BuMe₂Si substituents.⁶⁵ Similarly, radical **5** reacts 2×10^4 more slowly than **1**.⁶⁵ The effective protection of the radical center of **5** toward dimerization was explained by a protective substituents' "umbrella" around the radical center.⁶⁵ To obtain

silyl radicals stable at room temperature, the size of the substituents has to be increased beyond that in **8**, as is the case for **9** which is substituted with three large *t*-Bu₂MeSi substituents.

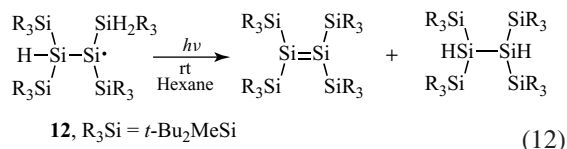
The enthalpies (ΔH) of the homolytic cleavage of the central Si–Si bond in disilanes can be obtained from temperature-dependent EPR measurements of the intensity of the radical's signal using (11), in which C is the concentration of the radical, T is the absolute temperature, and A is a constant. An example is shown in Figure 7 for radical **6**.⁶⁵ Temperature-dependent EPR measurements (Figure 7) yield ΔH values of 56 and 58 kcal mol^{−1} for the cleavage of the central Si–Si bond in **5a** and **6a**, respectively. These values are smaller by 9–11 kcal mol^{−1} than for Me₃Si–SiMe₃ (67 kcal mol^{−1}).⁷⁸ The weaker central Si–Si bond in **5a** and **6a** reflects the thermodynamic stabilization of the corresponding silyl radicals (**5** and **6**) by the α -silyl substituents relative to methyl groups (see also Table 1). The similar Si–Si bond cleavage energy in **5a** and **6a** reflects the fact that β -silyl substitution has practically no effect on the thermodynamic stability of the silyl radicals, in agreement with theoretical calculations,^{47,65} and the fact that the β -silyl groups in **5a** do not raise its ground state energy due to steric congestion as reflected in its short central Si–Si bond (Scheme 8).^{47,65} It was similarly estimated that ΔH for the cleavage of the central Si–Si bond of **8a** is only about 8 kcal mol^{−1}.⁶⁵ In agreement, at relatively high concentrations of **8a** ($\sim 10^{-2}$ – 10^{-3} M, hexane) obtained by oxidation of the corresponding anion, radical **8** was observed at 290 K due to the

8a $\rightleftharpoons$ **28** equilibrium.⁶⁵ The half-life of **8** at 298 K is ~ 1 day and it decays by hydrogen abstraction (Y. Apeloig, *et al.*, unpublished results).

$$\ln C^2 = \frac{\Delta H}{RT} - A \quad (11)$$

2.4.2 Photochemistry

Radical **9** is stable upon UV–Visible irradiation.⁵⁰ In contrast, the stable radical **12** (yellow solution in hexane) decays rapidly ($\tau_{1/2} \sim 100$ s) on irradiation at $\lambda > 400$ nm, to yield a 1:1 ratio of the corresponding disilene (blue colored) and the corresponding disilane (**12**).⁵⁰



The photoreactivity of **12** is due to its β -hydrogen. On irradiation, the radical undergoes photoexcitation (Scheme 9, step a), and then the photoexcited radical accepts an electron from another radical molecule forming an ion pair within a solvent cage (Scheme 9, step b) followed by proton transfer from the cation to the anion to yield the observed products (Scheme 9, step c).⁵⁰

Similarly, $(t\text{-Bu}_2\text{MeSi})_3\text{Si}^\bullet$ (**9**), which lacks β -hydrogens and is photostable, becomes photoreactive ($\tau_{1/2} \sim 100$ s), yielding $(t\text{-Bu}_2\text{MeSi})_3\text{SiH}$ in

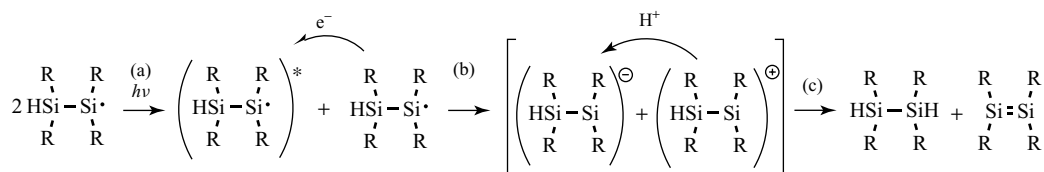
the presence of hydrogen donors such as 2-propanol or triethylsilane.⁵⁰

2.4.3 Oxidation, Reduction, and Ionization

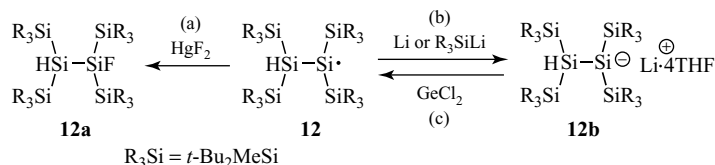
$(t\text{-Bu}_2\text{MeSi})_3\text{E}^\bullet$ ($\text{E} = \text{Si}, \text{Ge}, \text{Sn}$) radicals undergo both oxidation and reduction processes, yielding the corresponding cationic and anionic derivatives.⁶ Their first oxidation and reduction potentials in tetrahydrofuran (THF), as measured by cyclic voltammetry, are as follows: for the Si-centered radical $E_{\text{P(ox.)}} = 0.8$ V, $E_{1/2(\text{red.})} = -1.43$ V; for the Ge-centered radical $E_{\text{P(ox.)}} = 0.6$ V, $E_{1/2(\text{red.})} = -1.46$ V; and for the stable Sn-centered radical $E_{\text{P(ox.)}} = 0.2$ V, $E_{1/2(\text{red.})} = -1.41$ V.⁷⁹

UV photoelectron spectroscopy gives the following first ionization potentials for $(t\text{-Bu}_2\text{MeSi})_3\text{E}^\bullet$ ($\text{E} = \text{Si}, \text{Ge}, \text{Sn}$): 6.15 eV for $\text{E} = \text{Si}$; 6.0 eV for $\text{E} = \text{Ge}$; and 5.8 eV for $\text{E} = \text{Sn}$. These ionization energies correspond to the removal of an electron from the SOMO of the radicals and they decrease in the order $\text{Si} > \text{Ge} > \text{Sn}$, in agreement with the trend in their oxidation potentials and the ionization energies of the isolated atoms (Si (8.15 eV), Ge (7.90 eV), Sn (7.34 eV)).⁸⁰

Oxidation of radical **12** with HgF_2 yields the corresponding silyl fluoride (**12a**) (Scheme 10, path a), and its reduction with lithium metal in hexane or with $t\text{-Bu}_2\text{MeSiLi}$ in THF quantitatively yields the corresponding lithiosilane (**12b**) (Scheme 10, path b).⁵⁰ Oxidation of anion **12b** by GeCl_2 yields radical **12** (Scheme 10, path c).⁵⁰



Scheme 9 Proposed mechanism for the photoreactivity of radical **12**.



Scheme 10 Oxidation and reduction reactions of radical **12**.

2.5 Conformational Analysis of Stable Silyl Radicals in Solution

The preferred conformations of silyl radicals in solution can be determined by a combination of EPR spectroscopy and molecular orbital calculations. For demonstration, we discuss the conformations adopted in solution by oligosilyl radicals **12** and **13** (Table 2). Radical **12** was isolated and its structure was determined by X-ray crystallography. In the solid state, the radical center of **12** is planar ($\Sigma\theta = 359.8^\circ$)⁵⁰ similar to the stable radicals **9**⁴⁵ and **11** (Y. Apeloig, *et al.*, unpublished results). Calculation predict a planar Si center ($\Sigma\theta = 360^\circ$) also for radical **13**.⁵⁰

The EPR spectrum in hexane solution of **12** and **13**, both having a β -hydrogen, is shown in Figure 8. Both radicals exhibit the expected splittings with the α , β , and γ - ^{29}Si nuclei; that is, of 59.3, 7.3, and 10.4 G, respectively, for **12** (Figure 8a, Table 2), and 57.1, 7.5, and 10.0 G, respectively, for **13**. The g -factor and the $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ and $a_{\text{Si}}(^{29}\text{Si}_\beta)$ values of **12** and **13** are typical for planar silyl radicals (Table 2). There is one important difference in the EPR spectra of the two radicals. The EPR spectrum of **13** exhibits a doublet arising from coupling with the β -hydrogen with $a_{\text{H}}(^1\text{H}_\beta) = 1.1$ G (Figure 8b),⁵⁰ which is missing

in the spectrum of **12**. This difference allows the determination of the conformation adopted by these radicals in hexane solution. Theoretically, the splitting constant by H_β depends on the angle θ between the $\text{H}_\beta\text{--Si}_\beta$ bond and the principal axis of the $\text{Si}(3\text{p})$ orbital occupied by the unpaired electron, according to (13), where B_0 and B are constants.⁸¹ $a(\text{H}_\beta)$ can, therefore, serve as a sensitive conformational probe.^{81–84}

$$a(\text{H}^\beta) = B_0 + B \cos^2 \theta \quad (13)$$

In **12** (Figure 8a), where a doublet splitting is not observed ($a(\text{H}_\beta) \leq 0.4$ G), θ is close to 90° . In contrast, in **13**, $a(\text{H}_\beta) = 1.1$ G (Figure 8b) and therefore $\theta \neq 90^\circ$. DFT calculations at the UB3LYP/TZVP//UB3LYP/6-31G(d) level support the above conclusion, yielding the conformations shown in Figure 9 where in **12** $\theta = 82^\circ$ and no spin density is found on H_β , while in **13**, $\theta = 63^\circ$ and some spin density resides on H_β . Solving (13), using the measured $a(\text{H}_\beta)$ for **13**, the absence of $a(\text{H}_\beta)$ for **12**, and the calculated θ angles, gives $B = 5.4$ G and $B_0 \sim 0$ G. Thus, in branched polysilyl radicals the maximum value of $a(\text{H}_\beta)$, when $\theta = 0^\circ$, is 5.4 G. Based on this value, it can be concluded for example that in radical **14** where $a(\text{H}_\beta)$ is 0.65 G, $\theta = 70^\circ$. (Y. Apeloig, *et al.*, unpublished results.)

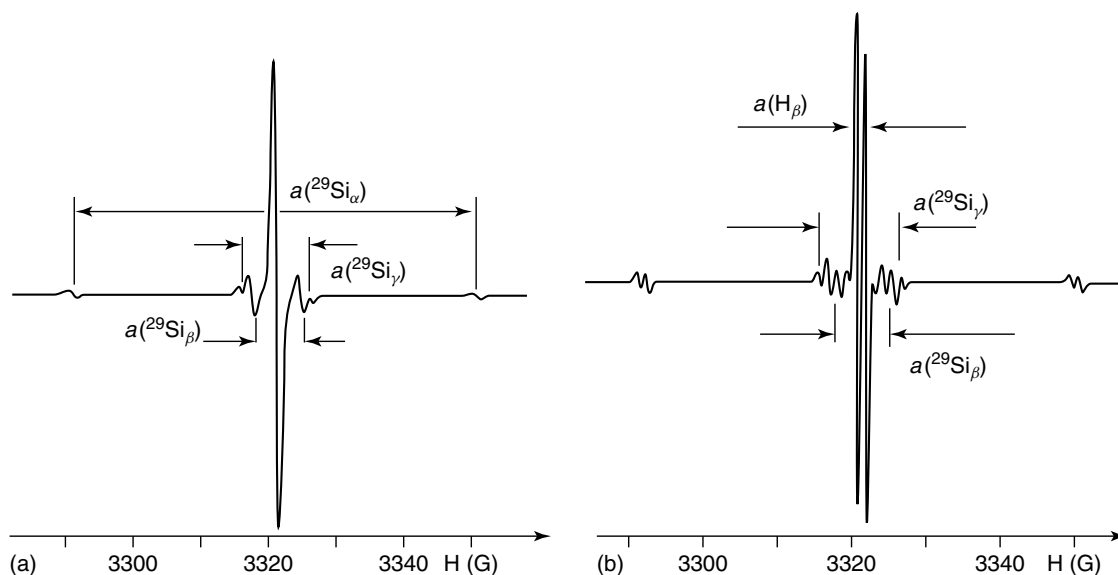


Figure 8 (a) EPR spectrum of **12** (290 K, hexane); (b) EPR spectrum of **13** (290 K, hexane). [Adapted with permission from Ref. 50. Copyright 2009 American Chemical Society.]

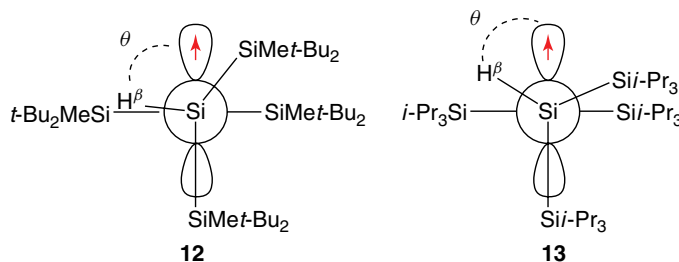


Figure 9 Newman projections of the preferred conformations of radicals **12** and **13**.

3 BIS(SILYL) SILICON-CENTERED RADICALS $X(R_3Si)_2Si^\bullet$

The EPR parameters, degree of pyramidity, and the kinetic stability of both short-lived and stable bis(silyl)silyl radicals $X(R_3Si)_2Si^\bullet$ are collected in Table 4.

3.1 $H(R_3Si)_2Si^\bullet$

Hydrogen-substituted bis(silyl)-substituted silyl radicals $H(R_3Si)_2Si^\bullet$ (**16–20**) were generated by various reactions and were comprehensively studied by EPR spectroscopy and DFT calculations (Table 4).⁵¹ Two bulky silyl substituents at the Si-radical center, even large ones such as *t*-Bu₂MeSi, are not sufficient to prevent their fast dimerization, and the half-life of radicals **16–20** is of $\tau_{1/2} \sim 1$ s (Table 4). This is true also for the methyl-substituted radical **21**. The most reactive radical in the series, $H(Me_3Si)_2Si^\bullet$, was characterized only by its *hfcc* with $^1H_\alpha$ (11.0 G).⁸⁴ The calculated geometries of the $H(R_3Si)_2Si^\bullet$ radicals and their experimental *hfccs* show that they are slightly pyramidal; for example, in **16** $\Sigma\theta(Si) = 354.1$ (Table 4).

In contrast to silyl radicals **16–20** which have relatively short lifetimes, the homologous C-centered radicals with two bulky *t*-Bu₂MeSi substituents, that is, $H(t-Bu_2MeSi)_2C^\bullet$ (**28**) or alkyl radicals with one *t*-Bu₂MeSi group and one bulky alkyl substituent,

that is, $(t-Bu_2MeSi)(1-Ad)HC^\bullet$ (**29**), are persistent at 240 K.⁵¹ Evidently, these substituents are sufficiently large to prevent dimerization of the C-centered radical, but not of the silyl radicals. In agreement, radical **29** decays via a pseudo-first-order kinetics, which is consistent with an H-abstraction decay mechanism.⁵¹ Thus, the decay mechanism is different for Si-centered radicals and C-centered radicals carrying the same silyl substituents: that is, H-abstraction for C-centered radicals versus dimerization for Si-centered radicals. This difference in behavior is due to two main factors⁵¹: (i) Si–Si bonds are much longer than C–C bonds and steric effects of the substituents are therefore much more effective in determining the dimerization rate of C-centered radicals; (ii) The C–H bonds produced by H-abstraction are significantly stronger than Si–H bonds (e.g., 104.8 kcal mol^{−1} for H₃C–H vs 90.3 kcal mol^{−1} for H₃Si–H⁵²), thus favoring H-abstraction for C-centered radicals.

3.2 $R'(R_3Si)_2Si^\bullet$ ($R' = \text{phenyl, mesityl}$)

$R'(R_3Si)_2Si^\bullet$ where $R' = \text{phenyl}$ (**23**) or 2,4,6-trimethylphenyl (mesityl) (**24**) were synthesized according to (14) and their important properties are summarized in Table 4.^{50,69} Radical **23** is persistent at room temperature but could not be isolated, while radical **24**, carrying the more sterically congested mesityl group, can be isolated.

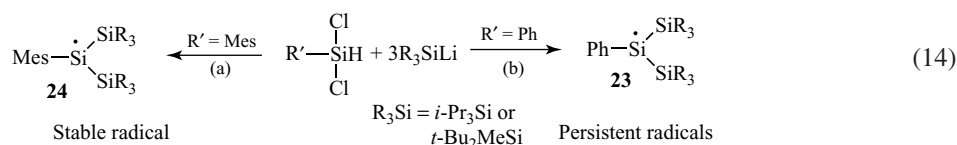


Table 4 EPR parameters, degree of pyramidality,^a and stability (at 298 K) of bis(silyl)substituted silyl radicals.

No.	Radical	$a_{\text{Si}}(^{29}\text{Si}_a)$ G	$a_{\text{X}}(\text{X})$, ^a G	g	$\Sigma\theta$ (Si) ^b	Stability	References
16	H(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	78.0 ^c	11.7 (¹ H _a)	2.005	354.1	$\tau_{1/2} \sim 1$ s	51
17	H(<i>i</i> -Pr ₃ Si) ₂ Si [•]	72.7	12.4 (¹ H _a)	2.005	352.1	$\tau_{1/2} \sim 1$ s	51
18	H(<i>t</i> -BuMe ₂ Si) ₂ Si [•]	79.8 ^c	11.0 (¹ H _a)	2.005	350.4	$\tau_{1/2} \sim 1$ s	51
19	H[(Me ₃ Si)Me ₂ Si] ₂ Si [•]	81.5	9.6 (¹ H _a)	2.005	348.9	$\tau_{1/2} \sim 1$ s	51
20	H[(Me ₃ Si) ₃ Si] ₂ Si [•]	83.7	10.1 (¹ H _a), 4.5 (²⁹ Si _β), 7.4 (²⁹ Si _γ)	2.005	350.2	$\tau_{1/2} \sim 1$ s	51
21	Me[(Me ₃ Si) ₃ Si] ₂ Si [•]	90.0	9.28 (¹ H _β), 0.44 (¹ H _γ)	2.0045		$\tau_{1/2} \sim 1$ s	3
22	F(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	110.0	31.9 (¹⁹ F _a)	2.0032	344.3	$\tau_{1/2} \sim 3$ s	51
23	Ph(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	72.0	6.5 (²⁹ Si _β)	2.0044	357.1	Persistent	69 and Y. Apeloig, <i>et al.</i> , unpublished results.
24	Mes(<i>t</i> -Bu ₂ MeSi) ₂ Si [•]	69.2	7.4 (²⁹ Si _β)	2.0045	359.9	Stable	69 and Y. Apeloig, <i>et al.</i> , unpublished results.
25	(<i>t</i> -BuHN)(<i>t</i> -BuMe ₂ Si) ₂ Si [•]	91.7	2.2 (¹⁴ N _a)	2.0036	340.4	$\tau_{1/2} \sim 3$ min	69 and Y. Apeloig, <i>et al.</i> , unpublished results.
26	Me(<i>i</i> -Pr ₃ Si) ₂ Si [•]	73.5	6.0 (²⁹ Si _β), 9.5 (¹ H _β)	2.0047	354.8	$\tau_{1/2} \sim 5$ min	69 and Y. Apeloig, <i>et al.</i> , unpublished results.
27	Ad(<i>t</i> -BuMe ₂ Si) ₂ Si [•]	79.1	14.5 (¹ H _β), 4.0 (²⁹ Si _β)	2.0045	346.6	Persistent	69 and Y. Apeloig, <i>et al.</i> , unpublished results.

^aAtoms X responsible for the quoted h_{fcc} are given in parentheses.^bCalculated sum of the bond angles at the radical center (in degree).^{51,69}^cValues are extrapolated from a lower temperature experiment using a correction of 0.1 G/10 K.

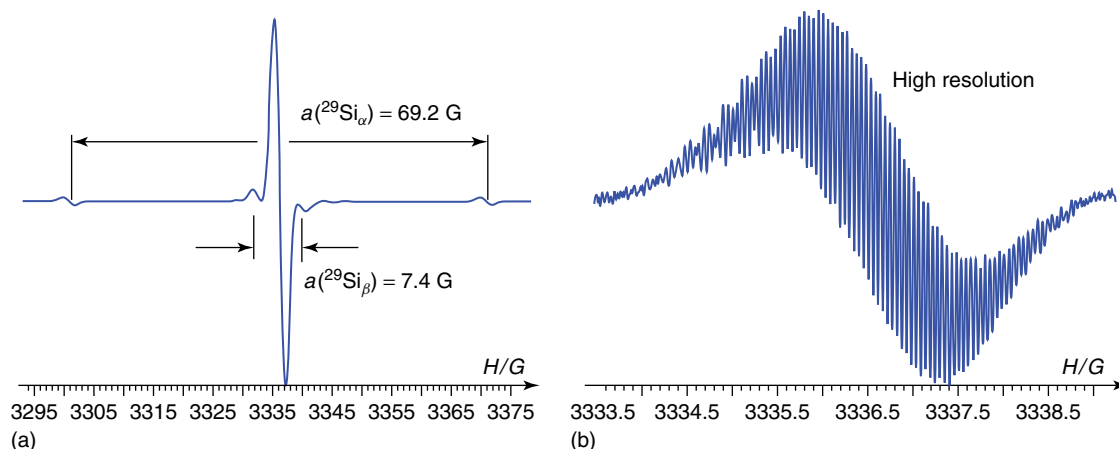


Figure 10 (a) EPR spectrum of radical **24** at 298 K; (b) Expanded central line at high resolution at 350 K.

The EPR spectrum of **24** (Figure 10a)⁶⁹ shows hyperfine coupling between the unpaired electron and both $^{29}\text{Si}_\alpha$ and $^{29}\text{Si}_\beta$. At high resolution, interactions with the hydrogens of the *tert*-butyl and methyl groups are also observed (Figure 10b).⁶⁹ The EPR spectrum of $\text{Ph}(t\text{-Bu}_2\text{MeSi})_2\text{Si}^\bullet$ (**23**) exhibits the same splittings, but with slightly different *hfccs* (Table 4). An interesting feature of both spectra is the absence of splitting from the aryl hydrogens. In contrast, such splitting were observed in the EPR spectra of the short-lived ($\tau_{1/2} \sim 1 \text{ s}$) trimesitylsilyl⁸⁵ and tris(3,5-di-*tert*-butylphenyl)silyl²³ radicals. The absence of *hfcc* with the aryl hydrogens in **23** and **24** shows that there is no delocalization of spin density into the π system of the aryl ring. Calculations for **23** and **24** (UB3LYP/6-31+G(d)) show that steric interactions force the aryl ring to be nearly perpendicular to the plane of the radical's SOMO, preventing conjugation with the aromatic π system.⁶⁹ For $\text{Ph}_3\text{Si}^\bullet$, calculations predict that the phenyl rings are rotated by $\sim 60^\circ$ relative to the SOMO's plane, resulting in small spin delocalization into the rings (Y. Apeloig, *et al.*, unpublished results).

3.3 Amino-Substituted Silyl Radical

$(t\text{-BuHN})(t\text{-BuMe}_2\text{Si})_2\text{Si}^\bullet$ (**25**) was generated by photolysis of $[(t\text{-BuMe}_2\text{Si})_2(t\text{-BuHN})\text{Si}]_2\text{Hg}$ (Y. Apeloig, *et al.*, unpublished results).⁶⁹ Radical **25** is significantly less stable than the analogous phenyl (**23**), mesityl (**24**), and adamantly (**27**) substituted

silyl radicals and its half lifetime is only 2–3 min. Calculations predict that **25** is pyramidal ($\Sigma\theta(\text{Si}) = 340.4^\circ$).⁶⁹ The EPR spectrum of **25** is characterized by $a_{\text{Si}}(^{29}\text{Si}_\alpha) = 91.7 \text{ G}$ and $a_{\text{N}}(^{14}\text{N}) = 2.2 \text{ G}$.

3.4 Triplet Silyl Biradical

The first stable triplet silyl biradical (**30**) was synthesized very recently by Sekiguchi and coworkers by the reductive dehalogenation of a *m*-bis(halosilyl)benzene (**15**) and was isolated and structurally characterized by X-ray crystallography.⁸⁶ The X-ray structure (Figure 11) shows that

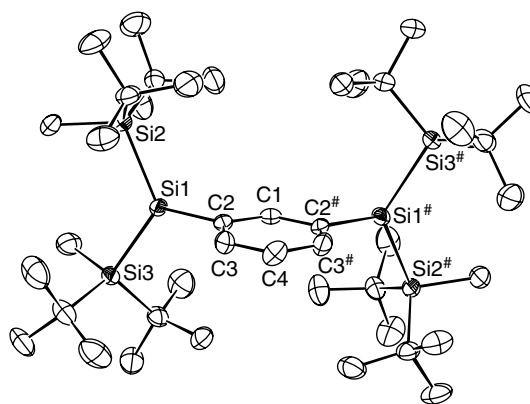
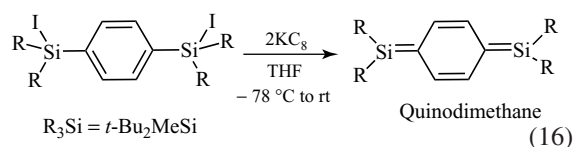
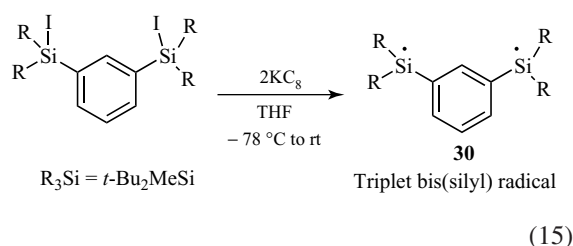


Figure 11 ORTEP diagram of the X-ray molecular structure of biradical **30**. [Adapted with permission from Ref. 86. Copyright 2011 American Chemical Society.]

the half-filled 3p(Si) orbital and the aromatic ring orbitals are orthogonal to each other (similarly to **23** and **24**), an arrangement that does not allow C=Si π bonding. Both Si-radical centers have a nearly trigonal-planar structure ($\Sigma\theta(\text{Si}) = 358.6^\circ$). The EPR spectrum of **30** is typical for triplet species with $D' = 138.0 \text{ G}$ and $E' = 17.2 \text{ G}$. In contrast to *m*-bis(halosilyl)benzene, the isomeric *p*-bis(halosilyl)benzene when reacted with KC_8 yields a diamagnetic quinodimethane species featuring two exocyclic Si=C double bonds (16).⁸⁶



4 ANION RADICALS AND METAL-SUBSTITUTED SILYL RADICALS

One-electron reduction of low-coordinated organosilicon compounds (e.g., disilenes, disilynes, silylenes) by alkali metals yields the corresponding anion-radical salts. These species can exist as intimate ion pairs, solvent-separated ion pairs, or free ions with weak coulombic interaction with the cation, depending on the solvent. For simplicity, we use the term anion radicals for all these charged species in strongly solvating media (e.g., THF, dimethoxymethane (DME), crown-ethers). In contrast, in poor solvating media (e.g., hexane, toluene), a tight contact ion pair with significant Si–M bonding is formed and we classify it as a metal-substituted silyl radical.

4.1 Reduction of Multiply-Bonded Silicon-Compounds

4.1.1 Disilenes

Anion radicals of stable disilenes have been studied extensively and the ones that are persistent or stable are collected in Table 5. Weidenbruch *et al.* were the first to report the EPR spectra of disilene anion radicals, those of tetramesityldisilene

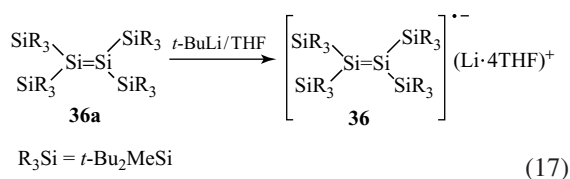
Table 5 EPR parameters and stability of persistent silyl anion radicals.

No.	Radical	$a_{\text{Si}}(^{29}\text{Si}_\alpha)$ G	$a_X(X),^a$ G	g	Stability	References
31	$[\text{Mes}_2\text{Si}=\text{SiMe}_2]^{*-}$	49.6	—	2.0031	Persistent	87
32	$[\text{t-Bu}_2\text{Si}=\text{SiBu-t}_2]^{*-}$	33.6	—	2.0035	Persistent	87
33	$[(i\text{-Pr}_3\text{Si})_2\text{Si}=\text{Si}(\text{SiPr-}i_3)_2]^{*-}$	24.5	—	2.0062	Persistent	88
34	$[(\text{t-BuMe}_2\text{Si})_2\text{Si}=\text{Si}(\text{SiMe}_2\text{Bu-t})_2]^{*-}$	29.2	—	2.0058	Persistent	88
35	$[(i\text{-Pr}_2\text{MeSi})_2\text{Si}=\text{Si}(\text{SiMePr-}i_2)_2]^{*-}$	31.8	2.5 ($^{29}\text{Si}_\beta$)	2.0063	Persistent	88
36	$[(\text{t-Bu}_2\text{MeSi})_2\text{Si}=\text{Si}(\text{SiMeBu-t}_2)_2]^{*-}$	24.5	—	2.0061	Stable	89
37	$[(\text{Dsi})_2i\text{-PrSi}\equiv\text{SiPr-}i(\text{Dsi})_2]^{*-}$	39.2	22.4 ($^{29}\text{Si}_\beta$), 2.3 ($^1\text{H}_\lambda$)	1.9996	Stable	90
38	$[(\text{t-Bu}_2\text{MeSi})_2\text{Si}=\text{PMes}]^{*-}(\text{THF})$	50.0	54.0 ($^{31}\text{P}_\alpha$)	2.0083	Persistent	91
39	$[(\text{t-Bu}_2\text{MeSi})_2\text{Si}=\text{PMes}]^{*-}(\text{benzene})$	65.0	15.0 ($^{31}\text{P}_\alpha$)	2.0076	Persistent	91
40	$(\text{t-Bu}_2\text{MeSi})_2\text{Si}^{*-}(\text{DME})$	29.1	10.2 ($^{29}\text{Si}_\beta$)	2.0074	Stable	92, 93
41		29.9	13.0 ($^{29}\text{Si}_\lambda$), 16.6 ($^{29}\text{Si}_\lambda$)	2.0077	Persistent	94

^a Atoms X responsible for the quoted $hfcc$ are given in parentheses.

(31) and of tetra-*tert*-butyldisilene (32) (Table 5), which were generated by the multiple reduction of the corresponding 1,2-dichlorodisilanes as the source of the disilenes and which were further reduced to the anion radicals.⁸⁷ Reduction of tetrakis(trialkylsilyl)disilenes: $R_2Si=SiR_2$, $R = SiPr-i_3$, $SiMe_2Bu-t$, $SiMePr-i_2$, by potassium in DME at room temperature gives the corresponding persistent disilene anion radicals **33–35**, respectively (Table 5).⁸⁸ Based on their *hfccs*, which are in the range 24–32 G (Table 5) and about one-half of the *hfccs* of the corresponding tris(trialkylsilyl)silyl radicals ($a(^{29}Si) = 55.5–63.8$ G) (Table 2), the authors concluded that the silicon atoms in **33–35** are nearly planar.⁸⁸

Reduction of $(t-Bu_2MeSi)_2Si=Si(SiMeBu-t_2)_2$ (**36a**) by *t*-BuLi in THF (17) yields the isolable anion radical **36** which crystallizes from THF as the $Li \cdot 4THF$ salt.⁸⁹



The molecular structure of **36** was determined by X-ray crystallography, which is shown in Figure 12.⁸⁹ The central Si1–Si2 bond length of 2.341 Å is 3.6% longer than that of disilene

36a (2.260 Å) and it is in the typical range of Si–Si single bonds. The twist angle around the central Si–Si bond, (i.e., the angles between the Si2–Si1–Si4 and Si5–Si2–Si6 planes) is 88°, indicating that, on reduction, the π (Si=Si) bond is broken, consistent with the extra electron entering the $\pi^*(Si=Si)$ orbital. The Si2 atom is planar ($\Sigma\theta(Si) = 359.9^\circ$), whereas Si1 is slightly pyramidal ($\Sigma\theta(Si) = 352.7^\circ$), indicating that Si2 has a radical character while Si1 has a silyl anion character.⁸⁹ The EPR spectrum of **36** (in 2-methyltetrahydrofuran at r.t.) shows a strong signal with $g = 2.0061$, accompanied by a pair of satellite lines (24.5 G) due to coupling of the unpaired electron with two magnetically equivalent silicon atoms,⁸⁹ indicating that the spin is delocalized over both the $^{29}Si1$ and $^{29}Si2$ nuclei.⁸⁹

4.1.2 Disilynes

Reaction of stable triply bonded disilyne **37a** with an equivalent amount of KC_8 in DME produces the disilyne anion radical **37**, which was isolated as dark brown crystals in 63% yield (18).⁹⁰ X-ray crystallography (Figure 13) reveals that **37** is a free anion radical with a Si1–K·4DME distance of 11 Å. The central Si–Si bond length of 2.1728(14) Å is 5% longer than in disilyne **37a** (2.0622(9) Å).⁹⁵ This is consistent with the notion that the additional

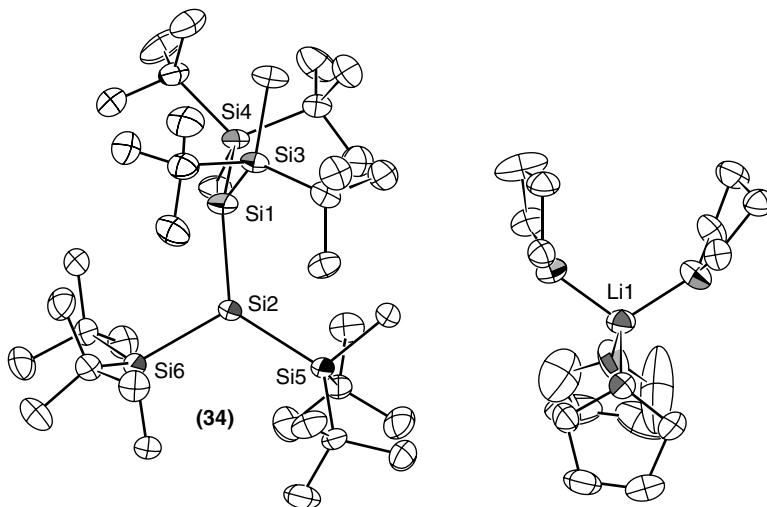


Figure 12 ORTEP diagram of the X-ray molecular structure of **36**. [Adapted with permission from Ref. 89. Copyright 2004 American Chemical Society.]

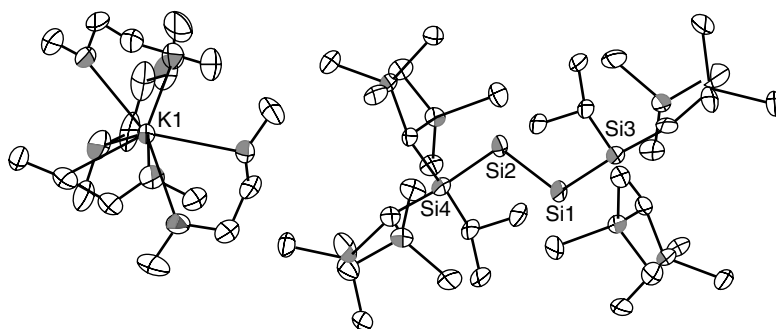
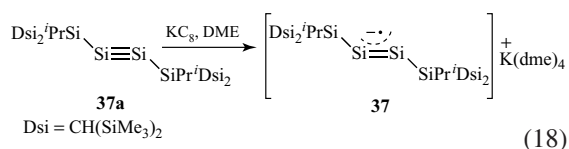


Figure 13 ORTEP diagram of the X-ray molecular structure of the disilyne anion radical **37**. [Adapted with permission from Ref. 90. Copyright 2007 American Chemical Society.]

electron enters the in-plane antibonding π^*_{in} orbital. The Si4–Si2–Si1 and Si3–Si1–Si2 angles of 112.8° and 113.9° respectively, are significantly smaller (i.e., the degree of bending is larger) than the corresponding bending angles of 137.4° in disilyne **37a**.⁹⁵ The fact that the two Si–Si–Si bending angles in **37** are essentially equal indicates that the unpaired electron is equally delocalized between the two central silicon atoms (Si1 and Si2).⁹⁰

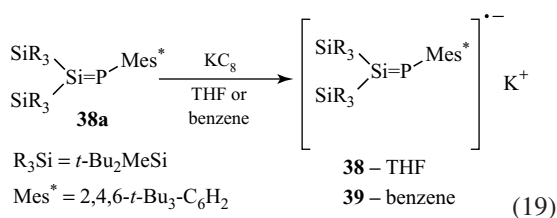


The EPR spectrum of **37** shows a triplet signal with a g -value of 1.9996. The triplet splitting (2.3 G) arises from the interaction of the unpaired electron with the two protons of the isopropyl groups. The central signal is accompanied by two pairs of satellite signals, due to coupling with the two magnetically equivalent $^{29}\text{Si}1$ and $^{29}\text{Si}2$ nuclei ($a_{\text{Si}}(^{29}\text{Si}1) = a_{\text{Si}}(^{29}\text{Si}2) = 39.2$ G) and with two $^{29}\text{Si}_\beta$ nuclei, ($a_{\text{Si}}(^{29}\text{Si}_\beta) = 22.4$ G) (Table 5).⁹⁰

4.1.3 Phosphasilene

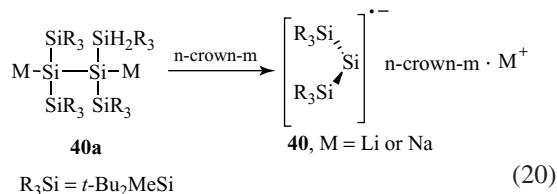
Reduction of phosphasilene $\text{R}_2\text{Si}=\text{PR}'$ (**38a**) with KC_8 yields the anion radical **38** (19), which is persistent at room temperature and was characterized by EPR spectroscopy.⁹¹ In THF, the EPR spectrum of **38** shows a doublet resulting from the coupling of the unpaired electron to the phosphorus nucleus ($a_{\text{P}}(^{31}\text{P}) = 54.0$ G), accompanied by a pair of silicon satellites ($a_{\text{Si}}(^{29}\text{Si}) = 50.0$ G). The EPR

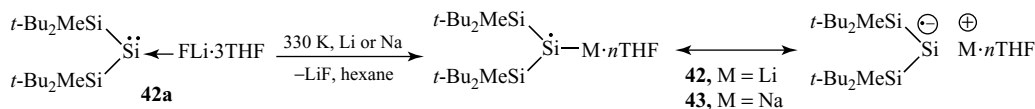
spectrum changes dramatically when the solvent is changed to nonpolar benzene. $a_{\text{P}}(^{31}\text{P})$ decreases significantly to 15.0 G, whereas $a_{\text{Si}}(^{29}\text{Si})$ increases to 65.0 G. This change can be explained by the localized electronic structure of the anion radical in benzene (**39**), where both the unpaired electron and the negative charge are localized on Si_α , and a more delocalized structure in polar THF where the unpaired electron is localized on Si_α and the negative charge is mainly on P.⁹¹



4.2 Reduction of Silylenes

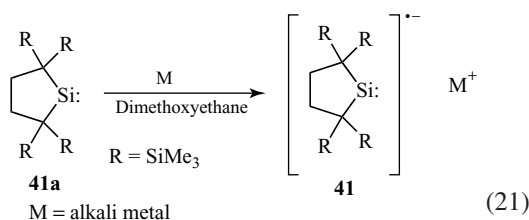
Several anion radicals of silylenes have been reported.^{92,93} Addition of crown-ethers in THF or DME to 1,2-dimetallasilane **40a** ($\text{M} = \text{Li}, \text{Na}$) leads to cleavage of the central Si–Si bond, yielding the corresponding stable silylene anion radicals ((20), Table 5).^{92,93} The EPR parameters of **40** are independent of the counter alkali cations (Li, Na), indicating that they are free ion pairs.





Scheme 11 Generation of Li- or Na-substituted silyl anion radicals **42** and **43**.

One-electron reduction of stable silylene (**41a**) by alkali metals yields the corresponding anion radicals **41** (21) (Table 5).⁹⁴ The EPR parameters of **41** in DME are $a_{\text{Si}}(^{29}\text{Si}_\alpha) = 29.9 \text{ G}$, $a_{\text{Si}}(^{29}\text{Si}_\gamma) = 13.0 \text{ G}$, and 16.6 G , $g = 2.0077$, and they are independent of the counter alkali cations (Li, Na, K, Cs, Rb), indicating that **41** is a free anion radical in DME.⁹⁴



Li- or Na-substituted silyl anion radicals **42** and **43** were observed when silylenoid **42a** was stirred at 330 K with lithium or sodium powder, respectively, in hexane (Scheme 11).⁹⁶ The EPR spectrum of **42** shows the expected quartet splitting of all signals by ^7Li ($I = 3/2$) and **43** shows quartet splitting of the signals by ^{23}Na ($I = 3/2$) (Table 5).⁹⁶

The $a_{\text{Si}}(^{29}\text{Si}_\alpha)$ values of anion radicals **40–43** (Tables 5 and 6) are the smallest and their g -values are the largest among related polysilyl radicals, indicating that the SOMO of **40–43** has a nearly pure $3p$ character.^{92–94, 96}

Comparison of the EPR spectra of **40**, **42**, and **43** in hexane and DME provides interesting information about their ionic character. In DME, $[(t\text{-Bu}_2\text{MeSi})_2\text{Si}]^{\cdot-} \text{Na}^+$ (**40**) has $a_{\text{Si}}(^{29}\text{Si}_\alpha) = 29.1 \text{ G}$, which is smaller than that of $(t\text{-Bu}_2\text{Me})_2\text{LiSi}^\cdot$ (**42**) or $(t\text{-Bu}_2\text{Me})_2\text{NaSi}^\cdot$ (**43**) in hexane, where $a_{\text{Si}}(^{29}\text{Si}_\alpha) = 33.0\text{--}34.0 \text{ G}$ (Table 6).^{96, 97} In **43**, $a_{\text{Na}}(^{23}\text{Na}) = 2.8 \text{ G}$, while in **40** coupling with ^{23}Na is not observed (Table 5).^{92, 93} This data is consistent with the description of these species as being covalently bound (i.e., metallosilyl radicals) in nonpolar solvents and separated anion radical ion-pairs in better solvating media such as ethers.

West *et al.* reported that the reduction of stable unsaturated N -heterocyclic silylene with potassium graphite in THF gives the corresponding 1,2-dilithiodisilane, which they suggested is formed via fast dimerization of the corresponding silylene anion-radical.⁹⁸

4.3 Alkali Metal- and Mercury-Substituted Silyl Radicals

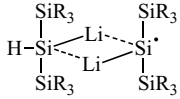
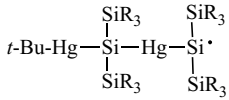
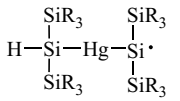
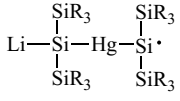
Silyl radicals monosubstituted with Li (**42**) or Na (**43**) were discussed in Section 4.2.

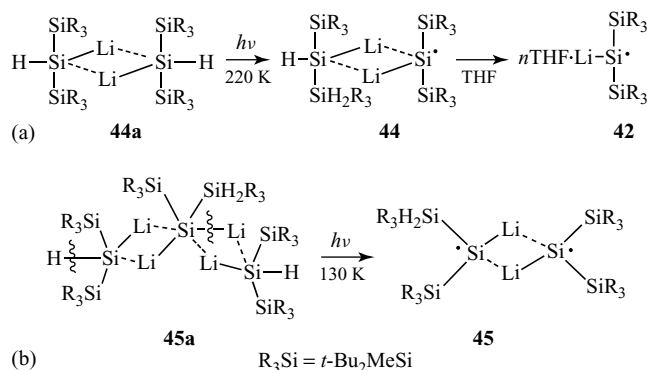
4.3.1 Aggregated Silyllithium Radicals

Aggregated lithiosilanes are photolytic precursors to the interesting silyllithium aggregated silyl radicals **44** and biradical **45** (Scheme 12).⁹⁷ UV irradiation of a hexane solution of silyllithium dimer **44a** at 220 K yields a septet EPR signal (Figure 14a), which results from the splitting of the main line ($g = 2.007$) by two equivalent ^7Li nuclei ($I = 3/2$) with $a_{\text{Li}}(^7\text{Li})$ of 4.17 G . The hyperfine structure of the EPR signal and the cyclic structure of precursor **44a** allows the confident assignment of the observed signal to cyclic **44** (Scheme 12a), which is the first known silyl radical that is part of an aggregated silyllithium skeleton.⁹⁷ Addition of THF to a hexane solution of **44** yields the stable lithium-substituted silicon-centered radical **42** exhibiting a quartet EPR signal ($a_{\text{Si}}(^{29}\text{Si}_\alpha) = 33.25 \text{ G}$, $a_{\text{Si}}(^{29}\text{Si}_\beta) = 9.5 \text{ G}$, $a_{\text{Li}}(^7\text{Li}) = 1.5 \text{ G}$, $g = 2.007$) (Figure 14b, Table 6). Thus, the addition of THF to radical **44** cleaves its cyclic Si_2Li_2 skeleton (Scheme 12a).⁹⁷

UV irradiation of a frozen hexane solution (130 K) of silyl lithium aggregate **45a** (Scheme 12b) produces a characteristic EPR signal of a triplet biradical⁸¹ with four sidebands from $\Delta M_s = 1$

Table 6 EPR parameters of persistent alkali metal- and mercury-substituted silyl radicals.

No.	Radical	$a_{\text{Si}}(^{29}\text{Si}_\alpha)$ G	$a_X(X),^a$ G	g	Stability	References
42	$(t\text{-Bu}_2\text{MeSi})_2\text{Si}^\bullet\text{---Li}\cdot n\text{THF}$ (hexane)	34.0	9.7 ($^{29}\text{Si}_\beta$), 1.6 (^7Li)	2.0075	Persistent	97
43	$(t\text{-Bu}_2\text{MeSi})_2\text{Si}^\bullet\text{---Na}\cdot n\text{THF}$ (hexane)	33.0	9.0 ($^{29}\text{Si}_\beta$), 2.8 (^{23}Na)	2.0074	Persistent	96
44		30.0	9.0 ($^{29}\text{Si}_\beta$), 4.17 (^7Li)	2.0073	Persistent	97
46		56.0	105.3 (^{199}Hg)	1.983	Persistent	71
47		56.0	104.9 (^{199}Hg)	1.984	Persistent	71
48		56.0	63.4 (^{199}Hg)	1.984	Persistent	71

^aThe atoms X responsible for the quoted *hfccs* are given in parentheses.**Scheme 12** Synthesis of aggregated silyllithium silyl radical **44** and diradical **45**.

transitions and a signal at half-field at 1675 G resulting from the forbidden $\Delta M_s = 2$ transition (Figure 14c).⁹⁷ The zero-field splitting parameter $|D'|$ of 172 G indicates a substantial interaction between the two radical centers with a calculated

distance (based on $|D'|^{81}$) of 435 pm, which is similar to that between the ring Si atoms in **45a** (457 pm).⁹⁷ This suggests that the two unpaired electrons are centered on the silicon atoms of the cyclic $\{(R'_2\text{Si})_2\text{Li}_2\}$ fragment with a geometry similar to

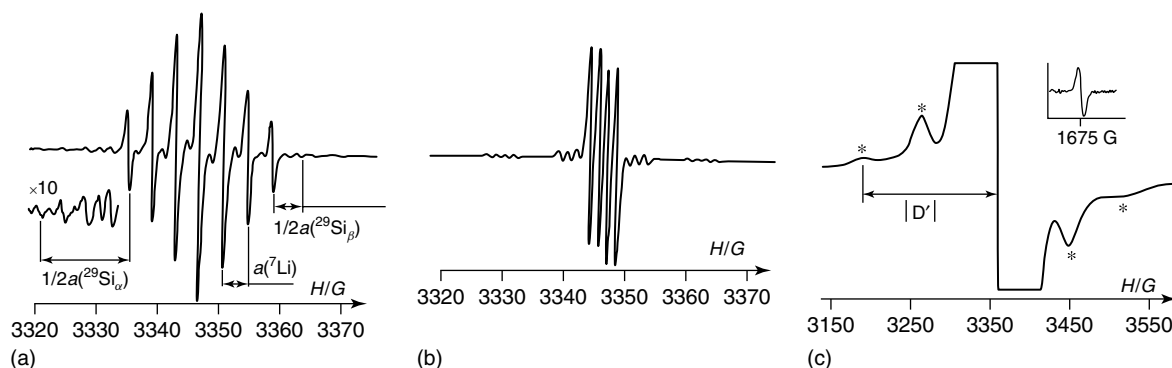
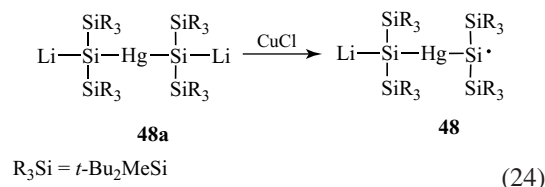
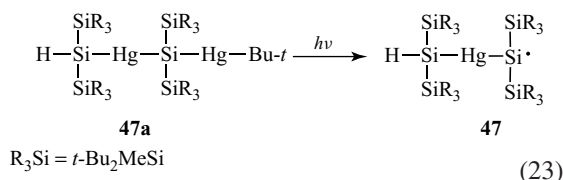


Figure 14 (a) EPR spectrum of **44** observed during UV irradiation of **44a** in hexane at 220 K. (b) EPR spectrum of silyl radical **42** observed after addition of THF to **44** in hexane at 300 K. (c) EPR spectrum of triplet bis(silyl) radical **45** (marked by “*”) during UV irradiation of **45a** at 130 K. The forbidden $\Delta M_s = 2$ absorption is shown in the inset. [Reproduced by permission from Ref. 97. Copyright 2005 Wiley-VCH Verlag GmbH & Co. KGaA.]

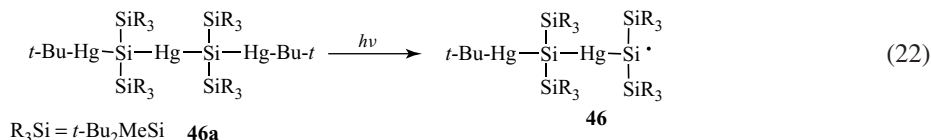
that in **45a** and thus the observed triplet bis-silyl radical is assigned the structure **45**.⁹⁷

4.3.2 Hg-Substituted Silyl Radicals

Photolysis ($\lambda > 300$ nm) for 10 s of silyl mercurials **46a** (22) and **47a** (23) or oxidation of **48a** (24) yields EPR spectra with g -factors of about 1.983 (Table 6).⁷¹ These g -factors are significantly smaller (upfield-shifted) relative to those of all other silyl radicals, which are in the range of $g = 2.004$ – 2.007 . The EPR spectra exhibiting the small g -factor (Figure 15) are assigned to mercury-substituted silyl radicals **46**–**48**. This assignment is supported by the observation of isotropic hyperfine interactions of the unpaired electron with the ^{199}Hg and ^{29}Si nuclei with satellite lines intensities corresponding to their natural abundances, and by the significantly upfield-shifted g -factor of 1.990 of the carbon analog $\text{ClHgH}_2\text{C}^\bullet$.⁹⁹



The magnitude of $a_{\text{Hg}}(^{199}\text{Hg})$ of 63–105 G in radicals **46**–**48** (Table 6) indicates that only 0.5–0.8% of the spin density resides in a 6s-type orbital of the mercury atom and the spin of these radicals is localized on the central silicon atom. This estimate is based on the fact that a full spin residing in the 6s orbital results in $a_{\text{Hg}}(^{199}\text{Hg})$ of $\sim 12\,000$ G.⁸¹ This huge $hfcc$ value implies that even small changes in the distribution of the spin density dictate meaningful changes in $a_{\text{Hg}}(^{199}\text{Hg})$.



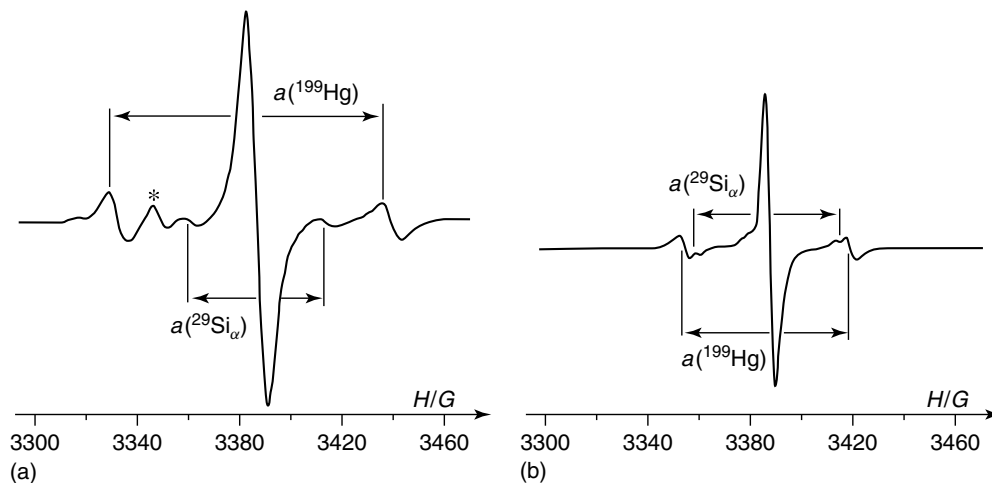


Figure 15 EPR spectra of (a) radical **46** obtained after UV irradiation ($\lambda = 300$ nm) of a hexane solution of **46a** at 200 K; a line of a nonassigned hypersilyl radical is marked by an asterisk. (b) Radical **48** in hexane at 290 K. [Adapted with permission from Ref. 71. Copyright 2005 American Chemical Society.]

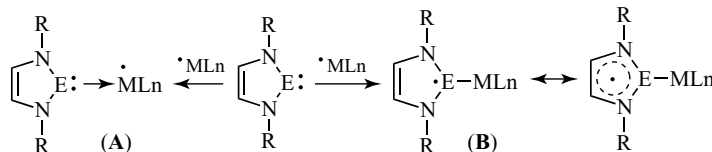
4.4 Transition-Metal-Substituted Silyl Radicals

The recent synthesis and isolation of stable silylenes¹⁰⁰ (and of other group-14 metallylenes^{101,102}) has opened new opportunities also for the synthesis of novel silyl radicals. New radicals, most of them persistent, were recently produced by Apeloig's group by the addition of transition-metal-centered radicals to stable *N*-heterocyclic silylenes,¹⁰³ germylene,¹⁰⁴ and carbene (Scheme 13).¹⁰⁵ These novel paramagnetic species **49–55** were studied by EPR spectroscopy (Table 7) and DFT calculations, revealing strong dependence of the spin density distribution on the nature of the main group E atom and of the transition metal M.

Two types of bonds form on addition of transition-metal fragments to divalent atoms: coordination (**A**) or covalent E–M (**B**) (Scheme 13). EPR spectroscopy combined with DFT calculations of

the produced metallo-silyl radical adducts allow the evaluation of the nature of the E–M bond in these paramagnetic species.

For example, the reaction of $(\text{CO})_5\text{Mn}^\bullet$ (produced by photolysis of $\text{Mn}_2(\text{CO})_{10}$) with unsaturated silylene **49a** yields radical **49** (25) which has a half-life of several weeks at room temperature. Radical **49** is characterized by a relatively small splitting of the main line by ^{55}Mn , ($a_{\text{Mn}}(^{55}\text{Mn}) = 8.9$ G) and by $a_{\text{N}}(2^{14}\text{N}) = a_{\text{H}}(2\text{H}) = 5.7$ G. The observed splitting by two magnetically equivalent ^{14}N nuclei and by two proton nuclei clearly indicates that the spin is delocalized over the entire heterocyclic moiety (type **B** in Scheme 13) (Table 7) (Y. Apeloig, *et al.*, unpublished results). Similarly, delocalized silyl radicals **51–53** of type **B** in Scheme 13 were observed in reactions of Re-, Co-, and Mo-centered radicals with silylene **49a**.^{103,104} In contrast, reaction of the analogous carbene with $(\text{CO})_5\text{Mn}^\bullet$ results in the substitution



Scheme 13 Formation of two bond types on the addition of transition-metal-centered radicals to the divalent center E of *N*-heterocyclic metallylenes.

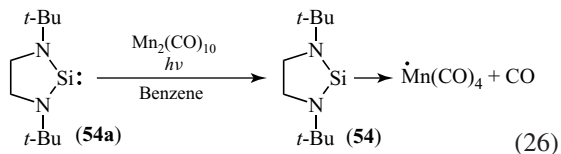
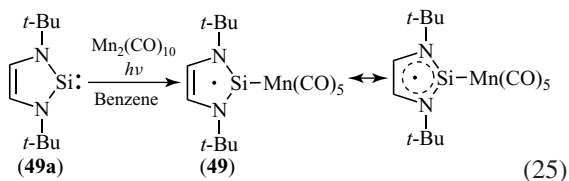
Table 7 EPR parameters of persistent transition metal-substituted silyl radicals obtained by addition to silylenes.

No.	Radical	$a_{\text{Si}}(^{29}\text{Si}_\alpha)$ G	$a_X(X)$, ^a G	g	Stability	References
49		^b	5.7 (¹⁴ N) 5.7 (¹ H) 8.9 (⁵⁵ Mn)	2.0027	Persistent	Y. Apeloig, <i>et al.</i> , unpublished results
50		^b	24.0 (⁵⁵ Mn)	2.023	Persistent	105
51		^b	7.1 (¹⁴ N) 4.7 (¹ H) 36.5 (^{185,187} Re)	2.0039	Persistent	103
52		^b	5.3 (¹⁴ N) 5.3 (¹ H) 6.4 (⁵⁹ Co)	2.003	Persistent	104
53		^b	5.7 (¹⁴ N) 5.7 (¹ H)	2.0027	Persistent	103
54		^b	13.6 (⁵⁵ Mn)	2.028	Persistent	Y. Apeloig, <i>et al.</i> , unpublished results
55		59.6 59.0	40.0 (^{185,187} Re) 38.8 (^{185,187} Re)	2.013 2.0127	Persistent	51

^aThe atoms X responsible for the quoted *hfccs* are given in parentheses.^bSatellite lines of ²⁹Si_α are not observed due to low signal/noise ratio.

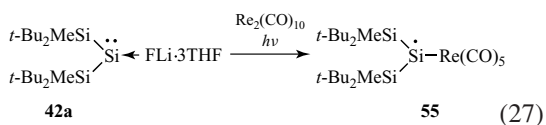
of one of the CO ligands, yielding a persistent Mn-centered radical (**50**) ($a_{\text{Mn}}(^{55}\text{Mn}) = 24.0 \text{ G}$).¹⁰⁵ The large $a_{\text{Mn}}(^{55}\text{Mn})$ value and the lack of splitting by the nitrogen and proton nuclei indicate that this radical is of type A in Scheme 13, with the spin localized mainly on the manganese.¹⁰⁵ Similar

reactions of a variety of transition-metal-centered radicals with saturated silylene **54a** (26) do not lead to radical adducts, except with $(\text{CO})_5\text{Mn}^\bullet$ yielding a persistent Mn-centered radical (**54**) ($a_{\text{Mn}}(^{55}\text{Mn}) = 13.6 \text{ G}$, $g = 2.028$) (Y. Apeloig, *et al.*, unpublished results).



In contrast to transition-metal-substituted silyl radicals derived from heterocyclic silylene **49a**, which are usually persistent, radical adducts of silylenes **49a** (and **54a**) with phosphorus-centered radicals, such as $(i\text{-PrO})_2(\text{O})\text{P}^\bullet$, are highly reactive and they are not observed by EPR.¹⁰⁶

A persistent Re-substituted acyclic Si-centered radical **55** is produced by UV irradiation of a 1 : 1 mixture of silylenoid (**42a**)⁹⁶ and $\text{Re}_2(\text{CO})_{10}$ in toluene (27).⁵¹



The EPR spectrum of the irradiated mixture of reaction (27) reveals the presence of two rotamers of radical **55** (**55a** and **55b**) in the ratio of about 30 : 70 (Figure 16). The intensity ratio of the signals of the two rotamers does not depend on the irradiation time or the temperature (in the range of 230–320 K). According to DFT calculations, in the more stable rotamer, the *t*-butyl groups of the silyl substituents are in *anti* arrangement and in the less stable rotamer both *t*-butyl groups are in a *syn* arrangement, the *anti* rotamer being more stable by 0.6 kcal mol⁻¹.⁵¹

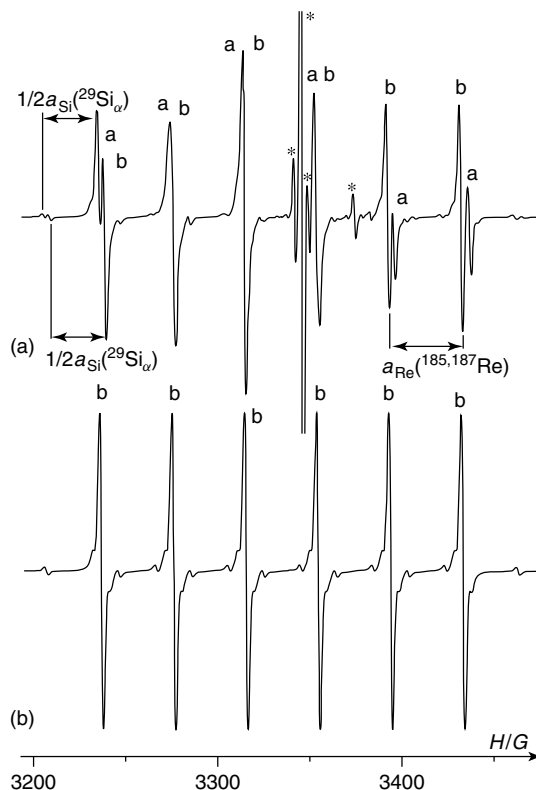
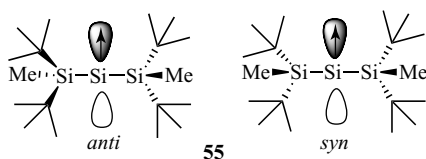


Figure 16 EPR spectra of silyl radical **55**: (a) experimental spectrum showing a superposition of the two rotamers of **55**. Signals of $(\text{t-Bu}_2\text{MeSi})_3\text{Si}^\bullet$ (a byproduct) are marked by an asterisk. (b) Simulated spectrum of rotamer **55b**. [Adapted with permission from Ref. 51. Copyright 2010 American Chemical Society.]

5 CONCLUSIONS AND OUTLOOK

The recent developments in the study of silyl radicals have been spectacular. Two decades ago, only short-lived silyl radicals were known and only few were spectroscopically characterized. Since then, many new types of persistent and stable silyl radicals have been synthesized, isolated, and characterized including by EPR spectroscopy and X-ray crystallography. These exciting developments were reviewed in this article.

Silyl radicals are of increasing interest not only to chemists but also to physicists and material scientists. We therefore believe that the chemistry of silyl radicals in general and of persistent and stable silyl radicals in particular will evolve in many new

directions in the future. Some of our thoughts on future developments are given below

1. Stable transition-metal complexes of silyl radicals may prove to be effective catalysts for a variety of reactions.
2. Stable silyl radicals may be used for photomagnetic switching.
3. The recently discovered photoreactivity of stable silyl radicals⁵⁰ may lead to the development of new, effective photoinitiators for radical polymerization.
4. Stable aggregates of metal-containing silyl radicals and silyl diradicals can be used as building blocks for novel molecular magnetic materials.
5. Synthesis of novel, stable silyl radicals and their isolation as crystalline materials may lead to novel molecular materials with unique properties. For example, our group has recently obtained a photoactive 1 : 1 cocrystal of $(t\text{-Bu}_2\text{MeSi})_3\text{Si}^\cdot$ with $(t\text{-Bu}_2\text{MeSi})_3\text{Si}^- \text{Li}^+ \cdot 4\text{THF}$ (Y. Apeloig, *et al.*, unpublished results.). This and similar cocrystals of silyl radicals and anions have the potential to exhibit interesting ionic and photoconductive properties.

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Physical Properties of Thiazyl Radicals Toward Conductive and Magnetic Materials

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1 INTRODUCTION

Research on molecule-based conductors, superconductors, and magnetic materials has been characterized by the enhancement of dimensionality in intermolecular interactions. The first molecular metal, tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ), exhibited a Peierls transition due to instability of the one-dimensional (1D) conducting pathway formed by the π - π overlap.¹ Increasing the dimensionality to overcome the 1D instability led to the discovery of molecular superconductors, such as those based on the tetramethyltetraselenafulvalene (TMTSF) and bis(ethylenedithio)tetrathiafulvalene (BEDT-TTF) donors.¹ More recent examples include the fullerene conductors, for example, K_xC_{60} , in which there are a three-dimensional (3D) network of C60 molecules.² A similar material development history is observed in the case of molecule-based magnetic materials. While the galvinoxyl radical, whose ferromagnetic interaction was found in the 1960s, exhibited a spin-Peierls-like transition, on which it lost its ferromagnetic properties,^{3–5} the first organic ferromagnet, p-NPNN, possessed a 3D network structure.^{6,7}

Heterocyclic thiazyl radicals possess unique chemical and physical properties.^{8–12} They can be

regarded as being on the borderline between organic and inorganic materials. They are chemically stable, in contrast to the instability of most organic radicals, so that they do not need protecting groups on their molecular skeletons. The lack of substituents permits relatively close packing in the solid state. Moreover, thiazyl radicals exhibit a large electronic polarization, leaving, respectively, a positively and a negatively polarized charge on sulfur and nitrogen. These charges form short intermolecular and interatomic S $\cdots$ N contacts. As a result, thiazyl radical solids often involve a multidimensional network consisting of face-to-face π - π overlaps and side-by-side S $\cdots$ N contacts. This is believed to bring about high- T_c magnetic ordering, conductive behavior, and hysteresis in phase transitions.

In this article, we describe the physical properties of thiazyl radicals, focusing on our recent studies on them. The studies on the other research groups are cited in the first figure of each section.

2 DRASTIC PHASE TRANSITIONS

Organic radicals often exhibit spin-Peierls-like phase transitions,¹³ associated with radical dimerization. Figure 1 shows the thiazyl radicals that are known to exhibit structural phase transitions.^{14–33}

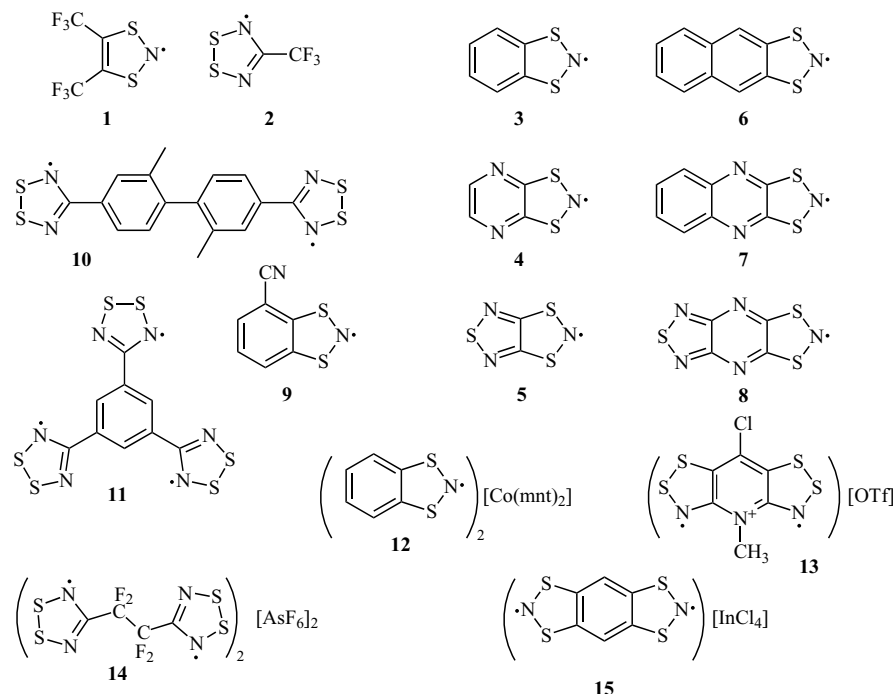


Figure 1 Thiazyl radicals that exhibit a structural phase transition with a sudden change in the temperature dependence of magnetic susceptibilities: **1** (Refs 14, 15), **2** (Refs 14), **3** (Refs 16, 17), **4** (Refs 18, 19), **5** (Refs 20–24), **6** (Ref. 25), **7** (Ref. 25), **8** (Ref. 26), **9** (Ref. 27), **10** (Ref. 28), **11** (Ref. 29), **12** (Ref. 30), **13** (Ref. 31), **14** (Ref. 32), and **15** (Ref. 33).

They include very drastic transitions, probably reflecting the strong spin-lattice interactions of this radical family. The singly occupied molecular orbital (SOMO) of thiazyl radicals always have a nodal plane between bonded sulfur and nitrogen, so that an intermolecular short contact between the S–N chemical moieties does not automatically mean a large overlap between the SOMOs (Figure 2). It is expected that a small change in the intermolecular arrangement would bring a significant change in the intermolecular overlap, namely in the magnetic interaction.

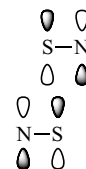


Figure 2 An intermolecular overlap between SOMOs of neighboring thiazyl radicals. Owing to the presence of a node of the SOMO at the center of the S–N bond, the two orbitals have nearly an orthogonal relation. This suggests a possible ferromagnetic coupling and a drastic change in the overlap caused by a small change in the geometry. The latter is believed to bring about strong spin–lattice interactions in thiazyl radicals.

2.1 Room-Temperature Magnetic Bistability in TTTA

1,3,5-Trithia-2,4,6-triazapentalenyl (TTTA) (**5**, Figure 1) was first synthesized by Wolmershäuser and Johann in 1989.³⁴ Recently, it was found that TTTA exhibits a first-order phase transition with a surprisingly wide thermal hysteresis loop around room temperature.^{20–24} Figure 3a depicts

the temperature dependence of the paramagnetic susceptibilities χ_p for TTTA. The bold arrow in this figure indicates the value of χ_p for the virgin sample just after sublimation crystallization. As the sample is cooled from room temperature, χ_p shows a slight decrease. In this temperature range, the value of $\chi_p T$ is circa $0.2 \text{ emu K mol}^{-1}$, which is much smaller than that of the Curie spin. This is probably caused by a 3D antiferromagnetic

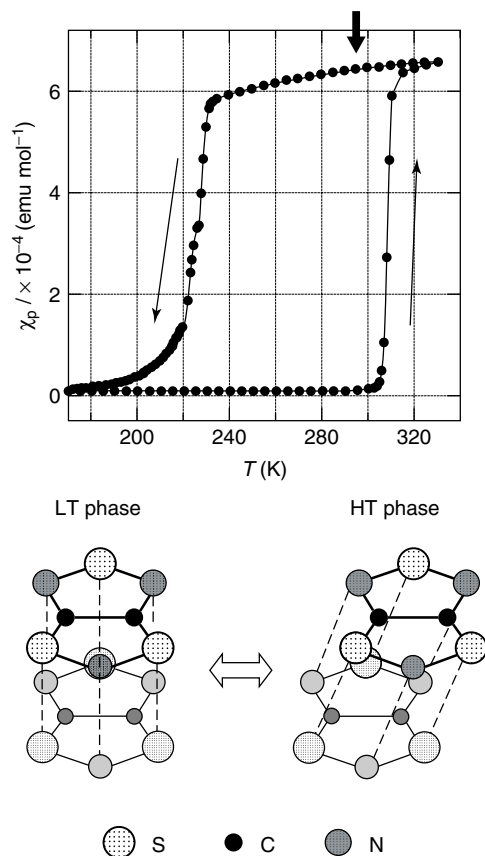


Figure 3 (a) Temperature dependence of the paramagnetic susceptibility χ_p for a polycrystalline sample of TTTA (5). The bold arrow indicates the χ_p value for the virgin sample just after sublimation. (b) Nearest neighbor intermolecular overlaps of TTTA in the HT and LT phases. The electrostatic interaction favors a shifted overlap, while the exchange interaction results in an eclipsed overlap. [Data taken from Ref. 20.]

interaction in the crystal of TTTA. At $T_{c\downarrow} = 230$ K, χ_p begins to decrease rapidly, becoming zero at 170 K; TTTA is intrinsically diamagnetic at low temperatures (LTs). When the sample is heated from a LT, a diamagnetic-to-paramagnetic transition is found at $T_{c\uparrow} = 305$ K, indicating the large hysteresis loop. Since this loop goes through room temperature (290 K), TTTA is regarded as a magnetically bistable material at room temperature.

Figure 4 shows the crystal structures of the high-temperature (HT) and the low-temperature (LT) phases of TTTA. The HT phase crystallizes in the monoclinic $P2_1/c$ space group. The structure consists of a polar 1D stacking column, in which the molecules are related by translational relations

with a constant interval. This stacking column is surrounded by six neighboring columns with very short $S \cdots N$ and $S \cdots S$ contacts. In contrast, TTTA exhibits a strong dimerization along the stacking direction in the crystal structure of the LT phase that belongs to the triclinic $P\bar{1}$ space group. This radical dimerization must be responsible for the diamagnetic properties of the LT phase. Figure 3b shows a schematic comparison between the nearest neighbor intermolecular arrangements in the two phases. It is notable that the molecules have an eclipsed overlap in the LT phase, in contrast to a shifted overlap in the HT phase. More specifically, the molecular planes in the LT phase dimer are not parallel; the distance between the $-S-N-S-$ moieties is shorter by circa $0.09 \text{ \AA}$ than that between the $-N-S-N-$ moieties, probably reflecting a bonding interaction between the unpaired electrons that are concentrated on the $-S-N-S-$ moieties. This suggests that bond formation is the main driving force of this phase transition.

It is expected that there is a competition between the exchange and electrostatic interactions (see Figure 3b). The exchange interaction favors an eclipsed overlap, such as that found in the LT phase, because this structure maximizes the intermolecular overlap between the SOMOs. However, this is the most disagreeable structure from the viewpoint of electrostatic energy because it includes intermolecular and interatomic contacts between polarized charges in the same sign, namely $S^{\delta+} \cdots S^{\delta+}$ and $N^{\delta-} \cdots N^{\delta-}$. It is presumably this competition that causes the drastic phase transitions in the thiazyl radical family.

Differential scanning calorimetry (DSC) measurements reveal an exothermic transition at 234 K on cooling and an endothermic one at 315 K on heating, respectively.²² The transition enthalpy ΔH values at $T_{c\downarrow}$ and $T_{c\uparrow}$ are determined to be 2210 and 2340 J mol^{-1} , respectively. The difference must be due to the fact that the HT and LT phases have different heat capacities. The transition entropies ΔS on cooling and heating are estimated to be $\Delta S_{\downarrow} = \Delta H_{\downarrow}/T_{c\downarrow} = 9.44 \text{ J K}^{-1} \text{ mol}^{-1}$ and $\Delta S_{\uparrow} = \Delta H_{\uparrow}/T_{c\uparrow} = 7.43 \text{ J K}^{-1} \text{ mol}^{-1}$, respectively. While the maximum estimation of the magnetic contribution is $R \ln 2$ ($= 5.76 \text{ J K}^{-1} \text{ mol}^{-1}$), the real contribution would be smaller than $R \ln 2$ because the HT phase involves rather strong antiferromagnetic interactions. Nevertheless, the ΔS values observed are larger than the maximum estimation. The excess

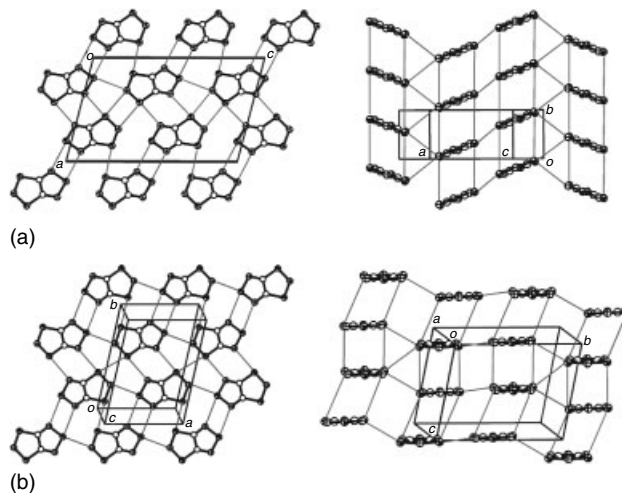


Figure 4 The crystal structures of TTTA (5): (a) the high-temperature phase and (b) the low-temperature phase. [Data taken from Ref. 20.]

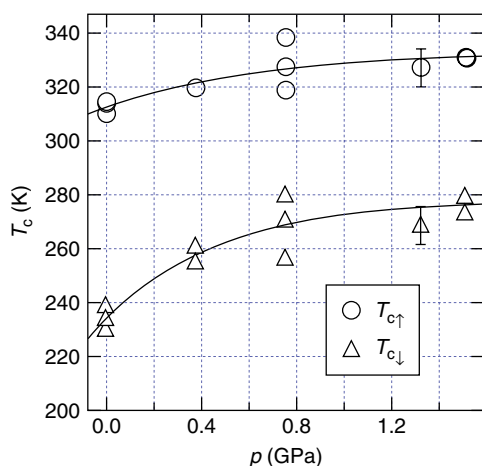


Figure 5 Pressure dependence of the transition temperatures, $T_{c\uparrow}$ and $T_{c\downarrow}$, for TTTA (5). Solid curves are eye guides. [Data taken from Ref. 24.]

entropy indicates involvement of the lattice system in the phase transition.

The temperature dependence of χ_p of TTTA was studied under 0.38, 0.75, and 1.5 GPa, and the pressure dependences of $T_{c\uparrow}$ and $T_{c\downarrow}$ were obtained.²⁴ The results are shown in Figure 5, indicating that both $T_{c\uparrow}$ and $T_{c\downarrow}$ exhibit significant increases with an increase in pressure. Thus, the bistable range shifts toward higher temperatures. Although room temperature (290 K) is just below $T_{c\uparrow}$ at ambient pressure, it falls in the

center of the hysteresis loop at 0.75 GPa. That is, room-temperature bistability can be stabilized by pressure. The two solid curves in Figure 5 are only eye guides, but the gradients at the ambient pressure are estimated to be roughly $dT_{c\downarrow}/dp = 45 \pm 20 \text{ K GPa}^{-1}$ and $dT_{c\uparrow}/dp = 20 \pm 10 \text{ K GPa}^{-1}$. The theoretical value of dT_c/dp is given by the Clapeyron equation, $dp/dT_c = \Delta S/\Delta V = \Delta H/(T_c \Delta V)$, where ΔV is the volume change, though this equation is valid only under thermal equilibrium. The enthalpy changes for the transitions in TTTA are obtained by DSC measurements, as described above. The difference between the unit cell volumes of the two phases is $3.4 \text{ \AA}^3$ at room temperature.^{20,22} Since the unit cell contains four molecules, the volume difference is $\Delta V_{RT} = 3.4 N_A/4 \text{ \AA}^3 \text{ mol}^{-1}$, where N_A is Avogadro's constant. The theoretical value for dT_c/dp at $p = 0 \text{ GPa}$ can be estimated to be 60 K GPa^{-1} under the assumption that $\Delta V = \Delta V_{RT}$. The agreement between the theoretical and experimental values is fairly good (the same order of magnitude), and the equation can explain the shift toward higher transition temperatures with increasing pressure.

The phase control of TTTA was also achieved using photoirradiation.²³ There is a very clear chromism between the crystal surfaces of the two phases under a polarized microscope, namely between red-purple in the HT phase and yellow-green in the LT phase. The photoinduced transition from the diamagnetic LT phase to the

paramagnetic HT phase was observed after a single-shot (6-ns pulse) irradiation at 2.64 eV at 296 K. In addition, a clear threshold was identified in the dependence of the LT-to-HT conversion efficiency on the excitation photon density. This strongly indicated that the observation was not a thermal effect, but a photoinduced phase transition.

2.2 Spin-Gap Formation Versus Antiferromagnetic Ordering in BDTA

1,3,2-Benzodithiazolyl (BDTA) (**3**, Figure 1) was synthesized by Wolmershäuser *et al.* in 1984.³⁵ Awere *et al.*¹⁶ reported its crystal structure: it consists of a centrosymmetric dimer, where the dimer units form a two-dimensional network with short S...S contacts (Figure 6). This is very similar to the structure of the κ -modification of (BEDT-TTF)₂X (BEDT-TTF = bis(ethylenedithio) tetrathia-fulvalene, X = Cu(NCS)₂, etc.), known as *organic superconductors* whose critical temperatures exceed 10 K.³⁶ Awere *et al.*¹⁶ also reported that BDTA was diamagnetic at least below the room temperature because of strong antiferromagnetic interactions in the structure. In this section, we will describe the complex phase transitions in BDTA, where a diamagnetic spin-gap phase, a paramagnetic phase, an antiferromagnetic ordered phase, and a liquid phase, interplay.¹⁷

Figure 7 depicts the temperature dependence of χ_p for BDTA above room temperature (open circles). BDTA is diamagnetic at room temperature due to its dimerized structure.¹⁶ On heating, however, BDTA exhibits a first-order

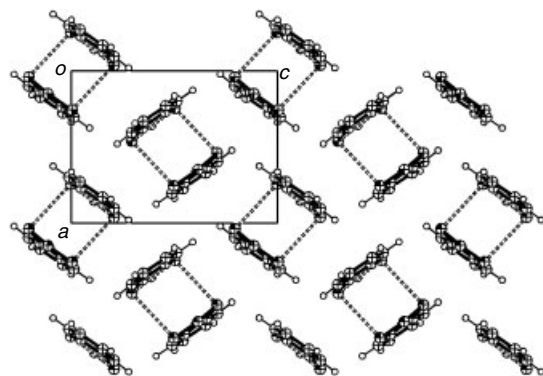


Figure 6 The crystal structure of BDTA (**3**). [Data taken from Ref. 16.]

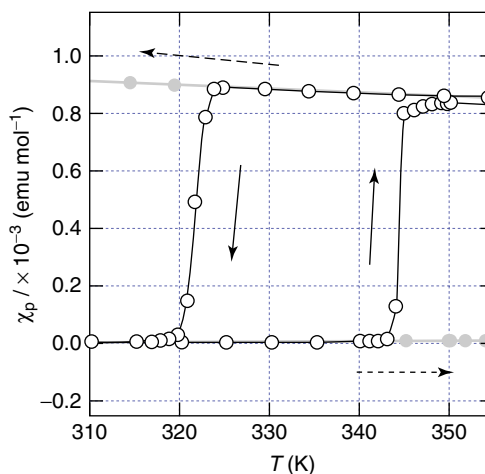


Figure 7 Temperature dependence of χ_p for BDTA (**3**) above room temperature. The gray plots indicate the effects of superheating and supercooling. [Data taken from Ref. 13.]

phase transition to a paramagnetic HT phase at 346 K, though the structure of this phase has not yet been identified. In the cooling process, a paramagnetic-to-diamagnetic transition is observed at 320 K, which is associated with the hysteresis of 26 K. This value is much smaller than that of TTTA, but still larger than the others in usual molecular solids. It is noted that this transition can be observed only for the aged BDTA samples, which probably include many lattice defects.

The most characteristic feature of BDTA is the occurrence of superheating and supercooling on phase transition above the room temperature. This always takes place in the case of fresh BDTA samples. The magnetic behavior in these nonequilibrium processes is shown in Figure 7 as gray circles. Figure 8 depicts the Gibbs free energy for BDTA determined by magnetic measurements and visual observation. In this figure, L and MO denote the liquid and antiferromagnetic ordered phases, respectively. The intersection between the LT and HT curves indicates the diamagnetic–paramagnetic phase transition at 346 K. On further heating of the superheated LT phase, the material melts at 360 K once, but the liquid immediately solidifies into the HT phase even on heating. This is because the free energies decrease in the order $LT > L > HT$ in the 360–364 K range. On heating, the LT phase relaxes into the HT phase through the L phase at 360 K. At 364 K, solid BDTA in the

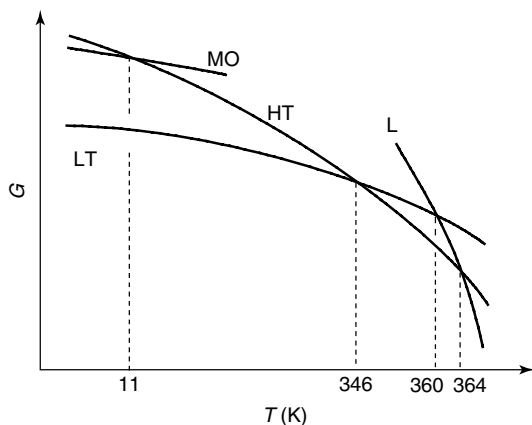


Figure 8 Gibbs energy phase diagram for BDTA (3). HT, high-temperature phase; LT, low-temperature phase; L, liquid; MO, antiferromagnetic ordered state. [Data taken from Ref. 13.]

HT phase exhibits a second melting. This process has been called *double melting* and has been observed, for example, in molecular crystals and organic polymers.³⁷

Supercooling of the HT phase also occurs (Figure 7) and further cooling results in antiferromagnetic ordering at 11 K (Figure 8). The temperature dependence of χ_p for the supercooled HT phase follows the Curie–Weiss law with $\theta = -93$ K and $C = 0.375$ emu K mol⁻¹ (fixed), where θ and C are the Weiss and Curie constants, respectively. Below 15 K, χ_p shows a slight decrease with a rather abrupt change around 11 K, suggesting the antiferromagnetic ordering. The temperature dependence of the heat capacity c_p exhibits a λ -shaped anomaly at 11 K, supporting the antiferromagnetic ordering at this temperature. The HT phase transforms into the MO phase below 11 K, as indicated in Figure 8. The structures of the HT and MO phases must be nearly the same. Thus, it is thought that the crystal structures for the spin-gap state and the antiferromagnetic ordered state are switched at the phase transition at 346 K. Alternative relationships between the spin gap state and the antiferromagnetic ordered state have been reported in low-dimensional magnetic materials, such as spin-Peierls compounds³⁸ and copper-oxide high- T_c superconductors.³⁹ While the competition between the two states occurs on the identical crystal structure in these materials, BDTA forms two states with different crystal structures that are linked at the structural phase transition.

2.3 Charge Transfer Phase Transition in (BDTA)₂[Co(mnt)₂]

A donor–acceptor-type organic charge-transfer (CT) complex, TTF-chloranil, exhibits a neutral-ionic phase transition, at which the degree of CT changes from 0.3 to 0.7 with various critical phenomena including quantum behavior.^{40,41} Recently, CT phase transitions have been observed in several transition-metal complexes.^{42–44} In this section, we will describe a CT phase transition in (BDTA)₂[Co(mnt)₂] (mnt²⁻ = maleonitriledithiolate) (12), which is accompanied by characteristic changes in molecular structure, intermolecular packing, and magnetic susceptibility.

Figure 9 shows the values of $\chi_p T$ for (BDTA)₂[Co(mnt)₂] against temperature T .³⁰ In the temperature range 200–300 K, the $\chi_p T$ value (0.61 emu K mol⁻¹) depends little on temperature, obeying the Curie law. On cooling, however, $\chi_p T$ rapidly decreases to 0.49 emu K mol⁻¹ at 180 K, followed by a Curie–Weiss behavior with a Weiss constant of $\theta = -4.7$ K. Figure 9 also shows the $\chi_p T$ values on heating, revealing a hysteresis loop of 20 K at the transition. This indicates that the anomaly at 190 K is caused by a first-order phase transition.

The geometry of (BDTA)₂[Co(mnt)₂] at 253 K is shown (Figure 10, b), in which one half of the unit is crystallographically independent.³⁰ The molecular planes of BDTA and [Co(mnt)₂] are nearly parallel, and the axial positions of the cobalt ion are occupied by the sulfurs on separate BDTA molecules at a distance of 3.1672(9) Å. This value is nearly the same as the interplanar distance, suggesting that BDTA should be regarded as a counter cation for [Co(mnt)₂]. It is known that the S–N bond length l_{SN} of BDTA is a good indicator of the charge ρ_{BDTA} on it. The removal of the unpaired electron in the SOMO of BDTA shortens the S–N bond lengths because the SOMO has an antibonding character on the S–N bonds. There is an empirical linear relation between l_{SN} and ρ_{BDTA} , with which ρ_{BDTA} is estimated to be 0.9 for BDTA in the HT phase; this corresponds to the formula (BDTA^{0.9+})₂[Co(mnt)₂]^{1.8-}. Since BDTA⁺ and [Co(mnt)₂]²⁻ are $S = 0$ and $1/2$ spin species, this formula unit possesses one unpaired electron.

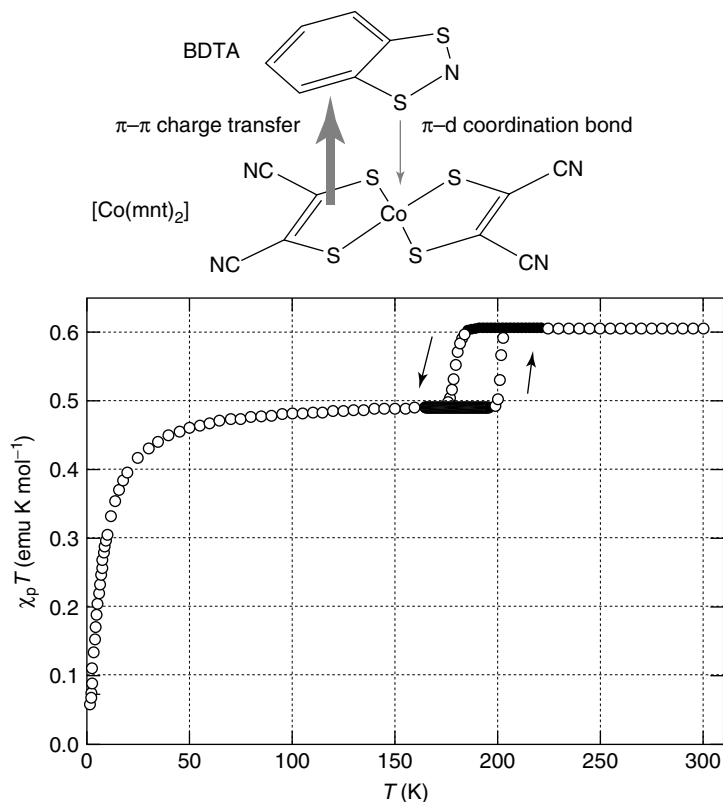


Figure 9 Temperature dependence of $\chi_p T$ for $(\text{BDTA})_2[\text{Co}(\text{mnt})_2]$ (**12**). The inset shows a possible mechanism of coordination bond formation at the phase transition of 190 K. [Data taken from Ref. 30.]

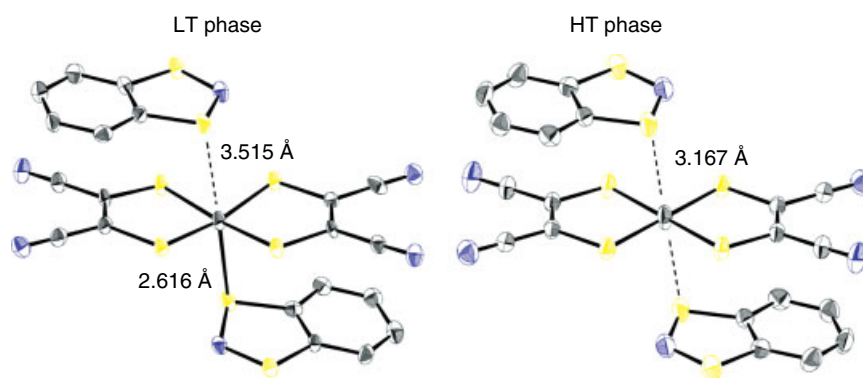


Figure 10 Crystal structures of $(\text{BDTA})_2[\text{Co}(\text{mnt})_2]$ (**12**) at 100 K (a) and 253 K (b). [Data taken from Ref. 30.]

The asymmetric unit of $(\text{BDTA})_2[\text{Co}(\text{mnt})_2]$ at 100 K includes two crystallographically independent BDTA molecules, A and B (Figure 10, a).³⁰ There is a Co...S axial coordination bond of 2.6163(18) Å between BDTA^{A} and $[\text{Co}(\text{mnt})_2]$,

while the Co...S distance is 3.5152(16) Å on the B side. Moreover, BDTA^{A} is significantly different in molecular structure; the average S–N bond length l_{SN} for BDTA^{A} (1.623(3) Å) is much longer than those for BDTA^{B} (1.605(3) Å) and BDTA in the

HT phase (1.603(2) Å). The charges on the two BDTA molecules in the LT phase are estimated to be $\rho_{\text{BDTA}}^{\text{A}} \approx 0.5$ and $\rho_{\text{BDTA}}^{\text{B}} \approx 0.9$, respectively. These values suggest a partial CT at the phase transition, namely $(\text{BDTA}^{0.9+})_2[\text{Co}(\text{mnt})_2]^{1.8-}$ (253 K) $\rightarrow$ $(\text{BDTA}^{0.9+})(\text{BDTA}^{0.5+})[\text{Co}(\text{mnt})_2]^{1.4-}$ (100 K).

The structural analyses indicate a partial CT by circa 0.4 for the phase transition at 190 K. This is further supported by the g -factors for the two phases, which are estimated from the Curie constants obtained by magnetic measurements to be $g = 2.55 \pm 0.10$ and 2.29 ± 0.10 for the HT and LT phases, respectively. Since the g -factor is governed by the distribution of the unpaired electron in the $(\text{BDTA})_2[\text{Co}(\text{mnt})_2]$ unit, it can be written as follows:

$$g^2 = (2 - 2\bar{\rho}_{\text{BDTA}})g_{\text{BDTA}}^2 + (2\bar{\rho}_{\text{BDTA}} - 1)g_{[\text{Co}(\text{mnt})_2]}^2 \quad (1)$$

where $\bar{\rho}_{\text{BDTA}}$ is the average charge on BDTA and g_{BDTA} ($= 2.006$) and $g_{[\text{Co}(\text{mnt})_2]}$ ($= 2.526$ of $[\text{N}(\text{C}_4\text{H}_9)_4]_2[\text{Co}(\text{mnt})_2]$) (Y. Umezono, W. Fujita, K. Awaga, H. B. Cui, and H. Kobayashi, unpublished data) are the g -factors for the neutral $S = 1/2$ BDTA radical and the $S = 1/2[\text{Co}(\text{mnt})_2]^{2-}$ dianion, respectively. Using the values of $\bar{\rho}_{\text{BDTA}}$ indicated in the structural analyses, 0.9 and 0.7 for the HT and LT phases, the two g -factors are calculated to be 2.43 and 2.23, respectively. These values are roughly in agreement with the corresponding values estimated from the Curie constants; the magnetic jump at the phase transition can be explained by the partial CT between BDTA and $[\text{Co}(\text{mnt})_2]$.

The structural and magnetic analyses reveal the CT phase transition, $(\text{BDTA}^{0.9+})_2[\text{Co}(\text{mnt})_2]^{1.8-}$ (253 K) $\leftrightarrow$ $(\text{BDTA}^{0.9+})(\text{BDTA}^{0.5+})[\text{Co}(\text{mnt})_2]^{1.4-}$ (100 K). This change in the degree of CT is smaller than those for the other CT transitions in the transition-metal complexes^{40,41}; that such a small change should bring about the coordination bond formation is peculiar to the present transition. This can be qualitatively explained (the inset of Figure 9). The electron transfer from $[\text{Co}(\text{mnt})_2]^{2-}$ to BDTA^+ through the π overlap decreases the positive charge on BDTA^+ and enhances the ability of BDTA to act as a ligand. Thus, BDTA forms a coordination bond, giving back the obtained electron partially to the vacant d-orbitals of the

cobalt ion in $[\text{Co}(\text{mnt})_2]$. This back donation makes the degree of CT smaller as a result. The phase transition in $(\text{BDTA})_2[\text{Co}(\text{mnt})_2]$ is considered to reflect a competing duality of BDTA as cation and ligand.

3 FERROMAGNETIC COUPLING AND ORDERING IN THIAZYL RADICALS

Figure 11 shows the thiazyl radicals that exhibit ferromagnetic intermolecular interactions and/or ferromagnetic (ferrimagnetic) ordering.^{45–55} The most well-known example is radical **17**, prepared by Banister *et al.*⁴⁶ This compound exhibits weak ferromagnetism with $T_N = 36$ K under high pressure (1 GPa).

3.1 Coordination Polymer in TTTA-Cu(hfac)₂

Thiazyl radicals are useful as ligands of transition-metal complexes.⁵⁶ The crystal structure of a 1:1 molecular compound, TTTA-Cu(hfac)₂ (**22**, Figure 11, Cu(hfac)₂ = bis(hexafluoroacetylacetonato)-copper(II)), is shown in Figure 9.⁵⁰ TTTA molecules occupy the axial positions of the elongated octahedron around the Cu(II) ion, and bridge the distance between the Cu(II) ions, resulting in an infinite zigzag chain along the b -axis. While various nitronyl nitroxides⁵⁷ and polynitroxyl radicals⁵⁸ are known to act as a bidentate bridging ligand and to form polymeric coordination compounds, the structure of TTTA-Cu(hfac)₂ clearly indicates similar chemical capability of the polycyclic thiazyl radicals. As shown in Figure 12, the Cu(II) ion is sandwiched between two TTTA molecules, labeled A and B, at distances of 2.342 and 2.478 Å from the Cu(II) ion. The former distance is shorter by more than 0.1 Å. The molecular plane of TTTA^A is nearly orthogonal to the plane defined by the four hfac oxygen atoms, while that of TTTA^B is significantly tilted.

The magnetic couplings between Cu(hfac)₂ and nitroxyl radicals have been previously discussed by Caneschi *et al.*⁵⁷ They explained the ferromagnetic couplings in these materials in terms of the orthogonality between the $d_{x^2-y^2}$ orbital of Cu(II) and the SOMOs of the organic radicals. By analogy, it is expected that the interaction between

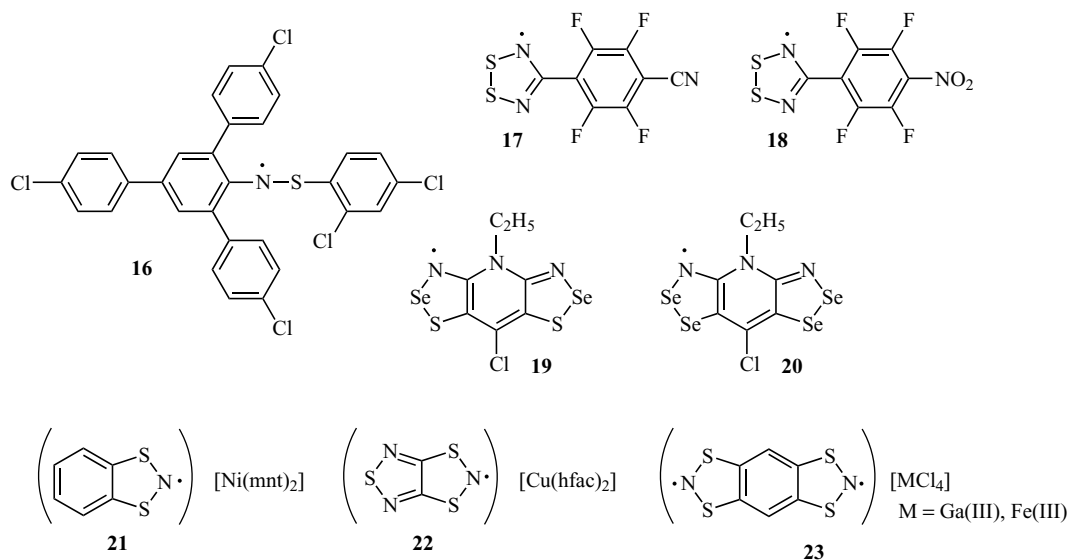


Figure 11 Thiazyl radicals that exhibit a ferromagnetic coupling and/or a magnetic ordering: **16** (Ref. 45), **17** (Ref. 46), **18** (Ref. 47), **19** (Ref. 48), **20** (Ref. 48), **21** (Ref. 49), **22** (Ref. 50), and **23** (Refs 51–55).

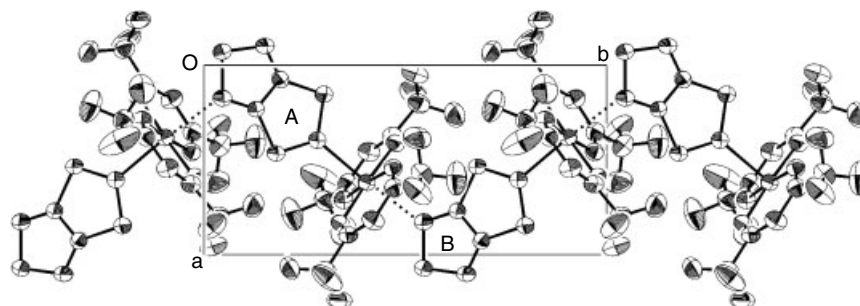


Figure 12 Crystal structure of coordination polymer, TTTA-Cu(hfac)₂ (**22**). [Data taken from Ref. 13.]

Cu(hfac)₂ and TTTA^A would be ferromagnetic. However, the Cu(hfac)₂–TTTA^B interaction is probably antiferromagnetic due to the overlap between the magnetic orbitals of Cu(II) and TTTA^B caused by the tilted structure.

The $\chi_p T$ value for TTTA-Cu(hfac)₂ increases with decreasing temperature down to circa 30 K, indicating a ferromagnetic coupling. After passing through a maximum at this temperature, $\chi_p T$ shows an abrupt decrease, suggesting a weak antiferromagnetic coupling between the ferromagnetic units. This is quite consistent with the coordination around the Cu(II) ion. The ferromagnetic coupling constant was determined to be $J/k_B = 5.1$ K. This is stronger than those in the axial coordination compounds

of Cu(hfac)₂ and nitroxyl radicals,⁵⁷ presumably because the energy level of the SOMO of TTTA is closer to those of the d-orbitals of Cu(II).

3.2 Ferromagnetism in BBDTA Salts Driven by Evaporation of Crystal Solvent

BBDTA was initially reported independently by Wolmershäuser *et al.*⁵¹ and by Wudl and coworkers.^{59,60} Wolmershäuser *et al.*⁵¹ also reported the crystal structure and the ⁵⁷Fe Mössbauer spectra of the radical cation salt BBDTA·Fe(III)Cl₄·CH₃CN (**23**, Figure 11), which suggested antiferromagnetic ordering of the Fe³⁺ magnetic moments below 6.6 K.

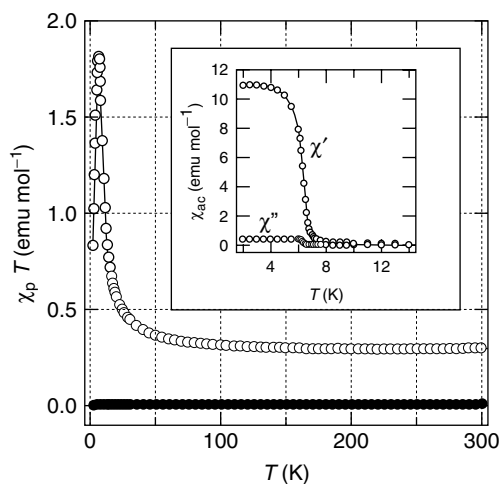


Figure 13 Temperature dependence of $\chi_p T$ for BBDTA·GaCl₄ (**23**) in the solvated (●) and nonsolvated form (○). The inset shows the temperature dependence of χ_{ac} for the nonsolvated form. [Data taken from Ref. 52.]

BBDTA·GaCl₄·CH₃CN is isostructural to BBDTA·FeCl₄·CH₃CN, consisting of a face-to-face radical dimer. The crystal solvent, CH₃CN, occupies the space beside BBDTA, coordinating to the sulfur atom. These dimers are stacked via short S···N contacts, forming a ladder-type structure. The GaCl₄[−] anions are located between the ladder layers. As shown in Figure 13 as closed circles, the $\chi_p T$ values for BBDTA·GaCl₄·CH₃CN are nearly zero in the whole temperature range. This nonmagnetic property can be ascribed to a strong antiferromagnetic interaction in the dimer.

There is a dramatic change in the bulk magnetic properties after evaporation of the crystal solvent. The open circles in Figure 13 show the magnetic data for a sample in which 75% of the CH₃CN has been removed by evacuation for 96 h. This material exhibits paramagnetism, in remarkable contrast to the nonmagnetic properties of the solvated form. The values of $\chi_p T$ show a gradual increase, suggesting a ferromagnetic coupling. Below 10 K, $\chi_p T$ increases rapidly, reaching 1.82 emu mol^{−1} at 6 K. The inset in Figure 13 shows the temperature dependence of the ac susceptibilities (χ' : in-plane, χ'' : out-of-plane) for the same sample. The plots of χ' show an anomaly below 6.7 K with a rapid increase in χ , indicating ferromagnetic ordering. The isothermal magnetization curve at 2 K for this sample shows an abrupt increase at lower fields

followed by quick saturation above 400 Oe. The presence of a negligibly small hysteresis loop with a width of less than 10 Oe indicates that the material obtained is a soft magnet.

The crystal growth of the solvent-free BBDTA·GaCl₄ revealed the polymorphism of this material; there were at least three forms, α (plates), β (needles), and γ (blocks). The γ -phase exhibits a ferromagnetic transition at 7.0 K in contrast to the diamagnetic properties of the other two forms, suggesting that the desolvated material obtained from BBDTA·GaCl₄·CH₃CN would be in the γ -phase.⁵⁴

BBDTA·FeCl₄·CH₃COCH₃ is isostructural to BBDTA·GaCl₄·CH₃CN and exhibits similar solvation effects. While the solvated material exhibits paramagnetic behavior with antiferromagnetic ordering at 6.3 K, the desolvated material includes a ferrimagnetic phase with $T_N = 44$ K.⁵³ This is much higher than the transition temperatures of the parent materials: 7 K for the ferromagnetic transition in BBDTA·GaCl₄ and 3 K for the antiferromagnetic transition in (C₂H₅)₄N·FeCl₄.⁶¹ A strong antiferromagnetic coupling between the magnetic moments on BBDTA and FeCl₄ is thought to afford this organic/inorganic hybrid system a higher ferrimagnetic transition temperature.

4 CONDUCTIVE THIAZYL RADICALS

Figure 14 shows the conductive thiazyl radicals with a room-temperature conductivity above 10^{−2} S cm^{−1}.^{62–69} Most of these materials were synthesized by the group of Oakley. The compounds in Figure 14 are all ion radical salts of thiazyl radicals, and exhibit semiconductive behavior, except the HT phase in **24**.

4.1 Carrier Doping for Mott Phase in TTTA

The magnetic bistability of TTTA (**5**) has been described in Section 2.1. Although the HT phase of this material consists of nearly regular stacking columns with electrostatic intercolumn interactions, this phase exhibits very poor conductivity of 10^{−8} Ω^{−1} cm^{−1} at room temperature with an activation energy of 0.33 eV under vacuum.¹² The conductivity for the LT phase is two orders of

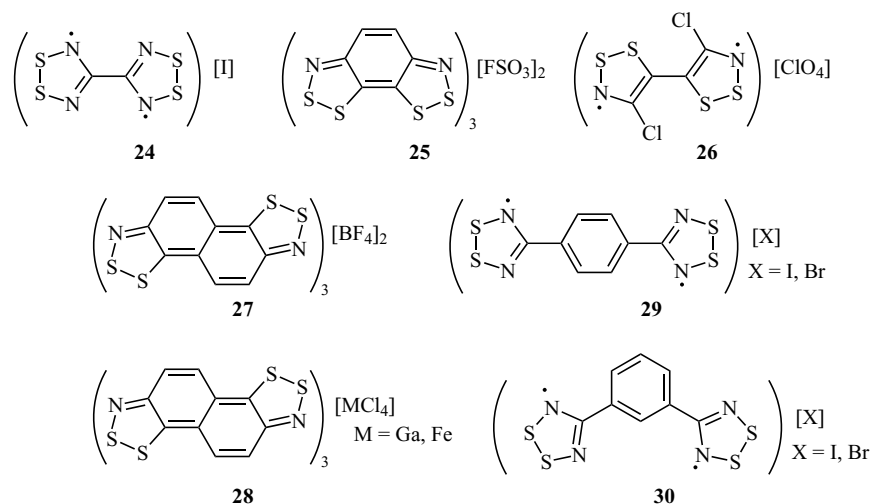


Figure 14 Conductive thiazyl radicals with a room-temperature conductivity higher than $10^{-2} \text{ S cm}^{-1}$: **24** (Ref. 62), **25** (Ref. 63), **26** (Ref. 64), **27** (Ref. 65), **28** (Refs 66, 67), **29** (Refs 68, 69), and **30** (Refs 68, 69).

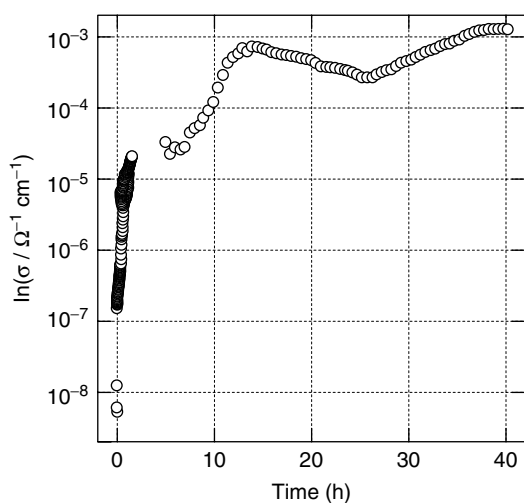


Figure 15 Time dependence of the conductivity of TTTA (**5**) during I_2 doping. [Data taken from Ref. 13.]

magnitude lower. Thus, it is highly possible that the HT phase can be regarded as a Mott insulator: strong on-site electron–electron repulsion results in electron localization.

Figure 15 shows the effects of I_2 doping for the HT phase of TTTA. The conductivity σ is quickly enhanced by four or five orders of magnitude, followed by saturation after 10 h.¹² This saturation is presumably due to a breakup of the crystal structure caused by penetration of the dopant. It is clearly

demonstrated that hole doping of the HT phase of TTTA brings about significant enhancement of the conductivity.

4.2 Nonlinear Electrical Transport in $\text{NT}_3 \cdot \text{GaCl}_4$

Barclay *et al.*⁶⁴ prepared NT and its 3:2 radical cation salt, $\text{NT}_3 \cdot (\text{BF}_4)_2$ (**27**). The crystal of **27**, consisting of $(\text{NT})_2^{2+}$ and NT^0 , exhibited relatively high conductivity.⁶⁵ Figure 16 schematically shows the network structure in the crystal of the 3:1 salt of NT, $\text{NT}_3 \cdot \text{GaCl}_4$ (**28**).^{66,67} This crystal consists of four kinds of NT molecules, denoted **a**, **b**, **c**, and **d**, with significantly different molecular structures. The molecules **a** and **b** form a two-dimensional (2D) square network with short, electrostatic $\text{S}^{\delta+} \dots \text{N}^{\delta-}$ contacts (layer A), and the molecules **c** and **d** form a similar network (layer B). The two layers are stacked with large π – π overlaps in the manner of BABBAB. The counter anion GaCl_4^- is located in a cavity surrounded by the four stacking columns of NT.^{66,67}

From the S–N bond distances, the charges on the four NT molecules are estimated to be 0.8 (molecule **a**), 0.5 (**c**), 0.1 (**b**), and 0 (**d**), respectively. The molecules **a** and **c** are charge-rich (R) and charge-intermediate (I), respectively, while molecules **b** and **d** are charge-poor (P). This clearly

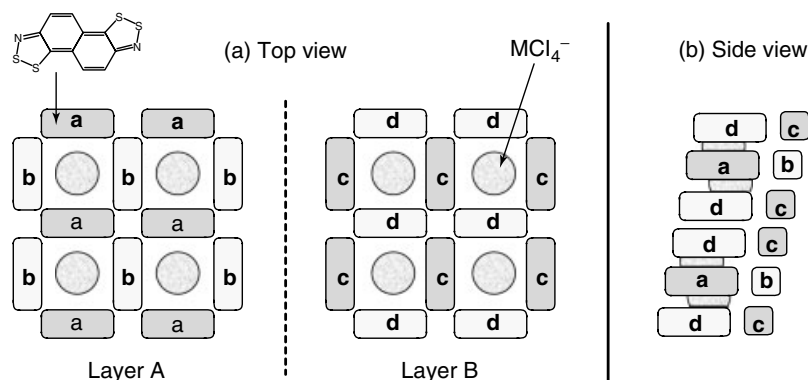


Figure 16 Schematic view of the crystal structure on (NT)₃[GaCl₄] (**28**). The molecules **a–d** are crystallographically independent. (a) 2D network structure caused by short S···N contacts. (b) Side view of the layered structure. [Data taken from Ref. 66.]

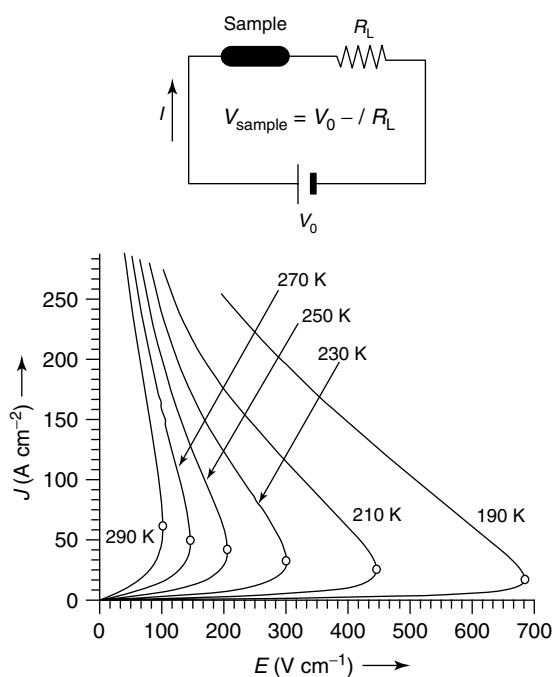


Figure 17 J – E characteristics for a crystal of (NT)₃[GaCl₄] (**28**) at various temperatures, taken by pulse field (25-ms width and 300-ms interval). The open circles show the turning points for the negative resistance effect. [Data taken from Ref. 66.]

indicates a 3D charge ordering. It is notable that the charge-rich (or -intermediate) and -poor molecules occupy the warp and weft positions in the 2D square network, in which the combination of R–R, I–I, or P–P is ruled out. Such a 3D charge alternation is gaining much attention as a characteristic insulating

state induced by intermolecular Coulomb repulsions in strongly correlated systems.^{70,71}

NT₃·GaCl₄ exhibits semiconductive properties with $\sigma_{\text{RT}} = 0.5 \text{ S cm}^{-1}$ and $\Delta E = 0.18 \text{ eV}$, where σ_{RT} is the room temperature conductivity and ΔE is the activation energy. Figure 17 shows the temperature dependence of the current density (J)–electric field (E) characteristics for NT₃·GaCl₄.^{66,67} At room temperature (290 K), the J – E curve exhibits a steep nonlinear rise and clearly indicates a so-called negative differential-resistance effect after passing through the turning point indicated by an open circle in this figure. This nonlinearity is considered to be caused by a partial melting of the charge ordering, because, if there is no charge ordering, the present material should have a five-sixth filled band that brings about metallic conduction. The threshold values for the electric field E_{T} and the current density J_{T} are 100 V cm^{-1} and 60 A cm^{-2} , respectively. It is very rare that this type of negative resistance effect is observed at room temperature in organic materials. In addition, the E_{T} value obtained for NT₃·GaCl₄ is much lower than those of the other organic materials showing nonlinear conductivity.^{8,72–78} By lowering the temperature from 290 K, the values of E_{T} and J_{T} exhibit a significant increase and decrease, respectively, making the negative resistance effect more drastic.

Figure 18 shows the effects of the DC current on the electron paramagnetic resonance (EPR) spectra of NT₃·GaCl₄ appearing at $g = 2.005$.⁶⁷ This value is typical for thiazyl radicals. When the current is loaded, the signal intensity exhibits a quick decrease and becomes one-third of the

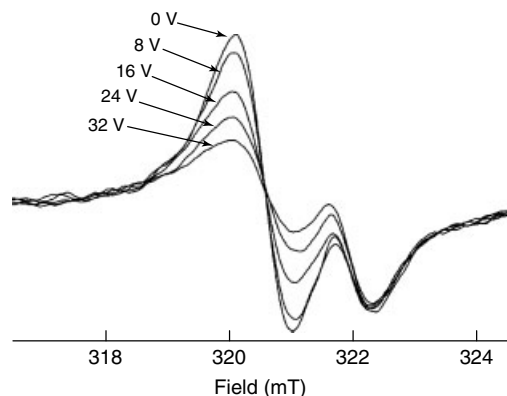


Figure 18 Current effects on the X-band EPR of $\text{NT}_3\text{-GaCl}_4$ (28). [Data taken from Ref. 67.]

original value at $J = 160 \text{ A cm}^{-2}$. In general, the current-induced nonlinear transport is inevitably associated with generation of the Joule heat, while most of them are probably diffused through the electrical wires. If the observed EPR behavior is only caused by heating, we need to assume an unrealistic sample temperature of $\sim 900 \text{ K}$. If the crystals of $\text{NT}_3\text{-GaCl}_4$ become homogeneously more conductive with an increase in J , there should be a line width broadening, caused by delocalization of the unpaired electrons. However, this is not the case. In general, the high conductive states induced by J are believed to be caused by the formation of filaments: the highly conductive pathways formed in the samples inhomogeneously.^{77,79,80} By analogy, the observed J dependence of the EPR for $\text{NT}_3\text{-GaCl}_4$ can be attributed to the inhomogeneous formation of highly conductive pathways, such as filament and surface, which shield the remaining part of the crystal from EPR microwave.

4.3 Photoconductivity of BDTDA

BDTDA is a so-called disjoint diradical, so that the molecular orbitals for the two unpaired electrons would be localized to separate five-membered rings and the exchange interactions between the two radical centers would be very small.⁶² The crystal structure of BDTDA consists of a face-to-face dimer, reflecting that the intermolecular interaction is stronger than the intramolecular interaction. Although BDTDA-I (24) is conductive,⁶² BDTDA

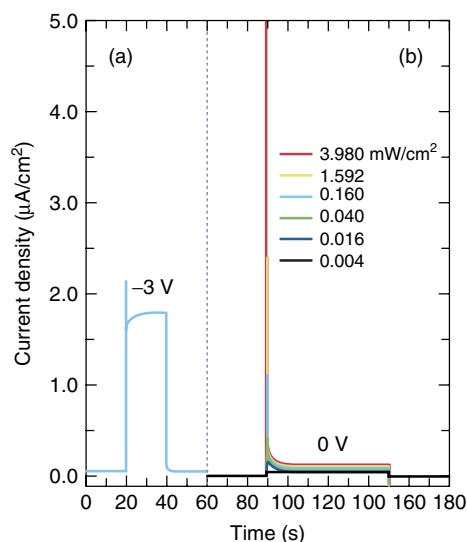


Figure 19 Photocurrent of an ITO/BDTDA/Al sandwich cell exposed to the 532-nm laser under 1.59-mW cm^{-2} irradiation from the ITO side at a reverse bias of -3 V (a) and at zero bias condition (b). [Data taken from Refs 81 and 86.]

itself is a poor conductor probably due to this dimerization. However, BDTDA can form highly oriented thin films that are expected to include a wide conduction band consisting of the LUMOs of the radical dimers.⁸¹ Figure 19a shows the photocurrent of an (+)ITO|BDTDA(300 nm)|Al(−) photocell, induced by the illumination of a green laser (532 nm) with a small reverse bias voltage V_{bias} of -3 V .⁸¹ BDTDA thin films exhibit a very high conductivity with a photoresponsivity of 3.5 mA/W and an on/off ratio of approximately 10^3 . They are comparable to those of the most-advanced organic polymer photodetectors for visible region.^{82–85}

Figure 19b shows the no-bias photocurrent of the same BDTDA photocell.⁸⁶ On illumination, a very large transient current appears, followed by a steady-state photocurrent and a negative spike just after the illumination. The quantum efficiency for the positive peak photocurrent reaches as high as 65% at the photon energy of 2.8 eV . This anomalous transient photocurrent is interpreted in terms of a highly efficient displacement current⁸⁷ caused by the establishment of a photoinduced space-charge zone and the bulk polarizations in the BDTDA films. The photoinduced displacement current in organic radical solids can provide a new operational principle for optoelectric conversion.

5 CONCLUSION

Thiazyl radicals are promising materials to exhibit unusual physical properties, such as drastic phase transitions, ferromagnetic couplings, and high conductivities, reflecting their chemical stabilities, strong intermolecular interactions, multidimensional crystal structures, and strong spin–lattice interactions. More interestingly, these properties can be manifested and/or modified by making intermolecular compounds; thiazyl radicals are useful building blocks of supramolecular compounds, because they can act as counter cations, donors, and ligands. In the near future, thiazyl radicals are expected to be utilized in developing organic electronics/spintronics.

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A Paradigm for the Radical-Mediated Photochemical Synthesis of Metal Nanostructures

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1 INTRODUCTION

Significant attention has been devoted to the study of nanotechnology and nanochemistry in the past quarter century.¹ The most common formation of colloidal nanoparticles has been achieved using bottom-up synthesis accomplished by reducing metal ions (M^{n+}) to their atomic state, M^0 , followed by spontaneous self-assembly. These reactions are generally performed in aqueous or organic solutions using thermal or photochemical methods with chemical reducing agents. The photochemical approach in aqueous environments is the focus of this contribution.

In many of the systems presented here, the reducing species is a free radical capable of donating an electron; in fact, it is very likely that the involvement of free radicals greatly exceeds the number of systems where this mechanistic pathway has been recognized or characterized in the literature. Radical generation plays an active role in the nucleation step; therefore, particle size, dispersity, and morphology can be finely tuned with the proper selection of reducing chemistry and the rate of these processes.

Many radicals show good electron donating properties, and among these, ketyl^{2,3} and α -aminoalkyl radicals^{4,5} are known for their strong reducing properties.⁶ Conveniently, a number of efficient photochemical methods are available for their generation.^{7,8} Once metal atoms are generated in solution, formation of nanoparticles is typically a spontaneous process governed by nucleation and growth periods, with fast radical generation generally favoring smaller monodispersed particles.

Control of synthesis parameters is therefore a challenge every chemist must consider when preparing nanostructures. Furthermore, even having the desirable size and morphology does not ensure particle stability, and thus, a wide range of approaches exist to achieve an acceptable nanoparticle life expectancy. Particularly, many nanoparticle synthetic procedures add stabilizers during the synthesis or shortly after the particles have been prepared. Such stabilizers may include ions, surfactants, thiols, polymers, and a wide range of natural and synthetic biomolecules.

From an applications-type perspective where a “custom” surface coverage is desired, the ideal starting point would be with a “naked” or unprotected nanoparticle, such that the exposed metal surface could be readily available for custom modification.

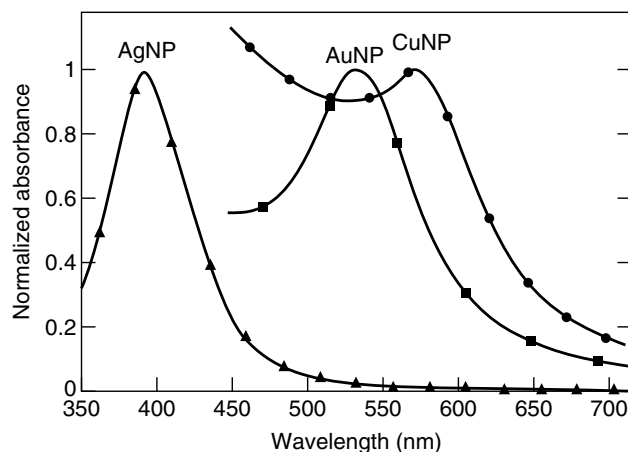


Figure 1 Normalized absorption spectra for noble metal nanoparticle in aqueous colloidal solutions. [Curves for AuNP and CuNP adapted from an earlier publication.]¹⁰

This contribution concentrates on the photochemical synthesis of noble metal nanoparticles, gold, silver, and copper in aqueous systems. Significant interest in noble metal nanoparticles arises from their optical properties. Noble metal nanoparticles possess strong collective oscillations of electrons in their conduction band and absorb strongly in the visible region. This absorption feature is referred to as the surface plasmon band (SPB), which is the summation of absorption and scattering modes, and shifts to lower frequencies with increased surface polarizability.⁹ For small spherical nanoparticles in colloidal aqueous suspensions, Figure 1 shows typical spectra.¹⁰

Small environmental changes result in SPB shifts related to particle size, particle shape (morphology), interparticle distance, refractive index, and temperature of the medium. New or enhanced absorption at long wavelengths can be due to increase in particle size, decrease in the interparticle distance, or formation of nonspherical morphologies.^{9,11}

2 WHY USE PHOTOCHEMISTRY?

A number of reliable methods to produce noble metal nanoparticles without using light are readily available and well established, particularly in the cases of gold and silver.^{12–14} While traditional approaches to colloidal preparations offer control over particle size and morphology by manipulation of reagent concentration, temperature, and variation

of the experimental protocol (e.g., order of addition of reagents), a photochemical approach offers spatial-temporal resolution, thus providing additional synthetic flexibility. The wavelength, light intensity, and temporal profile of the illumination can also be readily adjusted to facilitate control of size, morphology, and surface properties. Photochemical methods frequently lack the chemical complexity of thermal systems, can operate under milder conditions, and can leave significantly less chemical debris on the nanoparticles as compared with thermal processes.¹⁵

The frequently quoted advantages of photochemical methods, that is, *spatial and temporal control*, are just as applicable to nanoparticle synthesis as they are to conventional (film) photography, where the spatial distribution of light and the duration and timing of the exposure determine the quality of a photograph. Naturally, this advantage will apply to any imaging system, such as lithography.

Temporal control can have a much wider application; even when imaging is not important, the ability to turn the reaction on-and-off will represent a major tool for reaction control.

3 PHOTOCHEMICAL NANOPARTICLE PRECURSORS

What molecular properties are desirable in a precursor for efficient photochemical synthesis of nanoparticles? Clearly, the excited state of this precursor

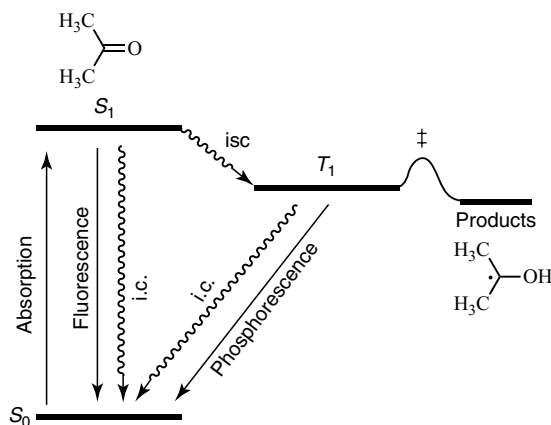


Figure 2 Jablonski diagram illustrating the photophysics of acetone and its reaction to give products of hydrogen abstraction leading to the ketyl radical. Abstraction is an activated process. The energy values for S_1 and T_1 are 84 and 78 kcal mol⁻¹, respectively. At room temperature $\Phi_{\text{fluorescence}} \leq 0.001$ and $\Phi_{\text{ISC}} \sim 1$.

must be able to generate reducing free radicals. Is this enough?

Let us consider the example of acetone. When excited by ultraviolet light, acetone produces its excited singlet state, which rapidly undergoes inter-system crossing (ISC) to form the triplet state, as shown in the Jablonski diagram of Figure 2.⁸

Acetone displays weak fluorescence and phosphorescence; however, these properties are only exhibited in the absence of oxygen or hydrogen donors.⁸ Both the excited singlet and triplet states are capable of hydrogen abstraction from suitable donors,¹⁶ although in general only abstraction of the triplet state is observed for the rather trivial reason that the short singlet lifetime of the singlet state makes abstraction (or more generally chemical reaction) unlikely. Thus, the acetone triplet state can abstract

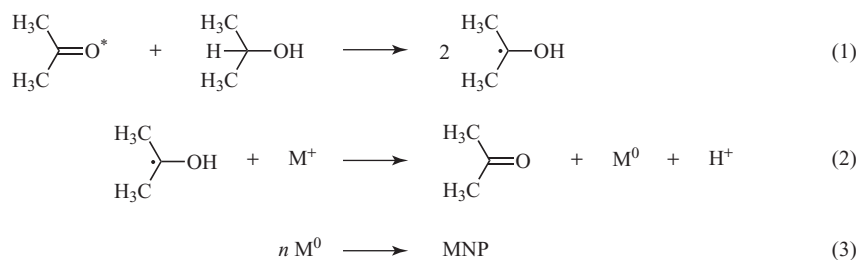
hydrogen from 2-propanol⁸ to generate two reducing radicals,³ as shown in Scheme 1.

Despite its favorable triplet reactivity, acetone's performance is limited by several factors. In particular, acetone absorbs light at a rather short wavelength (cutoff is ≤ 330 nm) and with a very modest extinction coefficient.⁸ Consequently, transition metal salts tend to compete for light absorption, thus reducing the efficiency of acetone photolysis. Competition for light absorption also implies that transition metal complexes can be subject to their own photodecomposition.

Furthermore, the lifetime of acetone triplets influences the yield of nanostructures. Acetone triplet lifetime is in the microsecond range^{17,18} and rate constants for hydrogen abstraction are two to four orders of magnitude slower than diffusion-controlled kinetics. The reason why this becomes a serious problem is because many transition metal ions (including the noble metals) are excellent quenchers of excited states (singlet and triplet), with rate constants that approach the diffusion-controlled limit.^{19,20} As a result, many (and probably most) acetone triplets would be quenched before they participate in reactions yielding free radicals, thus limiting the steady state concentration of reductive radicals in solution.

The result of poor absorption properties and quenching by transition metals underlines an inefficient process requiring very long irradiation times (hours). Quite simply when an excited state is quenched by a metal ion, it no longer can yield the desirable reducing free radical. A few representative triplet quenching rate constants by metal ions are given in Table 1.

There are, however, two highly desirable properties of acetone that should not be overlooked. First, all the organic products and reagents in Scheme 1



Scheme 1 Photoreduction of acetone ("*" indicates T_1 state) to yield a ketyl radical. Reaction (2) illustrates electron transfer to a monovalent metal ion which later forms metal nanoparticles (MNP).

Table 1 Rate constants for the quenching of excited triplet states by metal ions in solution at room temperature.^{19–21}

Triplet state	Medium	Ion	k_q (M ⁻¹ s ⁻¹)
Benzophenone	SDS micelles	Ag(I)	4.6×10^9
Azaxanthone	Acetonitrile	Au(I)	2.8×10^9
Azaxanthone	(3 : 1) Water : acetonitrile	Au(III)	1.03×10^{10}
Xanthone	Acetonitrile	Cu(acac) ₂ ^a	8.5×10^9
Benzophenone	Acetonitrile	Cu(acac) ₂ ^a	5.3×10^9

^aacac, acetylacetonate.

are volatile and thus easy to remove once the nanoparticle synthesis is complete. Second, notice that reaction (2) regenerates the reagent, that is, acetone. In this sense, the mechanism of Scheme 1 is a photocatalytic process.

While the “recipe” outlined in the following paradigm refers to ketyl radicals, the same concepts are applicable to other types of reducing radicals, including α -aminoalkyl radicals. Both these species can be viewed as caged electrons, ready to deliver when a suitable acceptor is available. We note that beyond the electron acceptor, a proton acceptor is also required; in water, this is not a problem, but in organic solvents, the scarcity of proton acceptors can hinder kinetics and efficiency of reaction.²²

4 A PARADIGM FOR THE SELECTION OF PHOTOCHEMICAL NANOPARTICLE PRECURSORS

The selection of a precursor for the photochemical synthesis of nanoparticles is similar to the selection of a photosensitizer for many other applications,⁸ although a few parameters reflecting the properties of transition metals and the resulting nanoparticles affect the details of the selection, that is,

1. Precursor absorbance at relatively long wavelength, such as the UVA region, for example, ~ 360 nm, where any absorption of the metal complex would interfere less.
2. Precursor chromophore with a high extinction coefficient, such that millimolar solutions can absorb a large fraction of the light ($\epsilon_{\text{UVA}} > 1000 \text{ M}^{-1} \text{ cm}^{-1}$).
3. High quantum yield of radical formation is an asset. Ideally, $\phi_{\text{decomposition}} > 0.1$.
4. Radical production via fast unimolecular cleavage, such as some examples of the Norrish type

I reaction.⁷ Fast generation of reducing radicals (that also requires point 3) enables a high steady state concentration and a short nucleation period.

5. If radical production must involve a bimolecular reaction, select a highly reactive precursor according to points 1–3, and couple with an exceptional hydrogen donor ($k_H \sim 10^7 \text{ M}^{-1} \text{ s}^{-1}$ or greater), or use segregation techniques (described later). Bimolecular reactions should be avoided,²⁰ particularly if unprotected particles are preferred.
6. The radical precursor must be soluble in the reaction media under typical colloidal synthesis conditions at millimolar concentrations.
7. It is best if the precursor and any reaction byproducts are minimized, by way of a simple, clean synthesis or volatile reagents/products that can be removed following nanoparticle synthesis.
8. For biological applications select precursors of low toxicity.

4.1 Bimolecular Routes to Photochemical Nanoparticle Synthesis

To further elaborate on points 4 and 5 above, in order to minimize transition metal quenching of excited states by transition metals, one must separate the radical formation process from quenching events. Such prevention can be achieved with spatial-temporal techniques. Time separation can be achieved by selecting a precursor with a short excited state lifetime, so that the metal ions (typically millimolar) cannot quench a significant fraction of the excited states.^{19,23,24} The efficiency of excited state survival (S_{surv}) can be estimated according to the following equation:

$$S_{\text{surv}} = \frac{\tau^{-1}}{\tau^{-1} + k_q[Q]} \quad (4)$$

where S_{surv} is the fraction of triplets surviving quenching, τ the triplet lifetime in the absence of quenchers, and $[Q]$ the quencher concentration. In our systems $[Q] = [M^{n+}]$.

If a long excited state lifetime of the precursor is unavoidable (i.e., >100 ns) then spatial separation is necessary; this is common for bimolecular systems. A typical strategy is to physically segregate the radical generation environment from the reducing environment that can be easily achieved with micelles, where transition metal ions and their salts can be expected to preferentially locate in the aqueous phase.^{19,20,25} In contrast, it is easy to design a system where organic precursors (e.g., benzophenone or 1-azaxanthone) have a preference for the organic microphase, such as the micelle, effectively protecting radical precursors from undesirable transition metal quenching. Interestingly, in the case of ketyl radicals, the presence of an OH group in the radical makes it sufficiently hydrophilic for it to exit the micelle and undergo the desirable electron transfer reaction to reduce the metal ions.¹⁷ This bimolecular approach and necessary segregation of events have been executed in a number of micellar and polymer systems.

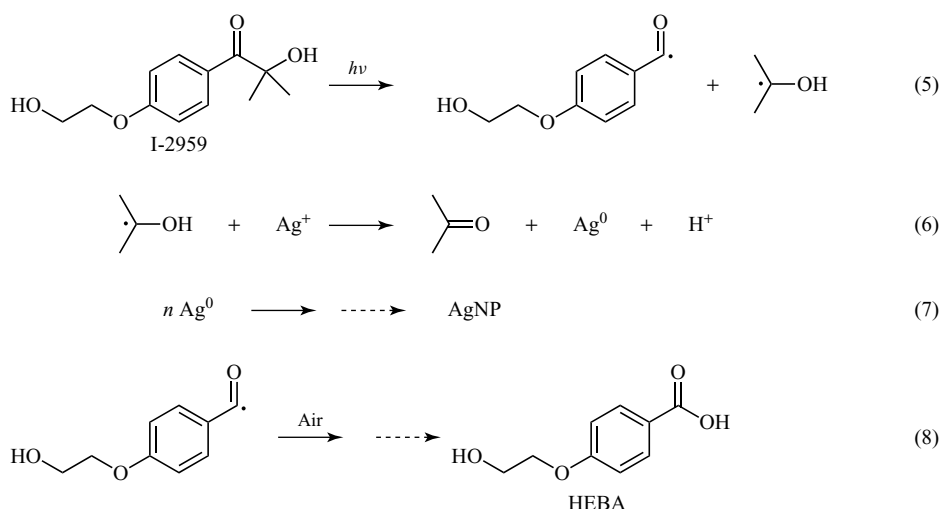
Among hydrogen donors, 1,4-cyclohexadiene has been a favorite, given its excellent H-donor properties and high volatility.^{19,20}

4.2 Unimolecular Routes to Photochemical Nanoparticle Synthesis

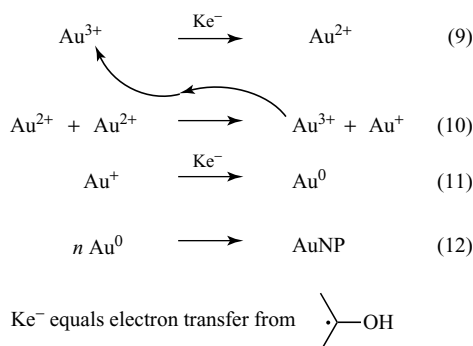
It is time to describe the radical precursor that has been a favorite in our Ottawa laboratories,^{23,26–28} Irgacure-2959 (I-2959) a molecule originally supplied to us as a gift by CIBA Specialty Chemicals. Scheme 2 illustrates the reaction mechanism in the case of Ag^+ .²⁹

What makes I-2959 such a desirable molecule? It complies with all the requirements in our paradigm, except 7, since one of the products (see reaction 8) is not very volatile. Conveniently, however, the benzoyl radical is oxidized to form the acid, 4-hydroxyethoxybenzoic acid (HEBA), under ambient conditions and contributes to provide particle stability and longevity through interactions with the particle surface. Furthermore, the amphiphilic properties of I-2959 have allowed its use in a wide range of solvents at the millimolar concentrations required for this work. Thus, it is possible to employ solvents such as water, tetrahydrofuran (THF), toluene,²⁸ and various micellar solutions.¹⁹

The photochemistry of I-2959 has been studied by Turro and coworkers,⁷ who established that Norrish type I cleavage occurs with a triplet lifetime of 11 ns and a quantum yield of 0.29 in acetonitrile. These properties are not only favorable for nanoparticle synthesis but are in fact also remarkable, given that



Scheme 2 Mechanism for photochemical nanoparticle synthesis (illustrated with silver) initiated by photodecomposition of I-2959. Reaction (5) is an example of Norrish type I cleavage. HEBA is a byproduct of the reaction formed in reaction (8), which probably includes radical trapping by oxygen,³⁰ formation of the peracid and eventual reduction to give HEBA.



Scheme 3 Multiple ketyl reductions and ion disproportionations lead to atomic gold, from which AuNPs are formed.

oxygen substitution at the 4 position must give the triplet state of I-2959 significant π, π^* character, which normally confers the excited state reduced reactivity in Norrish type I and II reactions.³¹

Our first application of I-2959 was in the production of gold nanoparticles (AuNPs), a study that stimulated much work within our Ottawa laboratories.²³ Scheme 3 simplifies the rather complex chemistry involved in the reduction of AuCl_4^- , the most common precursor for gold nanostructures. For convenience, we write the initial gold species as Au^{3+} , although we note that there are systems where the negative charge in AuCl_4^- can play an important role.²⁷

The simplicity of Scheme 2, where Ag^+ requires a single electron for reduction to its metallic form, contrasts with the case of Au^{3+} where three electrons are required. Reaction (9) forms Au(II), which disproportionates rapidly,³² as shown in reaction (10).¹⁹ Au(I) is then reduced by another ketyl radical (reaction 11) to generate atomic gold. Above a threshold concentration of gold atoms, nanoparticle growth is established. Table 2 shows representative rate constants for the reaction of

some ketyl radicals with metal ions. Table 2 also includes values for O_2 , given that this is a common competitive process.

In addition to I-2959, the precursor I-907 has also proven useful, known for its generation of α -amino alkyl radicals, and a valuable back-up when ketyl radicals do not reduce M^+ with appropriate kinetics, Scheme 4.

It is of course the redox properties of the radicals that make them so useful for nanoparticle synthesis. For the 2-hydroxypropyl ketyl radical in acetonitrile $E^0(\text{CH}_3)_2\text{CO}, \text{H}^+ / (\text{CH}_3)_2\text{C}^+\text{OH} = -0.37 \text{ V}$ versus normal hydrogen electrode (NHE), while for the $(\text{CH}_3)_2\text{NC}^+(\text{CH}_3)_2$ (a model for the isopropylmorpholino radical) in acetonitrile, $E^0 \sim -1.47 \text{ V}$ versus NHE.^{6,35,36}

There are several reasons why I-907 has not replaced I-2959 unless this favored precursor becomes ineffective. In particular, we frequently try to prepare nanoparticles with minimum interference from N, P, and S ligands,³⁷ clearly I-907 fails to achieve this. In addition, we have been concerned that the presence of free amines (*N*-isopropylmorpholine $\text{p}K_a = 9.3$) in the radicals precursor (i.e., I-907) could lead to dark generation of nanoparticles under basic conditions, since amines themselves are good reducing agents. This was not a significant problem under mildly acidic reaction conditions, although with hindsight it may reflect that I-907 was normally tested for systems that proved more reluctant to I-2959 photoreduction.

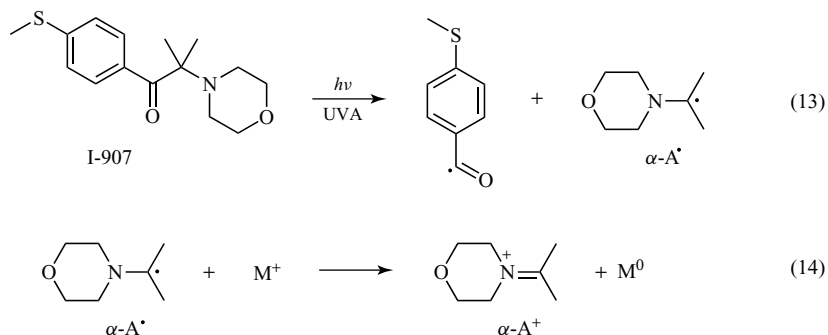
4.3 Initiator-Free Photochemical Nanoparticle Synthesis

The term *initiator-free* is used to describe systems where a specific photoinitiator is not added to the reaction mixture, but rather, that take advantage of

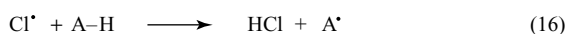
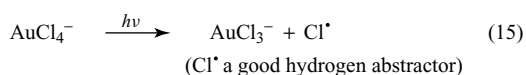
Table 2 Rate constants for the reaction of ketyl radicals with metal ions in solution at room temperature.^{19,33,34}

Radical	Scavenger	Conditions	Rate constant ($\text{M}^{-1} \text{s}^{-1}$)
Ketyl from acetone	Oxygen	Water	4.5×10^9
Ketyl from benzophenone	Au(I)	Acetonitrile	2.5×10^8
Ketyl from benzophenone	Au(III)	Acetonitrile	9.9×10^8
Ketyl from acetone	Cu(II)	Water	5×10^7
Ketyl from acetone	Cu(I) ^a	Water	5×10^9

^aThe reaction involves complex addition chemistry.



Scheme 4 Photodecomposition of Irgacure-907 leads to the formation of morpholine-derived α -aminoalkyl radicals, which can reduce many metallic ions to their atomic form.



Scheme 5 Photolysis of AuCl_4^- yields chlorine atoms that readily abstract hydrogen from a wide range of hydrogen donors.

photochemical characteristics already present in the metal precursor structure. Such opportunistic use of the metal precursor limits the amount of chemical debris retained by the nanoparticles. Here, the key strategy is that any other molecules that need to be added, such as hydrogen donors (and the resulting products) must be volatile, so that they can be readily removed once the synthesis is complete.

For the purpose of illustrating this strategy, we use the case of aqueous AuCl_4^- , a system that was recently studied in our laboratories.³⁸ Here, the key reaction is the photolysis of AuCl_4^- that yields chlorine atoms, in themselves powerful hydrogen abstractors³⁹ and thus capable of generating secondary free radicals, as illustrated in Scheme 5.

Reaction (16) in Scheme 5 can involve a wide range of H-donors, but it is important to select those where the resulting radical, $\text{A}^\bullet$, has appreciable reducing properties. A number of molecules examined in our laboratories³⁸ are shown in Scheme 6.

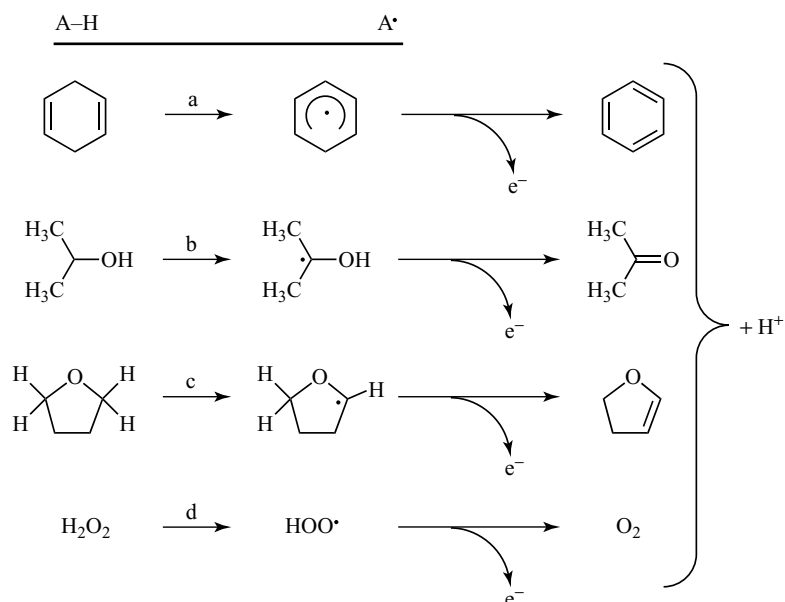
The radical in reaction (b) of Scheme 6 is of course the same as in equation (6) in Scheme 2, but in reaction (b), the 2-hydroxypropyl radical was produced from 2-propanol, and thus avoiding the generation of nonvolatile products. There is, however, a need for additional stabilizer if small, spherical nanoparticles are desired. Importantly, all

the donors in Scheme 6 have negligible absorption at ~ 350 nm, the preferred photolysis wavelength used for nanoparticle synthesis. Their spectral characteristics ensure that the reduction reaction is not dependent on excitation of the ligand-to-metal charge transfer (LMCT) of the metal complex.

Perhaps the most interesting molecule in Scheme 6 is hydrogen peroxide, used as a reducing agent in these applications. Here, the products are oxygen and water and is mediated by the $\text{HOO}^\bullet$ radical that donates an electron to Au(III) . The reaction then proceeds with the standard reduction steps until Au(0) is formed. Interestingly, the $\text{Au(I)} \rightarrow \text{Au(0)}$ step is catalyzed by AuNP , and thus as soon as the formation of nanoparticles commences, the reaction accelerates and quickly reaches completion.

The methodologies and references as they relate to the strategies of Scheme 6 are not meant to be exhaustive, but rather to emphasize work in the Ottawa laboratories. A noteworthy synthesis on AgNP was reported by Giuffrida *et al.*,⁴⁰ who showed that AgNP can be produced thermally from silver acetylacetonate; AgNP can also be obtained in an accelerated process by photolysis of the same precursor.

The strategies presented in this section offer the possibility to produce noble metal nanostructures employing clean technologies, but they do not guarantee that the desired shape or size will be obtained nor do they ensure the desirable long-term stability needed for many applications. Users of these methodologies need to adapt them incorporating the desired surface covering agents so as to prepare nanostructures that meet their requirements.



Scheme 6 Various volatile H-donors (A–H) can be used to generate free radicals that can donate an electron to appropriate acceptors, in particular, metal ions. In all cases, a proton is released that requires a suitable acceptor. In aqueous systems, water plays this role.

5 FACTORS THAT CONTROL THE OUTCOME OF NANOPARTICLE PHOTOCHEMICAL SYNTHESIS

Trying to list all factors that could influence the outcome of nanoparticle photochemical synthesis is an impossible task. Thus, this section deals with main factors that are either well known or that reflect our experience at the University of Ottawa. Each subsection deals with one of these parameters.

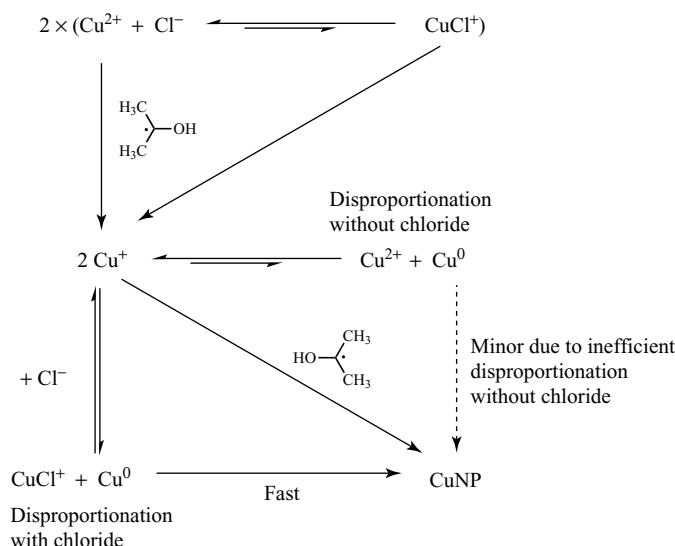
5.1 Light Intensity

As a general rule, faster reducing radical generation leads to shorter nucleation periods and thus smaller nanoparticles, as outlined in Scheme 1. In the case of photochemical processes, this also implies that smaller particles will be obtained at the higher light intensities.²³ Unfortunately, the relation between reciprocal particle size (diameter^{-1}) and dose (or irradiance) is not linear, and thus desirable very small particles may fall in a range of light intensities that is not achievable with conventional light sources.

Exposure to pulsed light sources, such as lasers, is not described in this contribution as a methodology for nanoparticle synthesis, although it is sometimes employed,^{41–43} and nanoparticle laser ablation can also be used as a method to modify nanoparticles.^{44–48}

5.2 Arrested Growth

If a given photochemical synthesis protocol produces nanoparticles that are too large for a planned application, it is possible to arrest the particle growth by adding small concentrations of stabilizing agents prior or during the synthesis. Given our preference for unprotected materials, we have concentrated on charge-stabilizing ligands and used compounds that do not lead to surface covalent bonds; for example, we avoid sulfur compounds. In the case of AgNP described herein, citrate salts have proven convenient as a way of limiting particle growth to 3–4 nm.^{29,49} Note that while citrate is frequently used as part of a reducing formulation, in this case, it is simply a capping ligand, since fast and efficient reduction is achieved by photochemical means, such as the use of I-2959 illustrated in Scheme 2.



Scheme 7 Mechanism for the synthesis of CuNP in aqueous solutions containing chloride. [For mechanistic details, see the original publication from which the mechanism shown was adapted.]²⁴

5.3 Counterion Influence

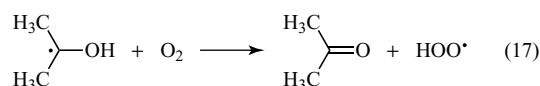
Every component present at the time of particle synthesis can influence nanoparticle size and morphology through ionic effects. For example, ionic strength is an important factor. However, there are systems where ionic components can be critical. This is the case of CuNP, where halides, in particular chloride, can determine the rate of particle formation as well as their polydispersity.²⁴ The complex mechanism involved is presented in Scheme 7. Different counterions (especially halides) and surfactants can “tune” the morphology and size of the nanostructures formed. In aqueous solutions, chloride ions catalyze the disproportionation that mediates the $\text{Cu(I)} \rightarrow \text{Cu(0)} \rightarrow \text{CuNP}$ conversion.

The rationale for the proposal of the mechanism of Scheme 7 can be found in the original publication.²⁴ As a consequence of these reactions, CuCl_2 yields highly polydispersed particles rapidly, while when using CuSO_4 , the reactions are slower, but the CuNPs are more monodisperse.

5.4 Atmosphere

Given that many of our synthesis procedures involve carbon-centered radicals, one could anticipate that

any oxygen in the reaction atmosphere could have an adverse effect on nanoparticle synthesis. This is in fact not always the case. AuNP prepared from I-2959, for example, are most stable when prepared under air.^{19,23} While initially puzzled by this result, we have identified HEBA as a photoproduct (Scheme 2), that contributes to particle stabilization. Most likely, formation of HEBA is mediated by the corresponding peracid. Note also that while O_2 will trap some ketyl radicals (reaction 17), the $\text{HOO}^\bullet$ radicals produced are also capable of gold reductions, as indicated in Scheme 6. Note that the generation of acid in reaction (6) and related processes, systematically lead to particle formation in acid media (thus making $\text{HOO}^\bullet$, rather than $\text{O}_2^{\bullet-}$ the dominant species). Benzoyl³⁰ and acetone ketyl radicals³³ react with oxygen with reported rate constants of $1.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $4.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, respectively.



Excessive oxygen (as in pure O_2 atmosphere) can be employed as a tool to delay AuNP formation and thus further control particle size and shape.

The formation of unprotected AgNP by reduction with ketyl radicals results in unstable colloids,

whether or not in the presence of oxygen. However, when kept in a reducing environment, by stabilizing with citrate ions, small silver nanoparticles (3–4 nm) can be generated with or without the presence of oxygen without a detectable effect of oxygen on final particle size or reaction rate. These solutions of citrate-stabilized AgNP are stable indefinitely under air when protected from light to avoid shape transformations (*vide infra*).⁴⁹ Solutions using I-2959 to form AgNP are, however, most commonly oxygen free to ensure maximum efficiency of the reducing precursor and thus a rapid nucleation of AgNP.

In the case of CuNP, these particles are very sensitive to air oxidation and oxidize readily to form Cu^{2+} in aqueous solution once exposed to air. The oxidation reaction typically takes 1–2 h. Thus, it is not possible to prepare and preserve the CuNP under aerated conditions.

5.5 Stoichiometry

The reaction stoichiometry is primarily governed by the number of electrons required to reduce the metal ions, for example, in the case of Au(III), three electrons are needed. Thus, typically when we employ I-2959, we prepare AuNP using 0.3¹⁹ or 0.33 mM²³ AuCl_4^- that would require 0.9–1.0 mM of I-2959; we normally use 1 mM, that is, stoichiometric or allowing for a slight excess of radical generator. For Cu(II) and Ag(I), the anticipated 2:1 and 1:1 stoichiometries work well.

In the case of AuNP, deficient stoichiometry (less reductant than needed for a stoichiometric ratio) tends to yield larger particles with average sizes around 70 nm. These particles are less stable compared to the ones prepared in a stoichiometry ratio as well as more polydisperse.

5.6 *In Situ* Stabilization

While the emphasis of our work has been on the synthesis of relatively unprotected nanoparticles, the methodologies presented here lend themselves to adaptation for *in situ* stabilization. The possibilities in this area are numerous and impossible to cover in this contribution. An important consideration

must be that ligands and stabilizers present during synthesis should not be effective radical traps that would likely interfere with the nanoparticle-forming free radical reactions discussed in this article.

We note that in the case of micellar solutions, some of the solubility rules mentioned earlier are relaxed, and it is possible to employ a wider range of initiators, such as conventional benzoin with poor aqueous solubility.¹⁹

5.7 Storage

AuNP have shown excellent stability (+5 years) when stored in plastic containers; they are also stable to ambient atmosphere. AuNP prepared in the charge-stabilized manner utilizing I-2959 have found, however, limited stability in glass containers (~1 day) and this is attributed to the favorable interaction with the negatively charged silica surface. In particular, instability is accompanied by a red shift of the SPB, suggesting particle agglomeration.

Very small (~3 nm) AgNP stores better in glass than plastic unless there is light, where some of the AgNP tend to deposit onto the glass. AgNP are indefinitely stable under air.

Owing to oxidation, as previously mentioned, CuNP storage is limited to an oxygen-free atmosphere such as in a glovebox or to the reservoir they were synthesized as long as oxygen does not diffuse into the system.

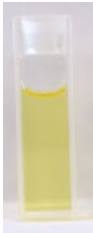
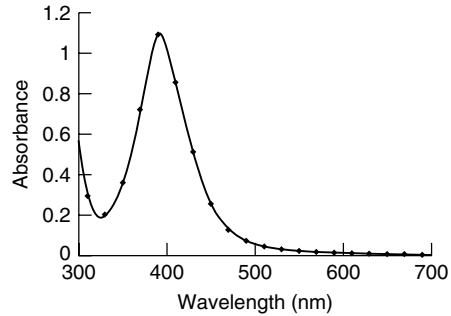
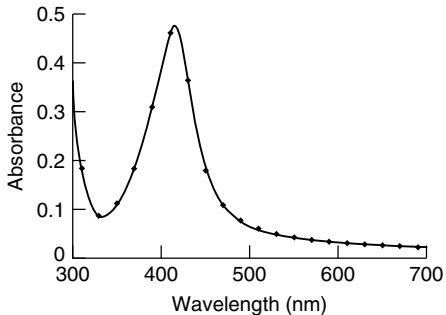
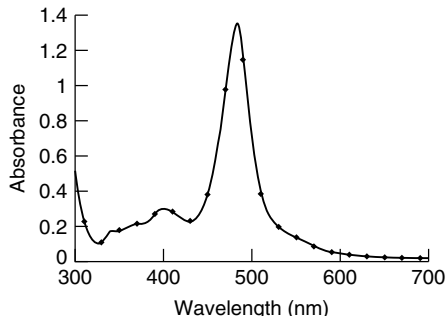
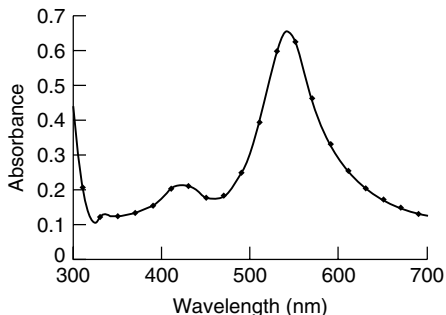
6 POSTSYNTHESIS PHOTOCHEMICAL MODIFICATION OF NANOSTRUCTURES

The range of modifications is so diverse that only a few cases can be included in this section. The examples that follow have been selected among those that have interested our Ottawa group.

6.1 Seeded Growth

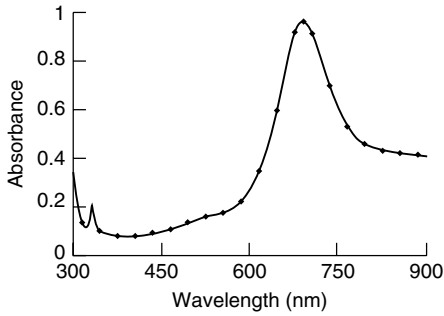
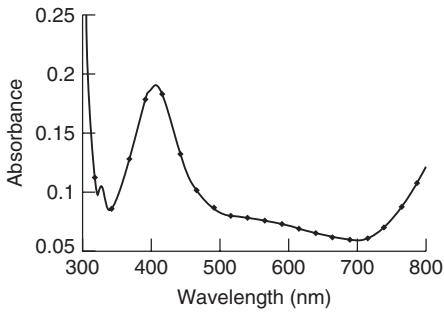
The unprotected nature of photochemically generated aqueous nanoparticles is an asset for additional growth through seed-mediated processes. Addition of photochemically generated AuNP to a dilute

Table 3 Characteristics of silver nanostructures obtained by LED irradiation of ~3 nm AgNP seeds.⁴⁹

λ_{LED}	Comments	Spectral data	Solution image	Spectrum ^a
N/A	3-nm spherical seeds	397 nm		
405 nm	Spheres, 26-h exposure	415 nm		
455 nm	Decahedra, 3-h exposure	480 nm		
505 nm	Predominantly hexagonal plates, 20-h exposure	540 nm		

(continued overleaf)

Table 3 (continued)

λ_{LED}	Comments	Spectral data	Solution image	Spectrum ^a
590/627 nm	Mostly triangular plates, long exposure >100 h	690 nm		
720 nm	Rods and thin plates, 1-week exposure	Near IR		

^a All plots correspond to exactly the same total silver concentration.

growth solution of the metal salt and mild reducing agent results in reduction of the metal salt via particle-mediated catalysis.¹⁰ The choice of mild reducing conditions is essential to minimize the generation of new AuNP, termed *secondary nucleation*. Ascorbic acid and hydroxylamine hydrochloride have been common choices in our laboratory for the seeding of AgNP and AuNP, respectively. Similar approaches were devised by Brown *et al.*⁵⁰ with citrate-mediated growth of AuNP seeds. Given that the particle surface itself is a site of reduction, the growth behavior involves the deposition of new layers of atoms; these form faster when more reducing agent is present, as the concentration of HAuCl₄ is held constant. Additionally, the lesser the concentration of seed added, the larger particles result from seeded growth.

In the case of AgNP, we have used ascorbic acid for growth of particles designed for Raman enhancement applications.²⁹

6.2 Light-Induced Morphology and Size Changes

Our research has shown that small AgNP seeds (about 3 nm in diameter) can be used to generate a range of morphologies (and a rainbow of particle colors) when irradiated with monochromatic light, which in our work was generated by a variety of inexpensive light-emitting diode (LEDs).⁴⁹ This simple methodology can be used to generate different morphologies while maintaining the chemical nature of the surface coverage. Table 3 summarizes the results obtained in these systems.⁴⁹

We have wondered whether the LED-induced changes shown in Table 2 could be reversed. We have observed that nanoparticle laser ablation can be used to return spherical AgNP, although the monodispersity of the original particles (or seeds) is not restored through the ablative process.¹⁰

Similar strategies may work with other metal nanoparticles, although to date these strategies have not been explored in our group.

6.3 Surface Chemical Modification

All the strategies for surface modification that are frequently employed with thermally produced nanoparticles can also be applied to photochemically produced ones; the unprotected nature of the particles described in this article frequently makes surface modification a facile process, and for example reaction of AgNP with thiols can occur in a few minutes. Similarly, passivation of the AuNP surface with a variety of ligands such as thiols, amines, biomolecules, or a silica shell has been achieved for subsequent application.

7 BEYOND AQUEOUS GOLD, SILVER, AND COPPER MONOMETALLIC NANOPARTICLES

The emphasis on noble metal nanoparticles in aqueous media described here provides a template to illustrate how simple free radical photoinitiators can be employed for the facile synthesis of metal nanoparticles, reflecting both the rich information available on these systems, as well as the work within our own laboratories. Similar strategies have been employed to prepare magnetic cobalt nanoparticles (CoNP) as well as platinum (PtNP) and ruthenium (RuNP) particles¹⁰ in nonaqueous systems; these last two materials are of interest for their catalytic properties. In addition, similar methodologies can be used for the synthesis of highly fluorescent silver nanoparticles AgFNP in nonpolar media, such as in THF and toluene; the fluorescence has been attributed to small silver clusters (including Ag₂) on the surface of small AgNP.²⁸ A separate study demonstrated that the dimerization of silver atoms ($2\text{Ag}^0 \rightarrow \text{Ag}_2$) is a diffusion-controlled reaction in organic media.²²

In a system currently under investigation, nanoparticles (e.g., AgNP) can be produced in a protein composite.

While all our examples above deal with monometallic particles, photochemical techniques

can also be employed to prepare bimetallic particles; we have demonstrated these processes for the Au–Ag system.^{26,27} These particles assemble according to the redox characteristics of the pair; thus, gold tends to reduce first to form the particle core, followed by silver reduction with plating to form a silver shell. True alloys can also be prepared by taking advantage of coulombic interactions involving Ag⁺ and AuCl₄[−].²⁷

8 CONCLUSION

Radical-mediated photochemical synthesis of metal nanoparticles offers remarkable flexibility in the synthesis of these materials. The paradigm presented here should be applicable to nanostructures made from many metals, beyond the noble metals used in our examples. Furthermore, size, morphology, and surface coverage are frequently “tunable.” The challenge is to develop new applications for these materials, such as biomedical uses, markers, sensors, electronics, photonics, and catalysis. The next decade will no doubt see further developments in these areas and in many more that we are yet to imagine.

ACKNOWLEDGMENTS

Thanks are due to the Natural Sciences and Engineering Research Council of Canada for ongoing support. Many coworkers from Ottawa have contributed to our learning about metal nanostructures, and their names appear in the references. Authors of this contribution have made detailed contributions to the synthesis of AuNP, AgNP, and CuNP.

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The History of Free Radical Chemistry

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1 INTRODUCTION

From the beginning of the nineteenth century, there were premonitions of the existence of free radicals,^{1–10} but only in 1900 was convincing evidence for these species found with Gomberg's discovery of the triphenylmethyl radical,^{11,12} a highly stabilized example. This was followed three decades later by Paneth's identification of simple alkyl radicals,^{13–15} which are a larger and more significant class, and are very reactive and short-lived. At the time, these discoveries were not based upon direct observation, as the yellow color of the tri-phenylmethyl radical was overlooked,¹⁶ and alkyl radicals are invisible. The originality of these discoveries is reflected by the fact that, while both were immediately widely noted, the initial triphenylmethyl radical discovery in particular was also met with disbelief. Neither was honored with the ultimate accolade of great discoveries, the Nobel Prize, although numerous later advances in free-radical chemistry, which were built on these discoveries, have achieved this distinction. The uniqueness of the original discoveries meant that their true significance could not be fully appreciated at the time.^{16–21}

This historical summary attempts to note significant new discoveries in free-radical chemistry in a generally chronological order, with inclusion of recent developments in some examples to illustrate advancements in long-established areas of study. The emphasis is on carbon free radicals, but basic developments in radical chemistry that profoundly affected these studies are included. The first third of

the twentieth century was marked by rapid exploration of the types of conjugated radicals that could be identified, and different ways for their generation. Kinetic studies of reactive radicals, particularly the halogens, were also explored. The experiments of Paneth then focused attention on the study of non-conjugated aliphatic radicals, and, with the broad outlines of the field established thereafter, studies have concentrated on new types of free radicals and new applications, and there has been a continuous development of new and useful chemistry that shows no sign of slowing; but the newer work is mostly beyond the scope of this survey. Many individuals participated in the advance of free-radical chemistry, and some of the most prominent original contributors are recognized where possible, but the constraints of space preclude mentioning many others who also made important discoveries. This article provides an overview of the development of many fundamentals of free radicals, while the definitive articles in this encyclopedia on the various topics provided by leaders in their study describe the current state of knowledge.

2 DISCOVERY OF THE TRIPHENYLMETHYL RADICAL

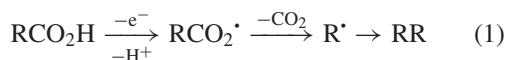
2.1 Free Radicals Before Gomberg

The early history of free radicals in organic chemistry prior to 1900 has been frequently reviewed,^{1–3} and is only briefly noted here, and developments

in the twentieth century have already been extensively summarized.^{16–21} While the term “radical” dates to the late eighteenth century, the existence of alkyl radicals gained new support in 1849, based both on the work of Kolbe,⁴ who reported the electrolytic decarboxylation of potassium acetate apparently forming free radicals such as “methyl” (CH₃), and of Frankland,⁵ who reported the formation of “ethyl” (C₂H₅) from the reaction of ethyl iodide with zinc. However, the development of valence theory shortly thereafter, particularly the concept of the tetravalency of carbon, led to the recognition that these “radicals” were dimers, and caused the general abandonment of free radicals as organic intermediates.

Downes and Blunt in 1879 reported that hydrogen peroxide in solution was destroyed by sunlight to form *two groupings* of the radical HO.⁶ They further speculated the same phenomenon occurred with chlorine, and stated: “We believe that the tendency of sunlight is to dissociate (or ‘weaken the internal bonds’ between). . . and thus to promote their combining energy.” This prescient interpretation was however not applied to hydroxyl radical reactivity with organic compounds, and is not mentioned in other reviews of the history of organic free radicals,^{1–3,16–20} or apparently not even previously cited by a chemist.

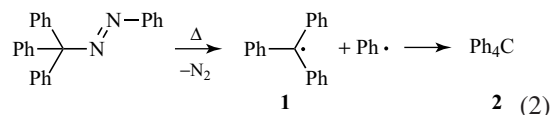
Even with this great missed opportunity, the concept did not disappear, and, in 1891, Crum Brown and Walker reintroduced the idea of electrolysis as involving radicals, (1),⁷ while Nef in 1897⁸ formulated a theory of organic reactivity with a major role for divalent carbon. Thus the possible existence of organic free radicals was waiting to be recognized, but the discovery did not result from a deliberate search, and recognition came from the need to explain new and unexpected experimental facts.



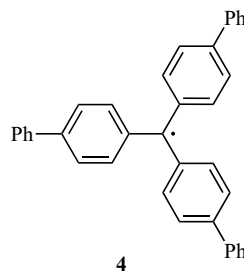
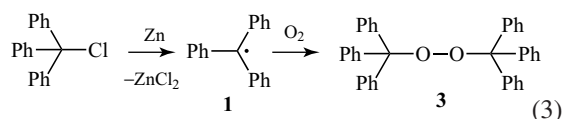
2.2 Discovery of the Triphenylmethyl Radical

The understanding of the structure of organic compounds had evolved during the nineteenth century but the concept of reactive intermediates was still incomplete, and reaction mechanisms were poorly understood. In a prelude to the discovery of free radicals, Gomberg in 1897 used

phenylazotriphenylmethane in the classic preparation of tetraphenylmethane (2), (2), a process now understood to result from coupling of the triphenylmethyl radical **1** and a phenyl radical, but he did not speculate about the source of the product.^{9,10}



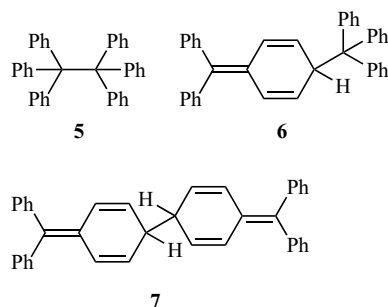
Then, in 1900, Gomberg made the bold announcement of the formation of the stable and persistent free radical triphenylmethyl **1** by reaction of tri-phenylmethyl chloride with silver or zinc metal giving a colored solution, with its radical character shown by the facile reaction with oxygen forming the peroxide **3** (3).^{11,12} This discovery was published in both German and English, and attracted the immediate attention of the world chemical community.^{16–21} There was also immediate skepticism, notably even in 1901: Norris presented a rebuttal entitled *On the Non-Existence of Trivalent Carbon*.^{22,23} This led to much further study with considerable controversy over the next decade, and the structure of **1** was finally settled by Wilhelm Schlenk and coworkers in 1910 when they obtained tris(4-biphenyl)methyl (**4**) as a deeply colored solid that was almost completely dissociated in solution, which confirmed the existence of **1**.²⁴



Removal of the solvent from the preparation of triphenylmethyl gave a colorless solid product with a dimeric structure for which the symmetrical head-to-head structure **5** as well as the unsymmetrical structure **6** (head-to-tail, Jacobson structure)²⁵ and **7** (tail-to-tail, Heintschel structure)^{26,27} were

given serious consideration. The dimer underwent dissociation in solution, and its properties were often hard to interpret, and the wrong structure, namely the head-to-head structure **5**, became accepted for more than half a century, as has been described by McBride.¹⁶ Only in 1968 was this finally corrected to the unsymmetrical structure **6** based on spectroscopic data by Lankamp, Nauta, and MacLean,²⁸ who made the surprising, but in retrospect completely predictable, finding that the triphenylmethyl dimer had the head-to-tail structure.

In retrospect,¹⁶ not only was the original evidence for the misidentified structure of the dimer rather flimsy, but techniques such as nuclear magnetic resonance (NMR), infrared (IR), and ultraviolet (UV) were also widely available that would have permitted correction of this structure well before 1968. As described below, a variety of head-to-head hexaphenylethane structures in which the steric hindrance in the head-to-head structure **5** is circumvented have subsequently been characterized.

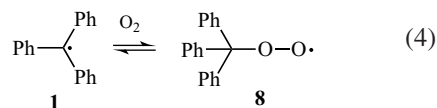


The preparation and identification of the stable triphenylmethyl radical was one of the most significant chemical discoveries of the time but, as already noted, was not honored by the award of the Nobel Prize. As revealed by the investigation by Lennart Ebersson^{18,19} in the Nobel archives, Gomberg was repeatedly nominated for the award, but due to a series of unfortunate circumstances the nominations were not accepted. Despite Gomberg's confident assertion in his first paper that he had proof of the existence of the radical, there was later some equivocation, and some contrary opinions, which were enough for the Nobel Committee not to approve the award. Initially, the existence of the radical in equilibrium with the dimer seemed questionable, but with the later preparation of the tris(4-biphenyl)methyl radical **4** as a stable solid the uncertainty vanished.²⁴ However, subsequent

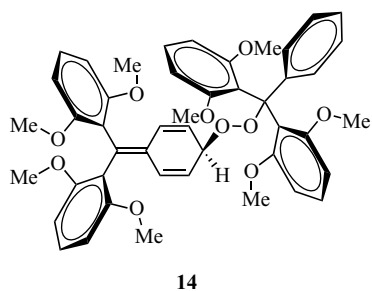
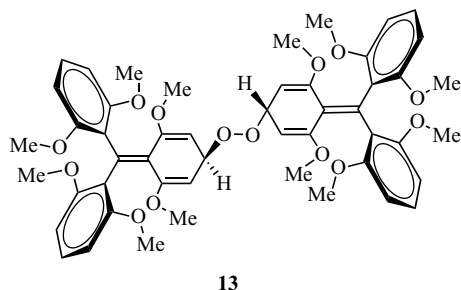
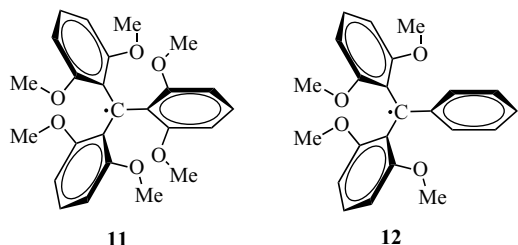
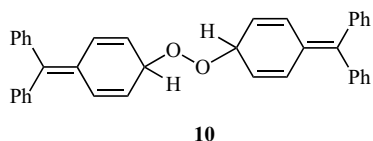
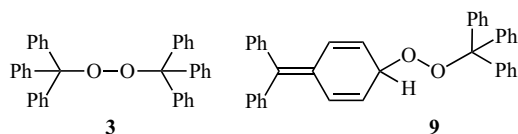
nominations were unsuccessful either because both Gomberg and Schlenk were not nominated in the same year, or because too much time had elapsed since the initial discovery. Even in 1940, Gomberg's name was still put forward, but without success. Gomberg's discovery was a clearly momentous discovery by a single individual, but, although well recognized by posterity, he did not receive the ultimate accolade he deserved.

2.3 Bis(triphenylmethyl) Peroxide

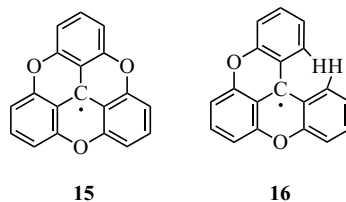
The reaction of the triphenylmethyl radical with oxygen to form the peroxide **3** discovered by Gomberg in 1900 as shown in (3) was a persuasive piece of evidence for the radical structure **1**,^{11,12} and the affinity of radicals for oxygen became known as one of their defining characteristics. As pointed out by McBride,¹⁶ Gomberg did not originally mention the color of the solution containing the radical, but in 1908 Schmidlin²⁹ reported that addition of O₂ to **1** discharged the radical color, and later the formation of an initial peroxy radical **8** was shown to be reversible (4).³⁰



Just as for the triphenylmethyl radical dimer, there are three plausible structures for the peroxide corresponding to the proposals for the radical dimer: namely, head-to-head (**3**), head-to-tail (**9**), and tail-to-tail (**10**). The head-to-head structure **3** was correctly identified, and substituted derivatives of **9** and **10** were later prepared. Thus the tris(2,6-dimethoxyphenyl)methyl radical **11**³¹ was crystallized and found^{32,33} to have a structure with two of the aryl rings twisted out the plane of the central carbon by 61°, while the third was almost coplanar with an 11° twist angle. This radical reacts slowly with oxygen and did not dimerize, but reaction of **11** and of the bis(2,6-dimethoxyphenyl)-phenylmethyl radical (**12**) in solution in the presence of air resulted in crystallization of the substituted Heintschel and Jacobson peroxides **13** and **14**, respectively, with the structures proven by NMR, and X-ray, respectively.^{32,33}

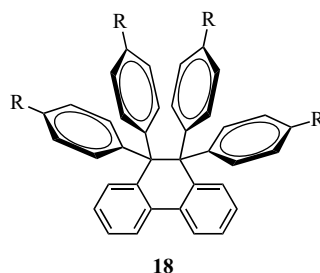
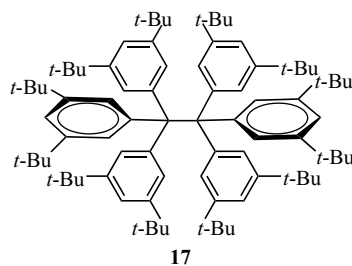


In contrast to **11**, the dimer of sesquixanthrydryl radical **15** was undissociated as a solid and gave weak ESR signals in solution.³¹ The radical **16** with only two oxygen bridges was quite sensitive to oxygen and was extensively dissociated in the solid state, and the 2,6-hydrogens caused twisting out of the plane.^{31,34} The solid dimer of **15** is an authentic hexaarylethane, with a central C–C bond length of 1.63 Å as measured by X-ray.^{34–36}



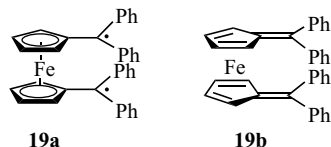
2.4 Hexaarylethanes

Authentic hexaphenylethane molecules with structures determined by X-ray include **17**, which is restricted from forming a head-to-tail dimer by the bulky substituents, with a central C–C bond length of 1.67(3) Å.³⁷ A different type of hexaphenylethane derivative is typified by **18**, which was already prepared in 1933 for R = H³⁸ and has the central bond constrained by its intramolecular character. The central C–C bond for **18** (R = MeO) was measured as 1.670(3) Å,³⁹ and related examples with similar intramolecular constriction have bond lengths that are even longer.^{40,41}



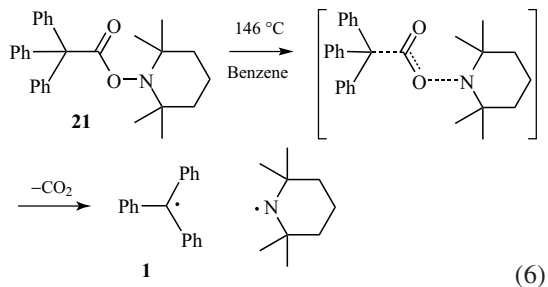
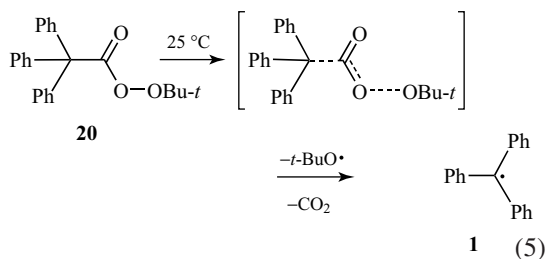
Preparation of a bis(diphenylpentafulvene) iron complex was reported, for which the structure was considered as either the bis(radical) **19a** or the bis(fulvene) **19b**.⁴² The fact that the X-ray-determined and calculated structure showed the exocyclic groups on the same side of the molecule was taken as favoring the diradical structure, with some attraction between the two radical

sites.⁴³ Computational studies agreed with this conclusion, and indicated that the diradical was a singlet.⁴⁴



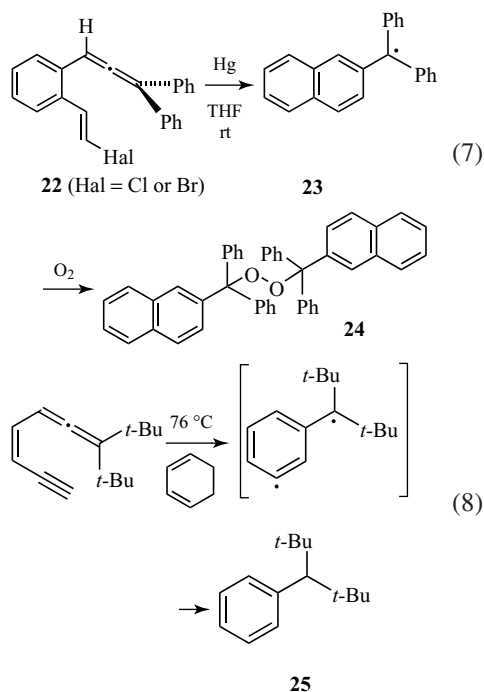
2.5 Other Routes to Triphenylmethyl Radicals

Wieland *et al.* in 1922⁴⁵ showed that $\text{Ph}_3\text{C}^\bullet$ (**1**) was formed in the decomposition of phenyl-azotriphenylmethane, and proposed that intermediate phenyl radicals were formed as well (2). Triphenylmethyl radicals are also generated thermally from the perester **20** even at 25 °C (5),⁴⁶ and at much higher temperature also form from the significantly less reactive triphenylacetoxyl *N*-2,2,6,6-tetramethylpiperidine **21** (6).⁴⁷ Reactivity studies demonstrated that both **20** and **21** decompose thermally with concerted two-bond cleavage forming triphenylmethyl radicals **1** and carbon dioxide. A variety of other dissociations of triarylmethyl (trityl)-substituted compounds have been reported to generate triarylmethyl radicals.⁴⁸



A novel route for the generation of triaryl-methyl radicals was by reaction of 1-(haloalkenyl)

-2-allenylbenzenes **22** in tetrahydrofuran (THF) at room temperature in the presence of mercury, resulting in cyclization to 2-naphthyldiphenylmethyl radical **23**, (7), as detected by electron paramagnetic resonance (EPR).⁴⁹ The radical formed a head-to-tail dimer involving the phenyl group, and was captured by oxygen to give the peroxide **24**.⁴⁹ Related ene-yne cyclizations have been examined, including a route to a di(radical) intermediate leading to **25** (8).^{50,51}



2.6 Properties of Triphenylmethyl Radicals

The theoretical basis for the understanding of free radicals was first provided by G. N. Lewis in 1916.^{52,53} His clear recognition of the electron-pair bond and the possibility of odd electron systems was heavily influenced by the work of pioneers such as Gomberg, Schlenk, and Wieland, who had shown remarkable prescience in formulating free-radical structures without, however, using the principles of electron-pair bonding. The theoretical study of the triphenylmethyl radical was later provided by Erich Hückel⁵⁴ at the 1933 Faraday conference on free radicals, which brought together many of the pioneers in the study of radicals.

With the advent of spectroscopic methods, particularly ESR and electron–nuclear double resonance (ENDOR) measurements,⁵⁵ the study of triphenylmethyl and other triarylmethyl radicals has been greatly facilitated, and the assignment of free-radical structures can usually be made with certainty.

3 ALIPHATIC FREE RADICALS AND DIRADICALS

3.1 The Discovery of Aliphatic Free Radicals

Gomberg's discovery and his subsequent work and that of the many others who joined in provided good evidence for the existence of stabilized arylmethyl radicals, but there was still skepticism regarding simple aliphatic radicals such as methyl and ethyl. The modern history of these species had begun with the suggestions of Crum Brown, (1),⁷ but further evidence for these was not forthcoming, despite the great interest in the study of aryl-substituted radicals.

Proof of the existence of aliphatic radicals was, however, unexpectedly provided, inspired by the method pioneered by Bonhoeffer⁵⁶ for showing the generation of atomic hydrogen. Beginning in 1929, Paneth and his coworkers adapted this technique and, in work that paralleled that of

Gomberg, provided a new conceptual framework for the remainder of the twentieth century and beyond.^{13–15} In their classic experiments, a metal organic compound such as tetramethyllead was passed through a hot zone in a glass tube and found to deposit a metallic mirror. When the gases from this procedure passed over a similar metal mirror in a cold section of the tube, the mirror was removed and tetramethyllead was reformed (Figure 1). This demonstrated the formation of methyl radicals in the hot zone where the mirror was laid down, followed by regeneration of the organometallic compound by reaction of the methyl radicals with the cold mirror (9). However, just as in the case of Gomberg's discovery, this paradigm shift initiated by Paneth was not recognized by the Nobel Prize.



This technique was promptly extended by F. O. Rice and coworkers showing that the pyrolysis of many organic compounds at 800–1000 °C removed metallic mirrors, implicating the formation of free radicals. The cleavage of larger free radicals into smaller radicals and olefins under these conditions was also proposed, (10), as well as chain reactions in which radicals abstract hydrogen from alkanes.^{57,58} Reactions of alkyl halides with metal atoms in the gas phase were also found by M. Polanyi and coworkers to yield alkyl radicals (11).^{59,60}

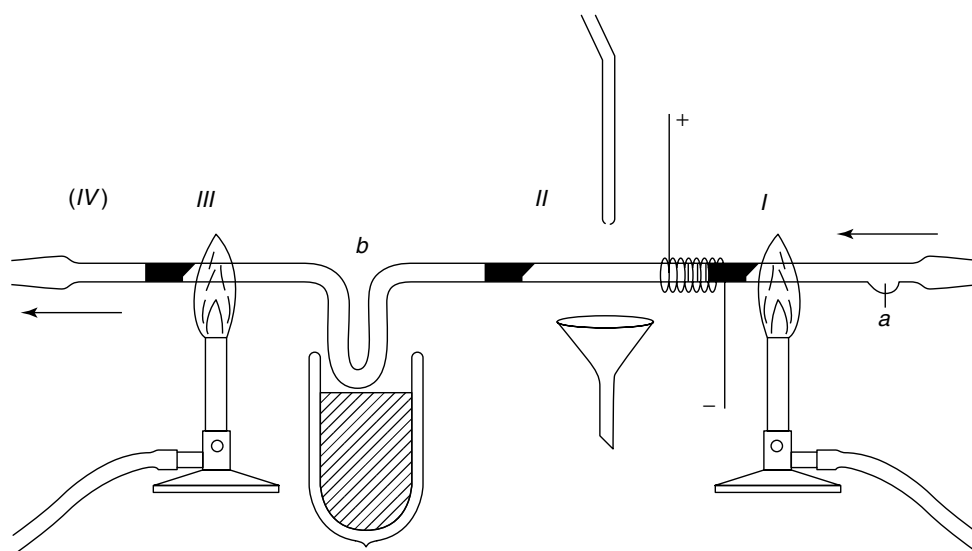
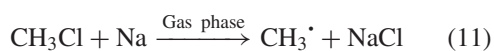
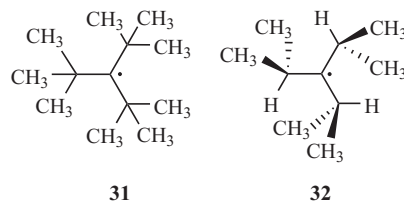
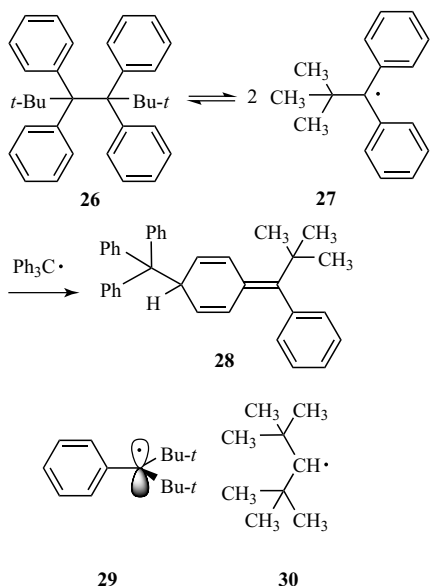


Figure 1 Paneth apparatus. [Reproduced from Ref. 13. © Wiley-VCH Verlag GmbH & Co. KGaA, 1929.]

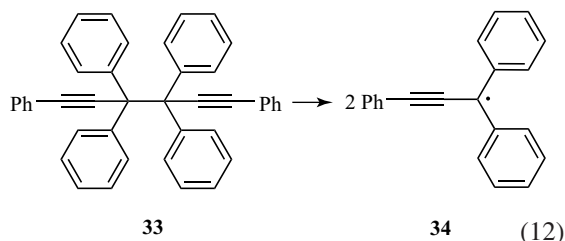


3.2 Steric Effects and Persistent Radicals

In his early work, Gomberg^{11,12} recognized that steric factors make a contribution to the stability of the triphenylmethyl radical, and Conant and Bigelow⁶¹ in 1928 demonstrated the ability of bulky groups to promote radical formation in the reversible dissociation at 50 °C of 1,2-(di-*tert*-butyl)tetraphenylethane (**26**) to the yellow colored radical **27**, which reacts rapidly with O₂. The radical **27** generated in the presence of Ph₃C[•] forms the mixed dimer **28**.⁶¹ As found almost 50 years later, the di-*tert*-butylbenzyl radical **29** is stable for several days in solution at room temperature, and the EPR spectrum indicates that the phenyl group is twisted into coplanarity with the singly occupied p orbital preventing spin delocalization.^{62,63} Even purely aliphatic radicals without β-hydrogens such as di-*tert*-methyl (**30**) and tri-*tert*-butylmethyl (**31**),⁶⁴ and also even triisopropylmethyl (**32**),⁶⁵ are sufficiently long-lived in solution for direct observation by EPR. These radicals also did not dimerize but decayed by other undetermined routes. Such radicals with kinetic stability have been classified as *persistent radicals*.⁶⁶

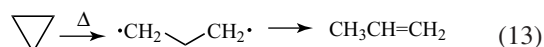


The importance of resonance stabilization of triarylmethyl radicals was summarized by Pauling and Wheland in 1933.⁶⁷ Earlier studies by Marvel and Munro had already shown that alkynyl groups with minimal steric barriers were also effective at promoting dissociation of the ethane **33** by stabilization of diarylmethyl radicals **34** (12).⁶⁸

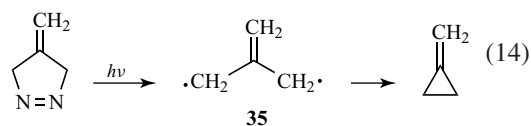


3.3 Diradicals in Aliphatic Rearrangements

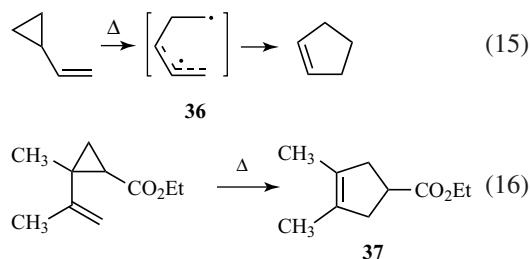
Tanatar discovered in 1896 the cyclopropane-to-propene rearrangement, (13),⁶⁹ which was later recognized as proceeding by the formation of a diradical followed by radical rearrangement in an aliphatic system. Chambers and Kistiakowsky⁷⁰ in 1934 measured the kinetics of this reaction, and suggested the radical pathway, (13), that is now generally accepted.



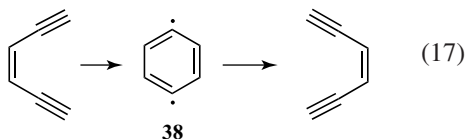
Another diradical species, trimethylenemethane (**35**), was discovered by Dowd in 1966⁷¹ from the cleavage of the pyrazoline, and was characterized by its ESR spectrum and kinetic measurements of its closure to methylenecyclopropane⁷² (14).



The thermal rearrangement of vinylcyclopropanes to cyclopentenes via a diradical intermediate **36**, (15), discovered independently by several groups, was the first reaction widely accepted as proceeding through a diradical intermediate,^{73–78} as supported by computational studies.⁷⁸ This reaction is a synthetically useful method for the preparation of cyclopentenes,⁷⁹ as in the synthesis of **37** (16).⁸⁰

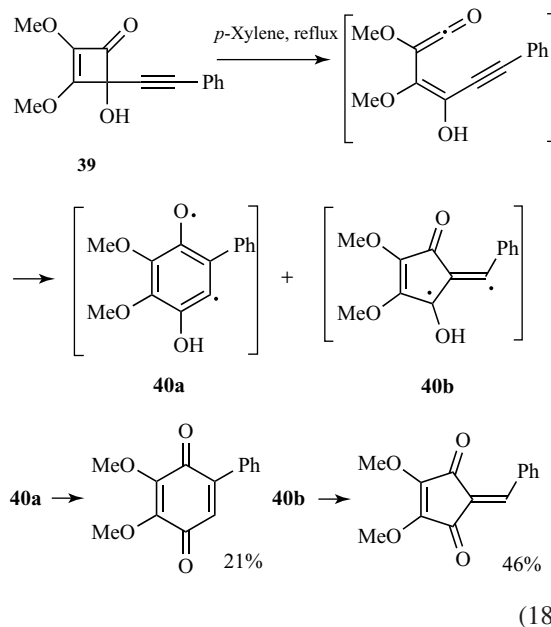


The degenerate cyclization of *Z*-hex-3-en-1,5-diyne, (17), known as the *Bergman rearrangement*, forms the diradical intermediate **38**, and was discovered in 1972, but was initially of largely mechanistic interest.^{81,82} Then it was discovered that this reaction occurs in the action of anticancer drugs, as with the antitumor agents calicheamicin and neocarzinostatin.^{83,84} Many further examples of this process have been studied, including enyne-allene cyclizations.⁸⁴



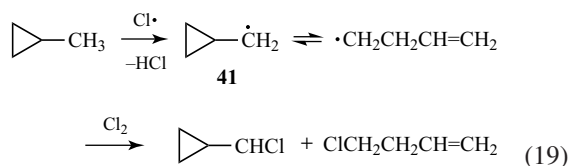
Enyne-ketene rearrangement is a useful but somewhat unappreciated route to free radicals, discovered with the investigation of the intramolecular cycloaddition of Enyne-ketenes and of aryldienylketenes giving rise to diradical intermediates. For example, **39** in refluxing *p*-xylene gives Enyne-ketene formation followed by competitive *p*-benzoquinone and cyclopentene-3,5-dione formation, in a process interpreted as involving the formation of diradical intermediates which lead to the observed products by hydrogen migration (18).⁸⁵ The competition between the two routes has been studied by computational methods, and is explained⁸⁶ as reflecting the ability of the phenyl substituent to stabilize the radical intermediate, favoring formation of the

five-membered ring, versus the gain in aromatic stabilization in formation of the six-membered ring product. The selectivity between the formation of two reactive diradical intermediates depending upon the substitution pattern allows the design of precursors in which the diradical intermediate can react intramolecularly favoring one product or the other, and has found wide application in synthesis.



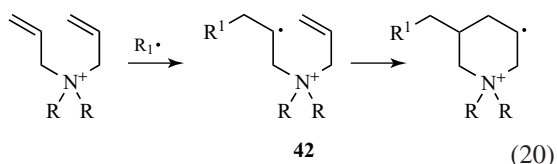
3.4 Rearrangements of Monoradicals

Radical rearrangements⁸⁷ were observed in 1951, Roberts and Mazur^{87,88} in the free-radical chlorination of methylcyclopropane gives a mixture of cyclopropylmethyl chloride and 4-chloro-1-butene (19). This reaction was studied further,⁸⁹ and in 1969 Kochi, Krusic, and Eaton⁹⁰ observed the cyclopropylcarbinyl radical **41** by EPR and also monitored the kinetics of this rearrangement.

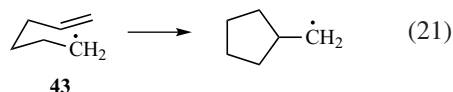


Radical addition to a diallylammonium species forming radicals **42** leading to six-membered rings

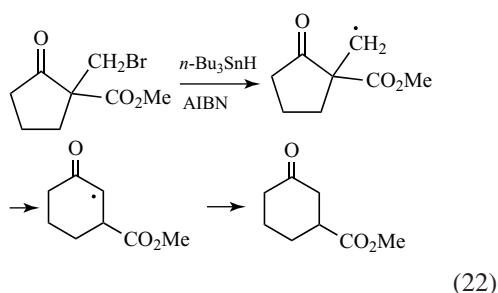
was discovered in 1957 as occurring during polymerizations (20).⁹¹ This cyclization/polymerization also occurs upon formation of radicals by additions to 1,6-heptadienes.⁹²



Other radical cyclizations have been subsequently reported,^{93,94} and cyclization of the hexenyl radical **43** forming the cyclopentylmethyl radical, (21), has been of significant utility in both synthetic and mechanistic study.^{95–97} The competition between formation of cyclopentylcarbinyl and cyclohexyl radicals often favors the former even though the latter is more stable, and this kinetic preference is explained by the more favorable geometry for bond formation from the radical site to C2 of the alkene. The effects of substituents on the double-bond, heteroatoms in the chain, and many other factors on the partitioning between these two paths have been examined.

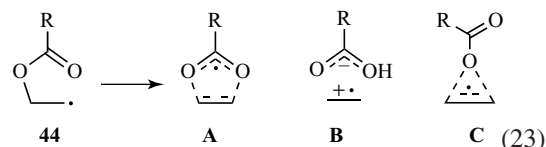


Ring-expansion reactions of free radicals are also useful in synthesis, (22), and examples were reported independently in 1987 by the groups of Beckwith *et al.*^{98,99} and Dowd and Choi.¹⁰⁰

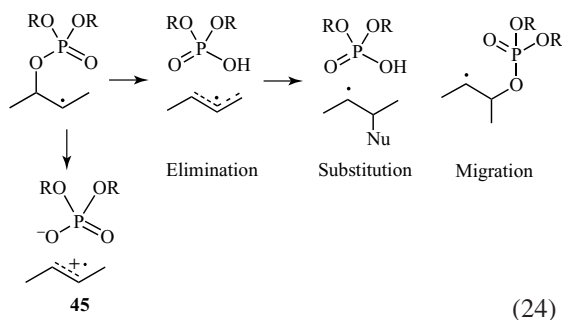


The radical rearrangement of acyloxy groups, (23), was also discovered independently by different groups (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**),^{101,102} and is known as the *Surzur–Tanner rearrangement*.¹⁰³ It was initially considered to involve a concerted [3,2] acyl

migration process of radical **44** through transition state **A**, but cleavage to a radical cation/anion pair **B** and a concerted 1,2-migration through transition state **C** have also been considered. Calculations support the originally proposed concerted [3,2] acyl shift.¹⁰⁴



The chemistry of radical sites adjacent to phosphoxy centers elicited interest because of the involvement of such species in DNA degradation processes.¹⁰⁵ These species can give rise to rearrangement, elimination, and substitution products, and for some time concerted eliminations and migrations as well as heterolysis to a radical cation and a phosphate anion were considered to be involved (24). Experimental studies of the 1,2-dibenzyl-2-(diphenylphosphoxy)-2-phenylethyl radical and complementary theoretical studies of 1,1-dimethyl-2-(dimethylphosphoxy)ethyl radical have been interpreted as indicating that a radical cation/anion pathway with initial formation of **45** is favored.¹⁰⁵

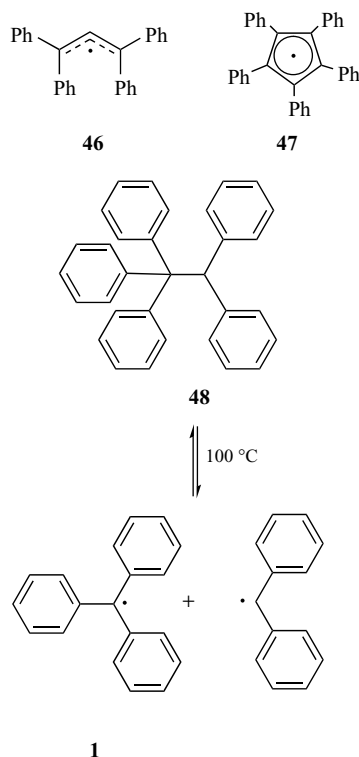


4 OTHER DELOCALIZED RADICALS

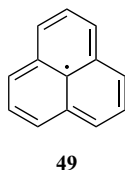
4.1 Monoradicals

Following the discovery of the triphenylmethyl radical, other types of persistent radicals and novel precursors have been investigated, including the tetraphenylallyl radical (**46**)¹⁰⁶ and the pentaphenylcyclopentadienyl radical **47**,¹⁰⁷ both reported by

Ziegler and coworkers. Pentaphenylethane (**48**) was also found to undergo reversible dissociation to free radicals at 100 °C.¹⁰⁸ A reported preparation of the pentaphenylethyl radical has not been reproduced, and this structure and its possible equilibration are evidently unproven.^{109–111}

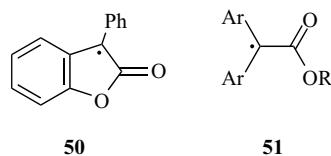


The phenalenyl radical (**49**) was first reported in 1957.¹¹² This planarized molecule has been extensively examined for possible electronic applications, and its derivatives form stacked “pancake” structures stabilized by pi bonding.¹¹³

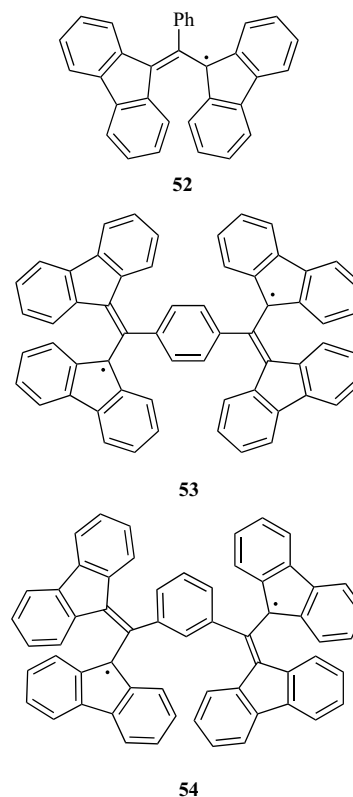


The long-lived acyl radical **50** was prepared by Löwenbein and Folberth;¹¹⁴ it reversibly forms a dimer, and reacts only slowly with oxygen to give a peroxide. Radical **50** and its analogs¹¹⁵ have found extensive recent application as chain-breaking antioxidants.^{116,117} These function by trapping

peroxyl radicals, and can completely suppress autoxidation. Diarylacetate radicals **51** also form readily, but undergo reversible formation of dimers, often with para coupling,^{118,119} and reaction with oxygen to form peroxides.^{120,121}

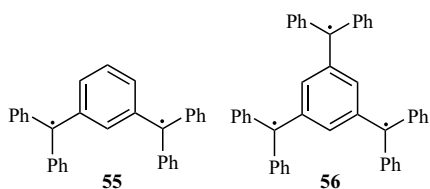


However, even in 1931 the idea of stable radicals met resistance, as Koelsch prepared and submitted for publication a report of the long-lived radical **52**, but the complete unreactivity of the radical toward oxygen seemed improbable, and the manuscript was rejected. In 1957, ESR spectroscopy of the same sample confirmed the identification, and the original manuscript was resubmitted and published.¹²² Further homologs such as **53** and **54** have been reported, and these are found to have singlet and triplet ground states, respectively.^{123,124}



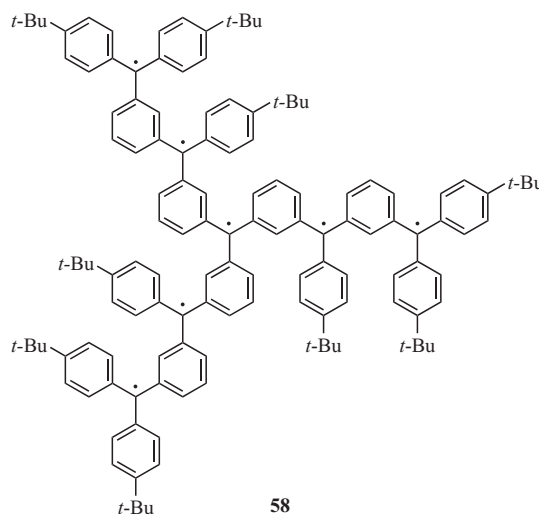
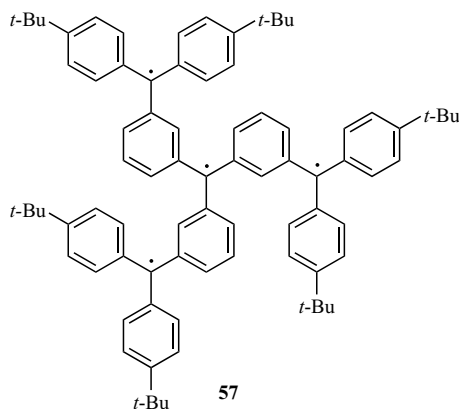
4.2 Di- and Polyradicals

The synthesis of non-Kekulé bi- and polyradicals, which are aromatic compounds for which no Kekulé structures are possible so that double bonds cannot be drawn to two or more of the carbons, has long been of interest. Such extensions of the triphenylmethyl radical motif of Gomberg include the stable diradical **55**, reported by Schlenk in 1915 (Schlenk diradical),¹²⁵ and the analogous 1,3,5-trisubstituted **56**, prepared by Leo in 1937.¹²⁶ These materials have potential application as molecular magnets,¹²⁷ and the study of “high-spin” molecules has continued (see **Physical Properties of Thiazyl Radicals Toward Conductive and Magnetic Materials**).^{128–133}

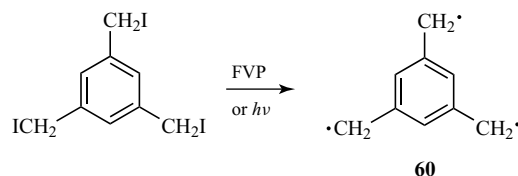
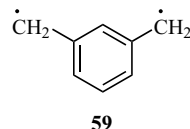


The tetra-radical **57** was prepared by oxidation of the corresponding tetra-anion with molecular iodine, and identified by the characteristic quintet EPR spectrum.¹³² The zero-field parameter (D/hc) was interpreted as showing threefold symmetry for **57**.¹³² Analogous hepta-radical **58** and deca-radicals have also been prepared.¹³³

More recently, *m*-xylene (**59**), the parent of the Schlenk diradical **55**, was observed upon photolysis of *m*-xylene in an Ar matrix at 10 K,¹³⁴ and the parent **60** of the Leo triradical **56** was prepared both by flash vacuum pyrolysis of the triiodide with

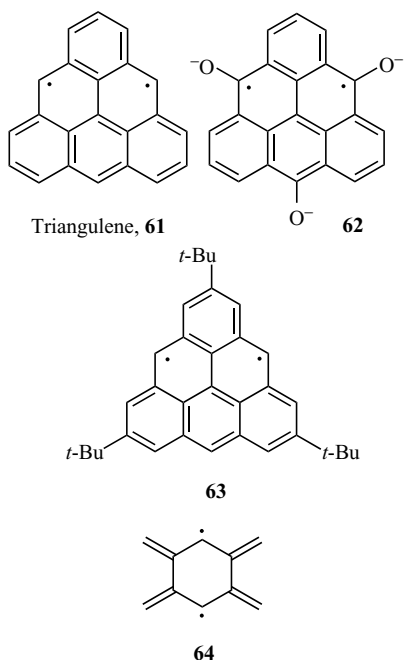


deposition in Ar at 10 K and by photolysis in Ar at 5 K, and was characterized by IR, UV-vis, and ESR spectroscopy.¹³⁵

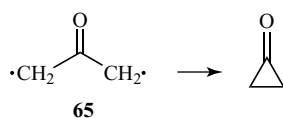


Non-Kekulé quinodimethanes are biradicaloids of a six-membered ring with methylene substituents, while non-Kekulé polynuclear aromatics are composed of several fused six-membered rings. The synthesis of triangulene (**61**), the simplest and still unknown non-Kekulé polynuclear aromatic, was first attempted by Clar in 1953,¹³⁶ while a trioxo-triangulene trianion **62** was observed by ESR in 1993,¹³⁷ and the synthesis and ESR detection of a sterically protected triangulene **63** was accomplished in 2001.¹³⁸

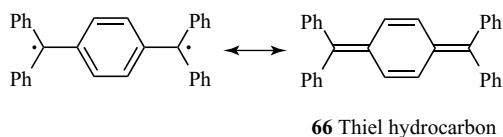
Tetramethylenebenzene **64**, a conjugated hydrocarbon in violation of Hund's rule, has been generated as an observable long-lived ground state singlet, as identified by the UV spectrum, and confirmed by extensive calculations.^{139–142} A short-lived triplet species also observed by ESR¹³⁹ in these studies is evidently not the triplet of **64**.^{140–142}



The oxyallyl diradical **65** has been shown by experimental and computational studies to be a singlet with a strong carbonyl π bond that closes without a barrier to cyclopropanone.¹⁴³ The hydrocarbon analog trimethylenemethane (**35**), described above, (14), was first observed in 1966, and underwent ring closure to methylenecyclopropane.⁷²

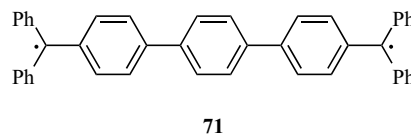
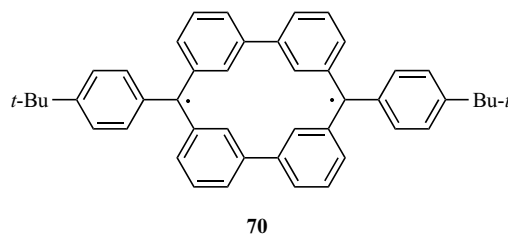
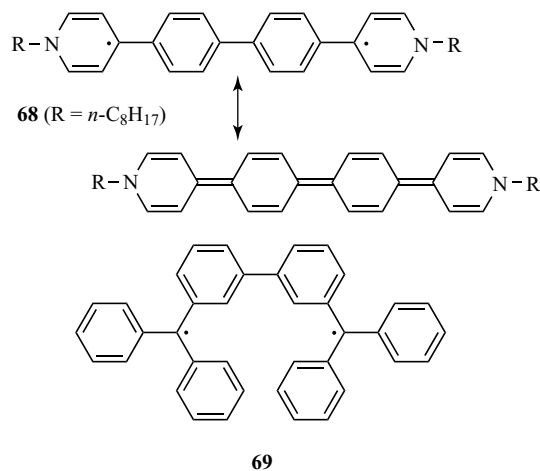
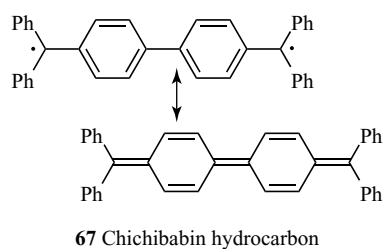


Tetraphenyl-*para*-xylylene **66** was prepared by Thiele and Balhorn in 1904 as an isolable species,¹⁴⁴ and has been characterized by X-ray.¹⁴⁵ This species however has some diradical character, and continues to attract attention after more than 100 years.



The Chichibabin hydrocarbon (**67**)¹⁴⁶ is a further example of an extended linear polyaromatic with diradical character, and is related to the Thiele's

radical **66**. It is unusual for a neutral, even-electron molecule with a closed-shell electronic structure such as **67** to display magnetic activity, and this species has been compared to extended viologens **68**.^{147,148} These yield ambiguous results for their electronic structure using EPR techniques, but **68** was found to have a singlet ground state as determined using Raman spectroscopy.¹⁴⁷ Earlier X-ray studies also favored a singlet structure for **67**, but with significant diradical character.¹⁴⁵ Other related diradicals include **69**,¹⁴⁹ **70**,¹⁵⁰ and the Muller hydrocarbon **71**.¹⁵¹



5 BIS(TRIPHENYLMETHYL) PEROXIDE AND FREE-RADICAL REARRANGEMENTS

Substrates containing the triphenylmethyl group played a decisive role in the discovery and elucidation of free-radical rearrangements (see **Radical Arylations**). In the first reported example, Wieland observed in 1911 that the Gomberg peroxide **3** rearranged upon heating to the pinacol ether **75** in a process attributed to initial dissociation forming an intermediate alkoxyl radical **72**, followed by rearrangement forming the radical **74** which dimerized to give **75** (25).¹⁵² Recent studies have shown this reaction occurs through a phenyl-bridged intermediate **73** (Figure 2), and this undergoes ring-opening giving radical **74**.¹⁵³ Further examples of such *O*-neophyl rearrangements have been reported.¹⁵⁴

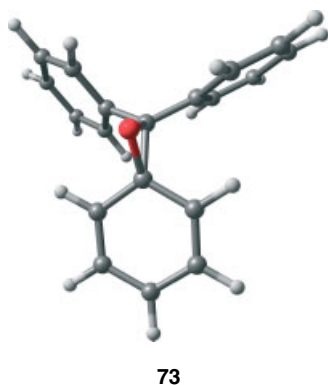
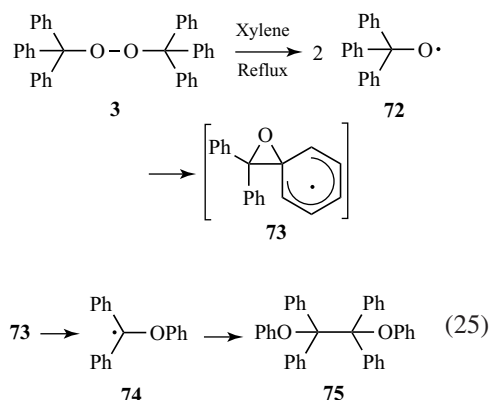
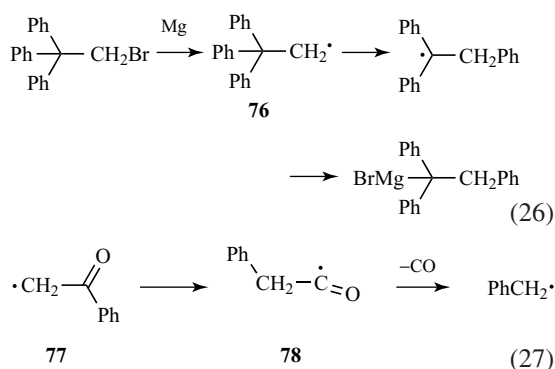


Figure 2 Intermediate phenyl-bridged radical from rearrangement of the trityloxyl radical **73**. [Reproduced from Ref. 153. © Wiley-VCH Verlag GmbH & Co. KGaA, 2010.]

In 1944 Urry and Kharasch reported the neophyl rearrangement, (26) in which neophyl bromide upon reaction with magnesium forms the radical **76**, which undergoes the analogous rearrangement of phenyl to carbon forming a stabilized radical which gives the rearranged Grignard reagent.¹⁵⁵ Subsequently, numerous such free-radical rearrangements of the neophyl type, (26), have appeared, and have been reviewed.¹⁵⁶ The McBay rearrangement discovered in 1974 involves phenyl migration with conversion of an enolic radical **77** to an acyl radical **78**, and this undergoes decarbonylation, forming the benzyl radical (27).^{157,158}

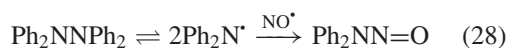


Other free-radical rearrangements are noted elsewhere (see **Radical Cation/Anion and Neutral Radicals: A Comparison**), including cyclopropane cleavage, ring-openings of cyclopropylcarbinyl radicals, cyclizations of alkenyl radicals, ring expansions, and rearrangements involving halogen and sulfur atoms.

6 HETEROATOM-CENTERED RADICALS

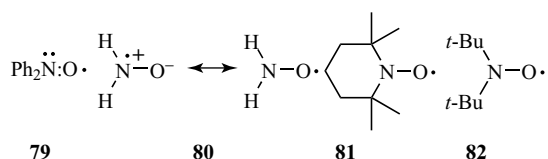
6.1 Nitrogen-Centered Radicals

The reversible dissociation of colorless tetraphenylhydrazine into the green diphenylaminyl radical at 100 °C was discovered by Wieland in 1911 (28), thus extending the free-radical concept to nitrogen.^{159–161} The rate of this reaction was measured in 1940 by trapping these radicals by nitric oxide, forming diphenylnitrosoamine.¹⁶²



6.2 Nitroxyl Radicals

Arylaminoxyls $\text{Ar}_2\text{NO}^\bullet$ were first reported by Wieland *et al.* in 1914^{163–165} using the tetravalent representation $\text{Ph}_2\text{N}=\text{O}$, and the radical electronic structure as represented by **79** was proposed by Banfield and Kenyon in 1926.¹⁶⁶ These species resemble nitric oxide (NO), and they may be represented as either a nitrogen- or oxygen-centered radical, as can aminoxyl, H_2NO (**80**). Aminoxyls substituted with aliphatic groups bearing alpha hydrogens are subject to disproportionation and are often not isolable. The preparation of the stable nitroxyl radical, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO, **81**) was reported by Lebedev and coworkers in 1959,^{167,168} followed shortly thereafter in 1961 by the preparation of di-*tert*-butylnitroxyl **82**,¹⁶⁹ and aliphatic aminoxyls have found wide application ever since (see **Nitroxides in Synthetic Radical Chemistry**). Important physiological roles of NO were found later; and NO was named as “Molecule of the Year” in 1992,¹⁷⁰ and studies of this molecule were recognized by the award of the 1998 Nobel Prize in Medicine.

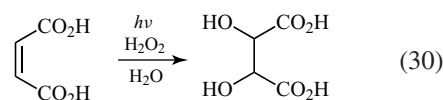


Because nitroxyl radicals do not react with most organic functional groups but combine with free radicals, they have found wide application as radical traps, and in “living” free radical polymerizations (see **Nitroxides in Synthetic Radical Chemistry** and **Fundamentals of Controlled/Living Radical Polymerization**).¹⁷¹ Nitroxyl radicals are also used as spin labels (see **Spin Labels and Spin Probes**), and are formed in spin trapping by nitroso compounds and nitrones (see below).

6.3 Oxygen-Centered Radicals

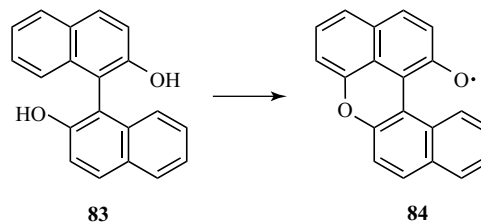
As noted in Section 2.1, Downes and Blunt in 1879 reported⁶ that hydrogen peroxide in solution was destroyed by sunlight to form two OH radicals, (29), and proposed that these were responsible for the high reactivity of the peroxide (see

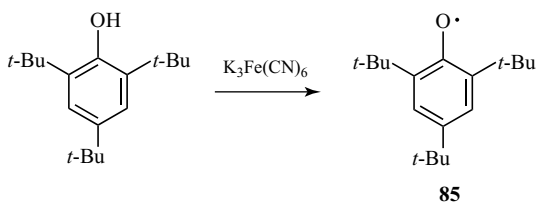
Photo Induced Radical Reactions). Later studies of hydrogen peroxide photolysis after almost 50 years gave spectral evidence for the presence of hydroxyl radicals,^{172–174} and addition of hydroxyl radicals to alkenes forming 1,2-diols was reported, (30),¹⁷⁵ but these reactions are not of preparative value.¹⁷⁶ The hydroxyl radical was detected in the interstellar medium in 1963,¹⁷⁷ and this has been a subject of continued study.¹⁷⁸ As described above, dissociation of triphenylmethyl peroxide forming the highly reactive triphenylmethoxyl radical **72** was discovered by Wieland in 1911 (25).¹⁵² *tert*-Butoxy radicals as well as other alkoxy radicals are available from a variety of precursors, including peroxides, peresters, and hypochlorites, and display high reactivity in hydrogen abstraction, as discussed below (see **Overview of Radical Initiation**).



6.3.1 Aryloxy Radicals

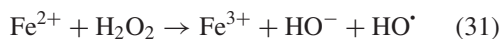
Oxidation of phenols produces aryloxy radicals, and these undergo dimerization with C–O bond formation at the ortho or para positions. The dihydroxynaphthol **83** upon ferricyanide oxidation gave an aryloxy radical which reacted by intramolecular cyclization,¹⁷⁹ and the radical **84** was later observed by ESR.^{180,181} The stable dark blue radical 2,4,6-tri-*tert*-butylphenoxyl **85** is formed as a solid by oxidation of the phenol with potassium ferricyanide.¹⁸² Other examples of phenol oxidation with aryloxy formation^{183–185} include the isolation of solid dimers, which have been shown to involve C–O bonding.





6.3.2 Fenton Reaction and Iron-Based Oxidations

The use of H_2O_2 and $\text{Fe}(\text{II})$ for oxidation was reported by Fenton in 1894,¹⁸⁶ and this reaction was proposed to involve hydroxyl radicals by Haber and Weiss (31).¹⁸⁷ This reaction was later developed by Waters¹⁸⁸ and then by Walling¹⁸⁹ for the oxidation of organic compounds by hydroxyl radicals. The details of the process have occasioned considerable debate.¹⁹⁰

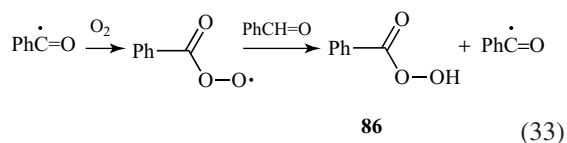


In 1983, Barton and coworkers reported the use of iron-based reagents in the functionalization of alkanes (32).^{191,192} The elucidation of the mechanisms has been contentious, but the role of free-radical reactions appears to be well established.^{193,194}



6.3.3 Peroxides and Peroxyl Radicals

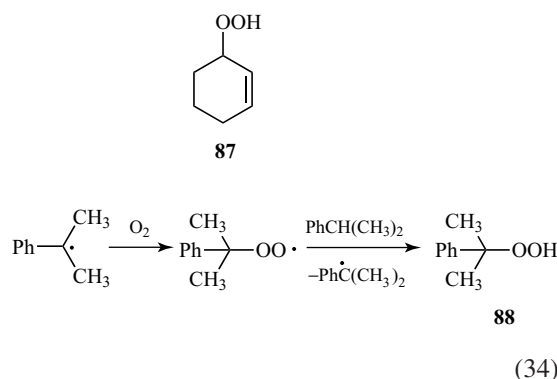
The conversion of benzaldehyde in the presence of air to benzoic acid was reported in 1832 by Wöhler and Liebig,¹⁹⁵ and in 1900 Baeyer and Villiger proposed perbenzoic acid (**86**) as an intermediate in the reaction.¹⁹⁶ The currently accepted free-radical chain mechanism for the process was proposed by Bäckström in 1934, involving an intermediate peroxy radical (33).¹⁹⁷ Bates and Spence already in 1931 had considered that photolysis of CH_3I forming $\text{CH}_3^\bullet$ in the presence of O_2 led to peroxy radicals $\text{CH}_3\text{OO}^\bullet$.¹⁹⁸



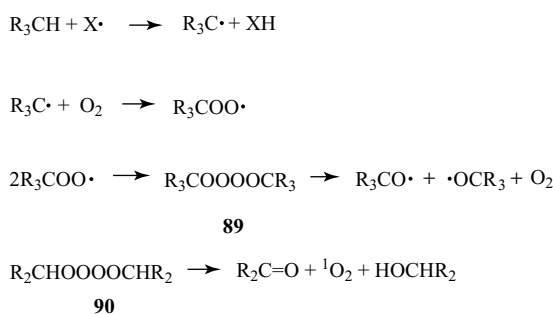
(33)

Gomberg's discovery in 1900 of the reaction of the triphenylmethyl radical with oxygen to form the peroxide was a strong piece of evidence for peroxy radical formation, (3), and the affinity of radicals for oxygen remains one of their defining characteristics. Haber and Willstätter in 1931¹⁹⁹ proposed a general role for free radicals in oxygen reactions which provided further recognition for such chemical processes.

The known reaction product of the oxidation of cyclohexene was assigned as the hydroperoxide **87** by Criegee in 1936.²⁰⁰ The oxidation of cumene to the hydroperoxide **88** proceeds by a chain mechanism, (34), and the conversion of the hydroperoxide by acid to phenol and acetone in what became a commercially important process was reported by Hock and Lang in 1944.²⁰¹



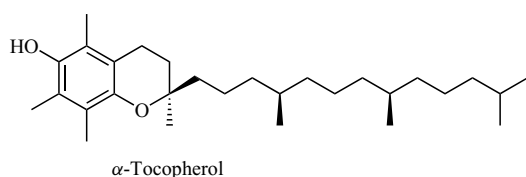
The oxidation of hydrocarbons (Scheme 1) is of continued interest.^{202,203} Initially formed alkyl radicals react with oxygen giving intermediate peroxy radicals, which undergo self-reaction to form transient tetraoxide intermediates **89**, as was shown by the direct observation of these intermediates at low



Scheme 1 Oxidation of hydrocarbons.

temperatures, and this was confirmed by the occurrence of isotope-scrambling when $^{16}\text{O}_2$ and $^{18}\text{O}_2$ were used in autoxidation with the formation of $^{16}\text{O}^{18}\text{O}$.^{204,205} Tetraoxides with secondary hydrogens (**90**) can undergo disproportionation with formation of singlet oxygen, which can be trapped with added 9,10-diphenylanthracene (Scheme 1).^{204,205}

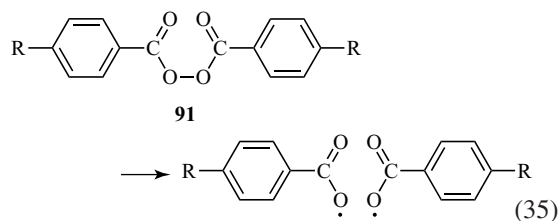
The biological antioxidant α -tocopherol (vitamin E) serves as a chain-breaking trap of peroxy radicals in hydrocarbon oxidation by hydrogen donation, and the resulting phenoxyl radical then eventually reacts with and destroys a second peroxy radical.^{206,207}



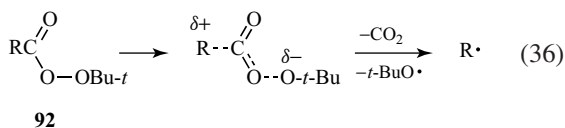
6.3.4 Diacyl Peroxides and Peroxy Esters

The thermal reactions of diacyl peroxides (**91**) were initially studied by Hermans, *et al.*^{208,209} and by Wieland,²¹⁰ but only gradually were these recognized as forming free radicals. The interpretation of the results was complicated by the phenomenon of induced decomposition, also discussed in Section 9.4, in which radicals are formed during the peroxide decomposition or from subsequent radical reactions with solvents, and these then reacted with the radical initiator. Thus, Wieland and Razuvaev²¹⁰ considered radical formation in these reactions but excluded this possibility. Walker and Wild²¹¹ studied the decomposition of acetyl peroxide by both thermal and photochemical means, and observed the formation of methane and ethane, and made a tentative suggestion that these could result from formation of acetoxo radicals $\text{CH}_3\text{CO}_2^\cdot$ which underwent decarboxylation to methyl radicals $\text{CH}_3^\cdot$, and these could combine to form ethane or react with solvent to form methane. The kinetics of benzoyl peroxide decomposition reactions were studied by D. J. Brown,²¹² and was suggested to involve the formation of benzoyloxy radicals, (35), which could form phenyl radicals by decarboxylation. Polar effects in rates of these reactions were found by Swain *et al.*,²¹³ who found a linear correlation of the rates with the Hammett σ values, with

$\rho = -0.38$. This was interpreted as resulting from the enhancement of the reactivity by electron donor substituents because of increased repulsion between the oxygens in the peroxy group in **91**.

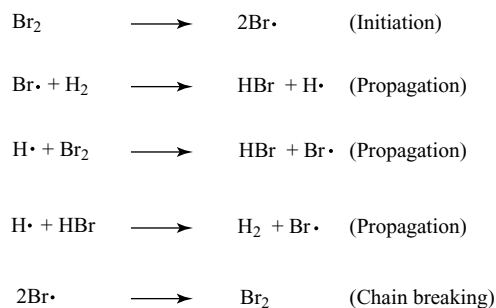


Ethyl peracetate was the first ester of a peroxy acid, as characterized by Baeyer and Villiger in 1901.²¹⁴ Kinetic studies of perester decomposition were reported by Blomquist and Ferris in 1951,²¹⁵ and in 1958 Bartlett and Hiatt²¹⁶ proposed that concerted multiple bond scission of peresters **92** could occur when stabilized radicals were formed, and that polar effects in peroxyester decomposition are also significant (36).

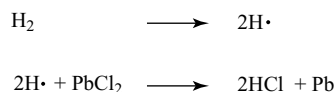


6.4 Halogen Radicals

In addition to proposing the dissociation of hydrogen peroxide to hydroxyl radicals, as noted in Section 2.1, Downes and Blunt in 1879 also suggested⁶ that chlorine molecules were dissociated by light to form two Cl radicals, and that these were responsible for the high reactivity of chlorine. The study of the kinetics of gas phase reactions of halogen free radicals was reported by Bodenstein and Lind in 1906,²¹⁷ as later summarized,²¹⁸ and it was found that reactions of H_2 with Cl_2 and Br_2 were complex processes. A radical chain mechanism for these reactions was proposed in 1919 by Christiansen, Herzfeld, and Polanyi (Scheme 2) (see **Halogen and Chalcogen Transfer Chemistry**).^{219–221} As described above, the theoretical basis for understanding these reaction in terms of free radicals was presented by G. N. Lewis in 1916, with the theory of the electron-pair bond, and free radicals, or “odd molecules.”^{52,53} Further



Scheme 2 Reactions of dihalides with H_2 under radical conditions.



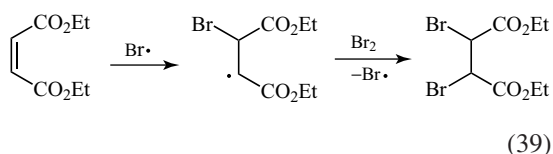
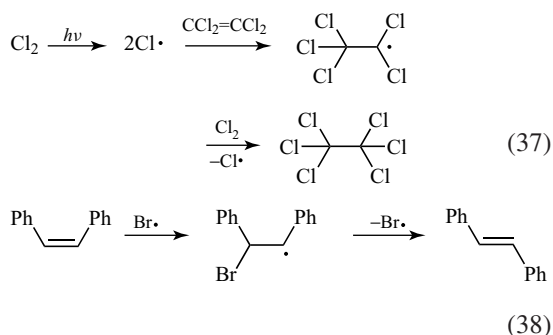
Scheme 3 Reduction of PbCl_2 with H radicals.

studies on chain reactions including the extension to explosions in gaseous systems were made by Hinshelwood and by Semenov,^{222–224} who shared the Nobel Prize in 1956.

In 1924, Bonhoeffer demonstrated the formation of atomic hydrogen using an electric discharge (Scheme 3). The presence of atomic hydrogen was shown by its ability to reduce metal salts.⁵⁶

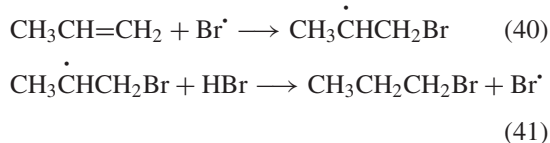
6.4.1 Free-Radical Additions

Michael Faraday reported in 1821 that chlorine addition to tetrachloroethylene forming hexachloroethane is stimulated by sunlight,²²⁵ indicating the involvement of a free-radical process. Later studies of this reaction showed inhibition of halogen addition by reaction of the intermediate radicals with oxygen,^{226–228} and a free-radical chain mechanism was proposed (37). Similar chain mechanisms were proposed in 1927 by Berthoud and Béraneck²²⁹ for the isomerization of stilbene catalyzed by Br_2 , (38), by Wachholtz²³⁰ for bromine addition to ethyl maleate, (39), and by Bauer and Daniels for cinnamic acid.²³¹ Further kinetic and mechanistic studies were reported for free-radical addition of Br_2 to phenanthrene,²³² and for the reaction of Cl_2 with benzene.²³³



6.4.2 The Peroxide Effect

The addition of HBr to allyl bromide in the presence of light and air occurs rapidly to yield 1,3-dibromopropane, whereas Kharasch and Mayo in 1933²³⁴ demonstrated that, in the absence of air and with purified reagents, the reaction is slow and 1,2-dibromopropane is formed. The latter reaction is the normal addition occurring by an ionic pathway giving the Markovnikov orientation. In 1933, the mechanism of the abnormal process (“anti-Markovnikov” addition) was not discussed, and it was only in 1937 that the free-radical chain mechanism was proposed by Kharasch and his coworkers for this process.^{235,236} The mechanism was extended to the reaction of propene with HBr, for which the role of peroxides in promoting the reaction was demonstrated in (40) and (41). The same mechanism was independently proposed in 1937 by Hey and Waters.²³⁷ This process is taught in most beginning organic chemistry courses, and has bedeviled many generations of students.



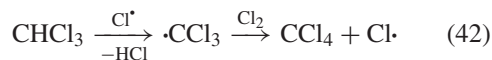
Interestingly, in 1934 Rice and Rice had incorrectly proposed⁵⁸ a free-radical chain mechanism for

the normal Markovnikov addition. They suggested that the anti-Markovnikov product arose from a different process, which was yet to be elucidated. In retrospect and with the benefit of hindsight, it is surprising that Kharasch was slow to recognize the peroxide effect as resulting from free-radical reactions, given the large body of precedent from other studies, particularly from his contemporaries Taylor and Rice. However, Kharasch approached these studies from a completely different perspective, and his work originated from a desire to develop a theory for polar reactions.²³⁸ Once he recognized the role of free radicals, he devoted the rest of his career to their study, and developed many of the modern concepts of these intermediates.

At the same time, Robert Robinson with Urushibara was studying the addition of HBr to fatty acids, and noticed that the direction of addition was reversed upon exposure to moist air, as first reported in 1933.^{239,240} Initially, these authors supposed that the moisture possibly caused the effect.²⁴⁰ Urushibara became Professor at Tokyo, and continued studies of the peroxide effect, and was the founder of organic free-radical studies in Japan.

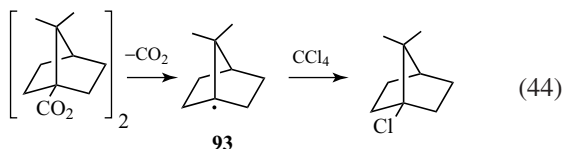
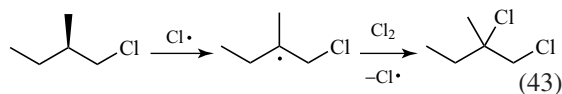
6.4.3 Free-Radical Halogenations

The halogenation reactions of alkanes found early applications, particularly in industrial processes, and in 1930 the kinetics of the gas-phase photochlorination of chloroform to carbon tetrachloride was reported by Schwab and Heyde, (42),²⁴¹ while the kinetics of the chlorination of methane was described by Pease and Walz in 1931.²⁴² Both these studies showed the currently accepted mechanism, which was extended to reactions in solution by Hass *et al.*^{243,244}



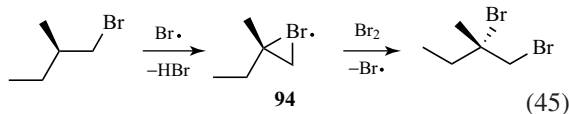
The free-radical halogenation mechanism of other alkanes was described by Kharasch and coworkers,^{245–247} and in 1940 Brown, Kharasch, and Chao found that during free-radical chlorination of optically active 2-methyl-1-butyl chloride, the product 1,2-dichloro-2-methylbutane was racemic, implying that the intermediate radical was either

planar or rapidly inverting (43).²⁴⁵ However, radical formation at a bridgehead center, constrained to maintain nonplanarity in bicycloheptyl intermediate **93**, was also demonstrated (44).²⁴⁶



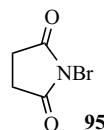
6.4.4 Migration and Bridging in Radicals

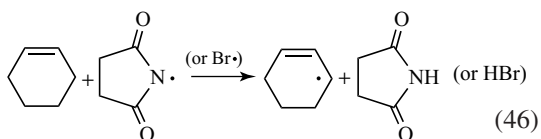
Migrations of chlorine, bromine, and thiol groups in free-radical reactions have been observed,^{248,249} and the role of bridging in these species has been a subject of some dispute.²⁵⁰ Reaction of a chiral substrate involving the bridged radical **94** gives an optically active product, (45), in direct contrast with chlorination in which racemization occurred in (43).



6.4.5 N-Bromosuccinimide

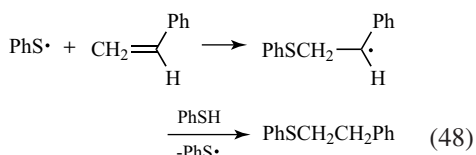
Wohl in 1919 reported that *N*-bromoacetamide (CH_3CONHBr)-induced allylic bromination.²⁵¹ Then, *N*-bromosuccinimide (**95**) was described in 1942 by Ziegler and coworkers to be useful in such free-radical bromination reactions, (46),²⁵² and the resulting widely utilized procedure is known as the *Wohl–Ziegler reaction*. In 1963, the mechanism of the reaction was proposed to involve halogen atoms in the hydrogen abstraction step,^{253,254} instead of succinimidyl radicals as had been commonly supposed.



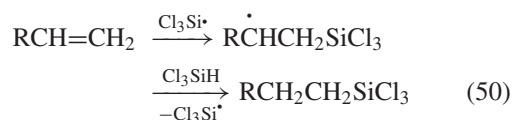


6.5 Sulfur-, Silicon-, and Tin-Centered Radicals

The effect of air and the acceleration by light of the addition of PhSH to styrene was observed in 1928,²⁵⁵ and in 1934 the formation of the PhS• radical from dissociation of PhSSPh and from reactions of PhSH was proposed.^{256,257} The use of peroxides to catalyze the reaction was reported by Jones and Reid in 1938,²⁵⁸ and in the same year the radical chain mechanism for this process was proposed (47) and (48).²⁵⁹

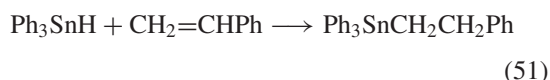


The formation of silyl radicals was reported in different laboratories in 1947 by Sommer and Whitmore, who discovered silane additions to alkenes (49) and (50),²⁶⁰ and by Barry *et al.* at Dow Chemicals.²⁶¹ These have been utilized extensively in both mechanistic and synthetic studies, including halide reductions (see **Silanes as Reducing Reagents in Radical Chemistry**).^{262,263}



Tin radicals were first reported by Noltes *et al.* in 1956,²⁶⁴ and their applications in organic chemistry were pioneered by Kuivila and coworkers.^{265,266} These species have proven to be of great utility in synthesis (see **Tin Hydrides and Functional Group Transformations**), particularly in reductions

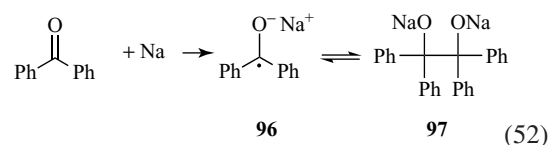
of organohalogen compounds, although their toxicity and other unfavorable properties have led to a search for substitutes.²⁶⁷ Interestingly, in the initial publication of addition of triphenyltin hydride to styrene, (51),²⁶⁴ it was proposed that the reaction did not involve a free-radical mechanism, as no inhibition by hydroquinone was detected.



7 ELECTRON TRANSFER PROCESSES

7.1 Carbonyl Reduction

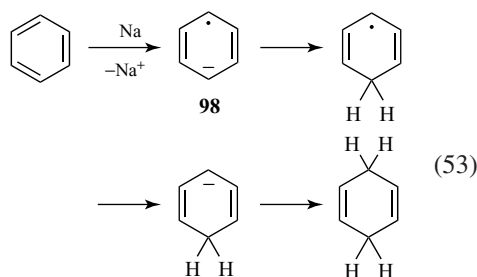
The reaction of sodium metal with benzophenone in ether gives rise to a blue color, as first observed by Beckmann and Paul in 1891.²⁶⁸ From the fact that reaction of this species with iodine or oxygen re-forms benzophenone, Schlenk and Weickel proposed in 1911 that this species was the ketyl radical **96** (52).²⁶⁹ Further experiments showed this was in equilibrium with the dimer **97**, which gives benzpinacol upon hydrolysis.²⁷⁰ Magnetic susceptibility measurements suggested that **96** was largely associated to the dimer,^{270,271} while the potassium derivative was largely dissociated.²⁷¹ Later, these radicals were investigated by ESR, and finally the structure of **96** was determined by X-ray crystallography.²⁷² In 1934, Favorsky and Nazarov proposed the formation of a ketyl radical anion from the aliphatic ketone *t*-Bu₂C=O,²⁷³ and the ESR spectrum of this radical was first observed in 1961.²⁷⁴ Studies of reduction of ketones by metals were extended to α,β -unsaturated ketones in 1926 by Conant and Cutter.²⁷⁵



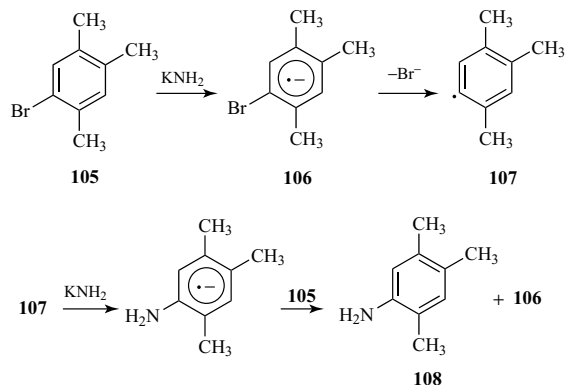
7.2 Birch Reduction

Birch in 1944²⁷⁶ extended the findings of Wooster and Godfrey,²⁷⁷ and demonstrated that Na metal

in ammonia reduces benzene, anisole, and other aromatics to 1,4-cyclohexadienes. This transformation is known as the *Birch reduction*, and has been extensively utilized in synthesis.²⁷⁸ Birch speculated about the mechanism of this reaction, but did not explicitly describe a radical pathway involving **98**, (53) until later, as described in his autobiography.²⁷⁹

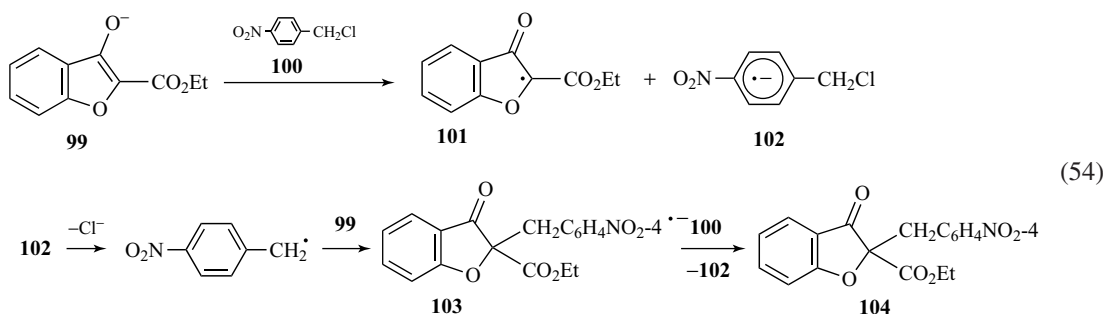


Kim and Bunnett in 1970 made the unexpected observations of reactions occurring by an electron transfer chain mechanism in aromatic systems (55).^{283,284} The selective formation of **108** from **105** showed that benzyne intermediates were not formed, and a chain reaction mechanism analogous to that found in the aliphatic systems above, (54),^{283–285} was proposed.



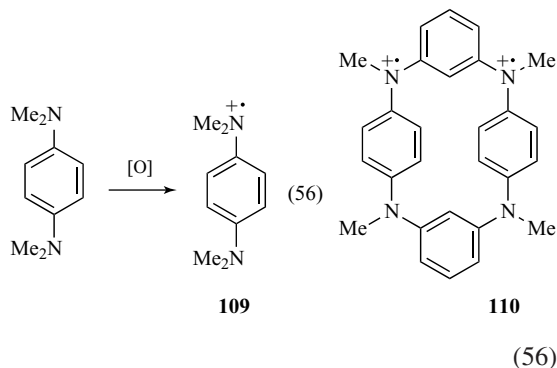
7.3 Electron Transfer in Substitution Reactions

Reactions occurring by an electron transfer chain reaction in aliphatic systems were reported independently in 1966 by the groups of Russell and Danen²⁸⁰ and Kornblum *et al.*^{281,282} Reaction of enolate **99** with 4-nitrobenzyl chloride (**100**) involves initial transfer of an electron to **100**, forming radical **101** together with radical anion **102** which loses chloride forming a benzylic radical which combines with **99** forming the radical anion **103** which transfers an electron to **100**, giving the product **104**, as well as another radical anion **102**, which continues the chain process (54).

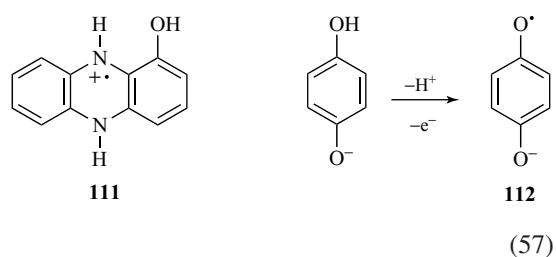


7.4 Radical Cations

Wurster and Sendtner already in 1879 had prepared crystalline salts containing radical cation **109**, (56).²⁸⁶ Subsequently, radical cations of many different structural types were prepared,^{287,288} including a cyclophane structure **110** containing two radical cations.²⁸⁹



Leonor Michaelis made extensive studies of oxidations in biological systems,^{290–293} and reported in 1931 the formation of the radical cation species **111**, which he designated as a semiquinone.^{290,291} Michaelis also studied the oxidation of quinone anions, and demonstrated the formation of semiquinone radical anions such as **112** (57).^{292,293} Quantitative linear free energy correlations of oxidation potentials with the rates of formation of these species were found by Dimroth.²⁹⁴

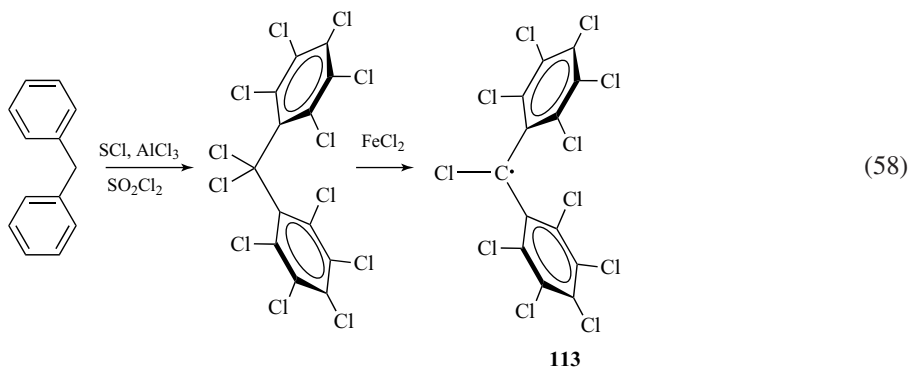


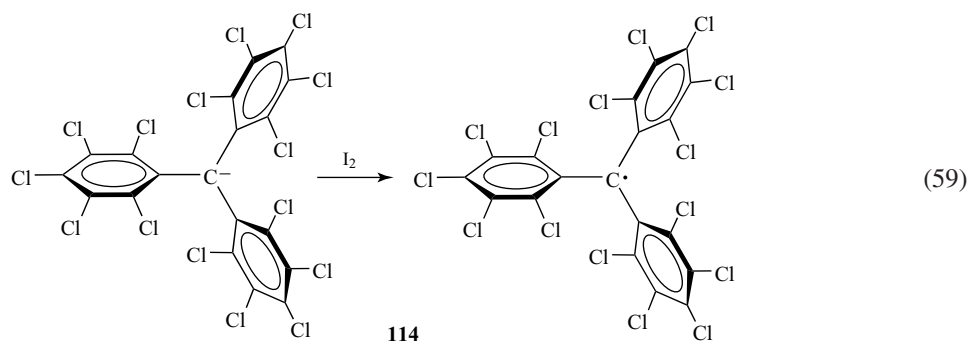
Oxidative electron transfer from a polycyclic aromatic compound was found by Weiss in 1941, who obtained crystalline salts of $C_{14}H_{10}^+$ from oxidation of anthracene, as well as salts from coronene, 1,2-benzperylene, and 3,4-benzpyrene (see **Redox Properties of Radicals**).²⁹⁵

8 NEW CLASSES OF TRIARYLMETHYL RADICALS

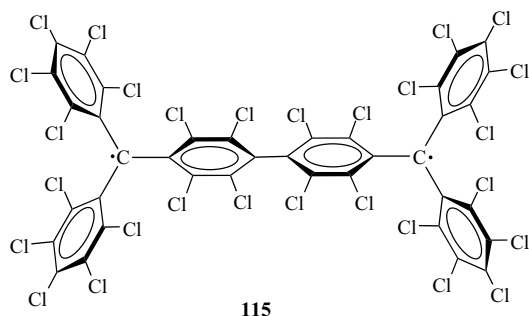
8.1 Perchlorinated Triarylmethyl Radicals

Perchlorination of aromatic compounds using a reagent composed of sulfur monochloride and aluminum chloride in sulfuryl chloride (SCM reagent), introduced in 1960,²⁹⁶ has proved very effective in the preparation of a new class of stable triarylmethyls. In 1971, this method was applied to the formation of perchlorinated diphenyl- and triphenylmethane, and conversion of the former to the radical perchlorodiphenylmethyl (**113**) could be effected by reduction with $FeCl_2$, (58) and, more generally, the radical perchlorotriphenylmethyl (**114**) was prepared by conversion of the chlorocarbon to the anion with NaOH in dimethylsulfoxide (DMSO), and oxidation of the corresponding anion with iodine (59).^{297,298} These radicals have lifetimes in air of decades, and are characterized as inert carbon free radicals.^{297,298} The *ortho*-chlorines on the aryl rings effectively shield the central radical site, preventing reactions of the chlorinated radicals.

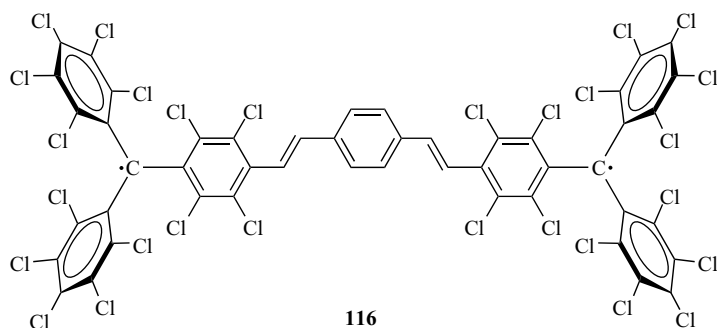
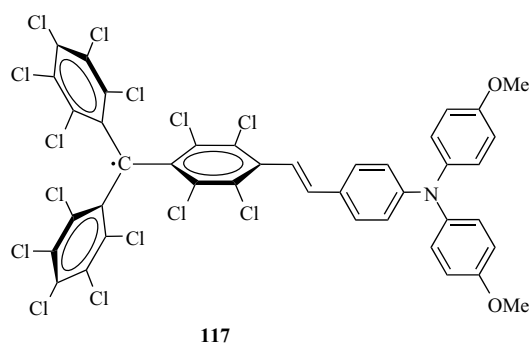




These studies have been extended to perchlorinated diradical **115**, and to the corresponding radical cations and radical anions, which have single-electron transfer equilibria,²⁹⁸ and to the highly but not completely perchlorinated diradical **116**.²⁹⁹



susceptible to electron transfer, either reduction to carbanions or oxidation to carbocations (see **Redox Properties of Radicals**).²⁹⁸



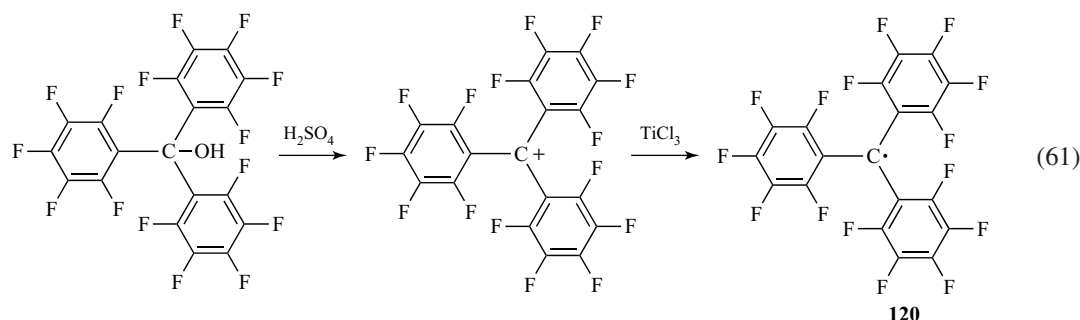
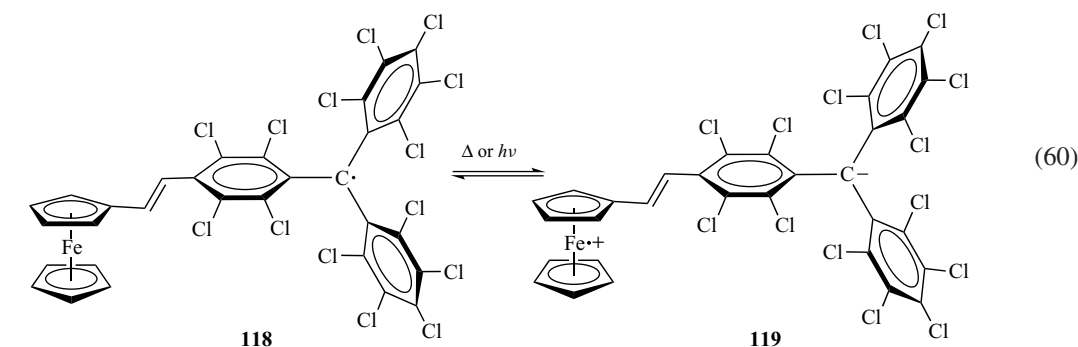
There is essentially no delocalization of the free electron into the twisted perchlorophenyl rings, but, because of the steric shielding, normal atom transfer reactions or radical combination reactions are strongly inhibited. While these radicals are remarkably inert to almost all reagents, they are

Perchlorinated triarylmethyl radical **117** combining perchlorotriphenylmethyl and bis(4-methoxyphenyl)amine moieties was used to study electron transfer and charge transfer properties. The absorption spectrum of this highly soluble compound was studied in 13 solvents.

The electronic coupling and the dipole moments of the ground and excited states were also determined.^{299,300}

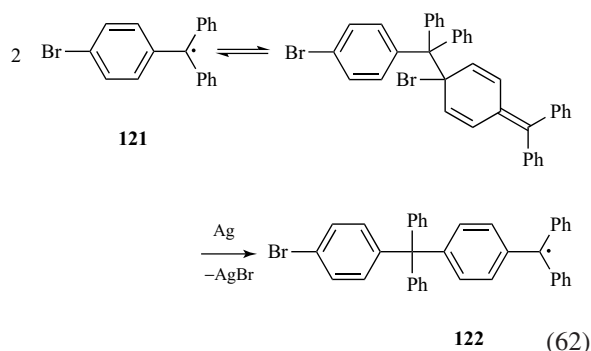
The dependence of the UV spectra of the transition from radical **118** to the zwitterion **119** was examined as the solvent composition was varied and the process changed from the normal to the inverted Marcus region (60).³⁰¹

which was captured as the peroxide.³⁰⁴ Similarly, 4-fluorophenyl(diphenyl)methyl chloride lost fluorine on treatment with silver, indicating the formation of an analogous radical,³⁰⁵ but halogens in the 3-position are inert under these conditions.³⁰⁶



Perfluorinated triphenylmethyl radical **120** was generated by the reduction of the corresponding carbocation, and gave an EPR spectrum measured in benzene (61).^{302,303}

Earlier studies of less substituted (4-halophenyl)diarylmethyl radicals indicated that these underwent dehalogenation upon the formation of unsymmetrical dimers. For example, reaction of 4-bromophenyl(diphenyl)methyl chloride with silver evidently proceeds with the formation of radical **121**, which after dimerization lost the allylic bromine forming **122** (62),



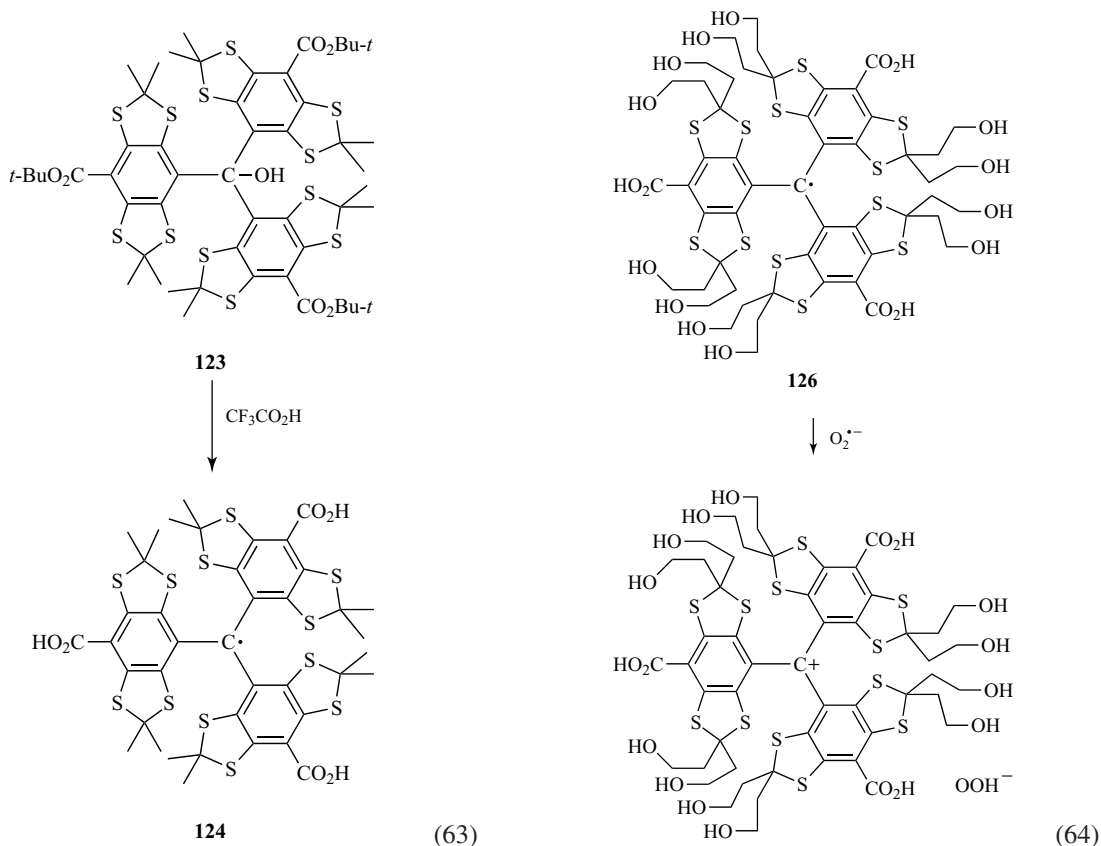
8.2 Tetrathiatriarylmethyl (TAM) or Trityl Triarylmethyl Radicals

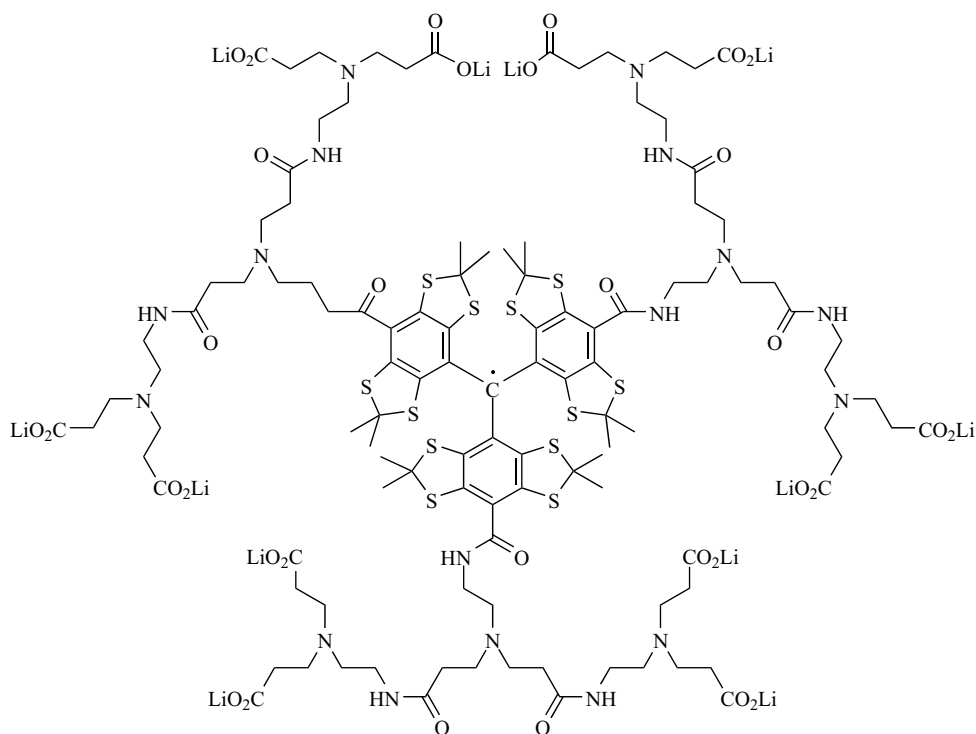
A recent development in the study of triarylmethyl radicals has been with tetrathiatriarylmethyl (TAM) trityl radicals which are finding extensive and increasing use in imaging applications using EPR spectroscopy because of their extraordinary stability in cells and tissues, narrow line widths resulting in high analytical resolution at concentrations in the micrometer range, and enhanced sensitivity to oxygen.^{307–315} These compounds and various structural variations were originally developed in industry for use as contrast agents in Overhauser magnetic resonance imaging (OMRI), and were first reported in the patent literature.³⁰⁹ Important characteristics of these materials are the narrow signals promoted by the absence of inhomogeneous hyperfine couplings. An earlier preparation of these compounds³¹⁰ has been improved by a convenient large-scale synthesis of **123** and the sodium salt

of **124** (known as *Finland trityl*).³¹¹ The radical **124** was formed in one step in quantitative yield by treatment of the tri(*tert*-butyl ester) **123** in neat trifluoroacetic acid at room temperature (63).³¹¹

These serve as dual-function pH and oxygen probes. Dendritic TAM molecules were prepared in which encapsulation of the radical by the dendrimer enhances their stability and solubility in water over a wide pH range, and the Cu(II) complex of **125** is a highly effective pH probe.³¹⁴

Another of these widely studied radicals is Oxo63 (**126**), which has been extensively derivatized for optimum properties.^{312,315} This reacts with superoxide ($O_2^{\cdot-}$) radicals, (64), and was used for the assay of superoxide by monitoring the newly formed product absorption peak at 546 nm, and gave good agreement with the widely used cytochrome *c* method of superoxide detection.³¹⁵





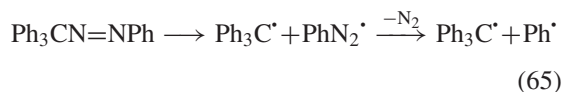
125

9 RADICAL PROCESSES

9.1 Free-Radical Initiators

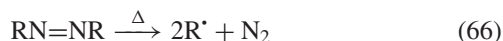
9.1.1 Azo Compounds (Diazenes) as Sources of Free Radicals

As described above, phenylazotriphenylmethane, (2), was used by Gomberg^{9,10} in the classic preparation of tetraphenylmethane. Wieland *et al.*, in 1922,⁴⁵ showed that $\text{Ph}_3\text{C}^\bullet$ (1) was formed in this reaction, and proposed phenyl radicals were formed as well (65).



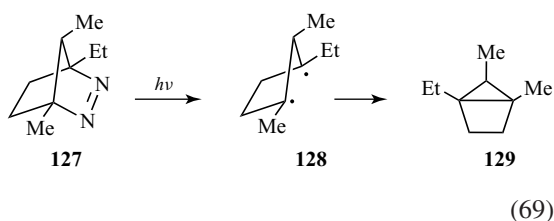
In the 1920s, kinetic studies by Ramsperger^{316–319} on the thermal reactions of azoalkanes demonstrated that substituent effects on both sides of the molecule could affect the ease of decomposition, implying

concerted reaction if suitably stable radicals could be formed, and were interpreted as showing that these reacted in one step to form two alkyl radicals and N_2 (66) (see **Overview of Radical Initiation**). However, later consideration of this reaction suggested that, for azomethane ($\text{R}=\text{CH}_3$), initial one-bond cleavage occurs.³²⁰ In 1933, Leermakers³²¹ used the Paneth mirror technique to demonstrate that methyl radicals were indeed generated upon pyrolysis of azomethane. Studies by two different groups in 1934 established that methyl radicals from azomethane abstract hydrogen from CH_3CHO in a chain reaction forming methane (67),^{322,323} and in 1938 it was found that during azomethane photolysis essentially all of the methyl radicals could be trapped by nitric oxide (68).³²⁴ Extensive further work on substituent effects in diazene reactions has been reviewed, including examination of polar, conjugative, and steric substituent effects.³²⁰



In 1998, Zewail and coworkers re-examined the decomposition of azomethane ($\text{CH}_3\text{N}_2\text{CH}_3$) with laser excitation at 310 nm and found the two C–N bond-breaking reactions to occur in separate steps on the femtosecond timescale, with detection of the intermediate $\text{CH}_3\text{N}_2^\bullet$.³²⁵ For studies of such fast reactions, Zewail was awarded the 1999 Nobel Prize in Chemistry.

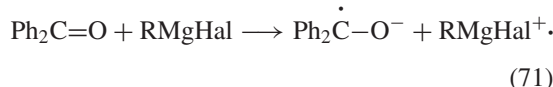
Photochemical denitrogenation of the stereolabeled diazabicyclo[2.2.1]heptene **127** leads to a mixture of inverted and retained bicyclo[2.1.0]pentane (housane) products, and the role of solvent viscosity in this reaction has been examined by Adam *et al.* and interpreted in terms of the frictional impediment (viscosity effect) on the bond rotation in the inversion of the diradical intermediate **128**, leading to the product **129** (69).³²⁶



9.2 Free-Radical Formation in Grignard Reactions

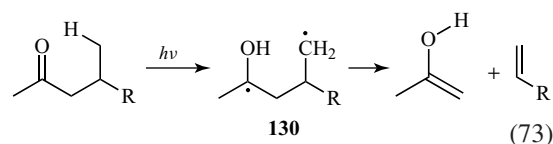
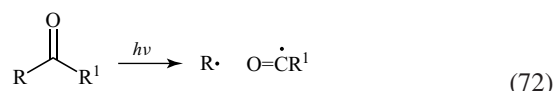
The formation of coupling and reduction products in the Grignard reactions of alkyl halides with magnesium led to the suggestion by Gomberg and Bachmann that free radicals are formed in these processes, (70),³²⁷ and this has been generally accepted.³²⁸ However, there has been a long and contentious debate as to the extent that the reactions of these radicals occur while adsorbed on the metal surface as opposed to freely diffusing through the solution and back to the metal surface.³²⁹ The reactions of Grignard reagents with carbonyl compounds have also been found to proceed by

single-electron transfer processes in some examples (71).^{330,331}

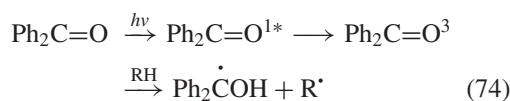


9.3 Photochemical Generation of Free Radicals from Ketones

The photolysis of ketones was suggested by Norrish *et al.*^{332,333} to involve the formation of free radicals, and this was confirmed by experiments in which metallic mirrors were removed.^{334,335} In the type I reaction, an initial cleavage of the C–C bond forming an acyl radical was suggested to occur upon photoexcitation, (72), and this can be followed by the loss of carbon monoxide giving a further alkyl or aryl radical (see **Synthetic Radical Photochemistry**). The type II cleavage involves the initial formation of a biradical intermediate **130**, (73), and was directly observed by Zewail and coworkers.³³⁶



The assignment of the excited state of benzophenone as a triplet biradical which could act as a sensitizer was made by Hammond and Moore in 1959, (74),³³⁷ and this led to a great surge in radical study using photochemical techniques. The role of photoexcited benzophenone as a diradical initiator for benzaldehyde oxidation was previously shown explicitly by Bäckström in 1934 (74).¹⁹⁷

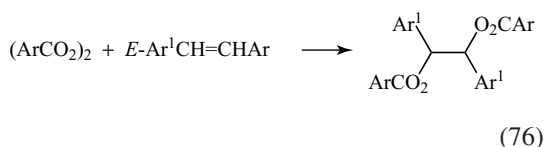


9.4 Induced Decomposition of Radical Initiators

The phenomenon of induced decomposition, in which radicals derived from reaction of the solvent (SH) with the initiator benzoyl peroxide consume some of the initiator, was elucidated by Bartlett and Nozaki, (75),^{338,339} and by Cass.³⁴⁰ These results helped in the elucidation of many of the difficulties in interpreting the results of reactions of radical initiators, as noted above.



The direct reaction of free radical initiators with nonradical substrates such as tertiary amines resulting in the formation of free radicals has also been observed.^{341–343} Other examples are the reaction of diacyl peroxides with alkenes, (76),³⁴⁴ and the reaction of hypochlorites with alkenes and alkynes.³⁴⁵



9.5 The Cage Effect

The cage effect, or the enhanced probability for recombination of two radicals formed in close proximity in solution with impediment to separation due to collisions with surrounding solvent molecules, was discussed by Franck and Rabinowitch in 1934,³⁴⁶ and Rabinowitch and Wood³⁴⁷ used a “pinball” illustration of this process (Figure 3). The theory of this reaction was further developed by Noyes.³⁴⁸

The effect of solvent viscosity on cage effects in solution was demonstrated in 1967 by Kiefer and Traylor (77).³⁴⁹ Thus the viscosity of the solvent had a major effect on the yield of di-*tert*-butyl peroxide formed from cage recombination of the *tert*-butoxy radical pair formed from thermolysis of di-*tert*-butyl peroxyoxalate (**131**). The efficiency of cage combination was also affected by the initial separation in the radical pairs formed from different

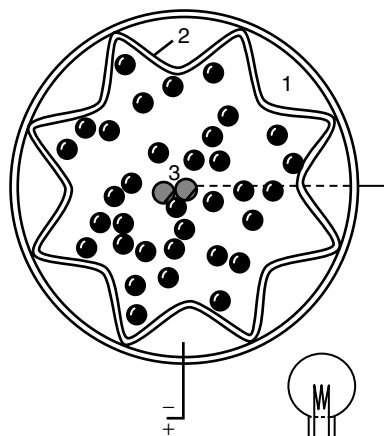
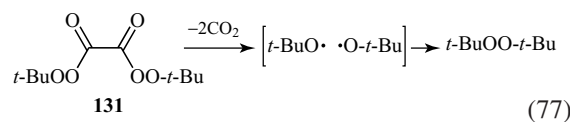


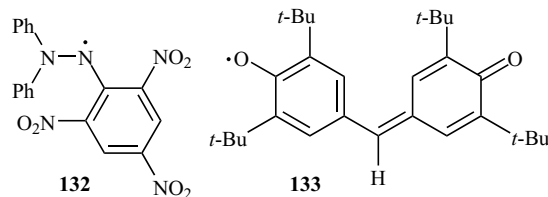
Figure 3 Apparatus for simulating the cage effect. [J. Franck and E. Rabinowitch, *Trans. Faraday Soc.*, 1934, **30**, 120–130. Reproduced by permission of The Royal Society of Chemistry.]

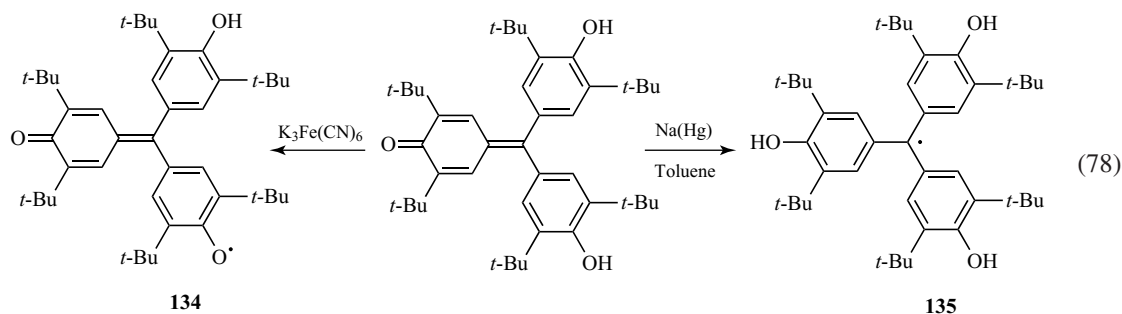
precursors. The effect of mass on cage recombination has also been shown, using organometallic radicals.³⁵⁰ Generation of radical pairs constrained in zeolites involve “supercages”, as investigated by Turro *et al.*^{351,352}



9.6 Free-Radical Inhibitors: DPPH and Galvinoxyl

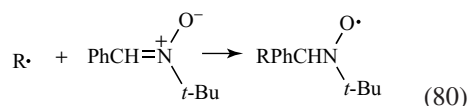
The stable free radical diphenylpicrylhydrazyl (**132**) was first prepared by Goldschmidt and Renn in 1922,³⁵³ and this³⁵⁴ and galvinoxyl (**133**)³⁵⁵ have frequently found application as radical scavengers in kinetic studies.³⁵⁶ The triaryl analogs **134** and **135** of **133** have also been generated by oxidation–reduction processes (78).³⁵⁷





9.7 Spin Trapping

The additions of transient radicals to nitroso compounds, (79)^{358,359} and to nitrones, (80),³⁶⁰ were found to form stable nitroxyl radicals, and these may be conveniently detected by ESR for the identification of the transient radicals. This technique has been extensively applied in chemical and biological systems.^{361–367}

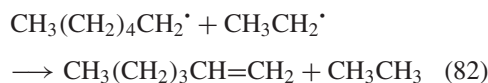
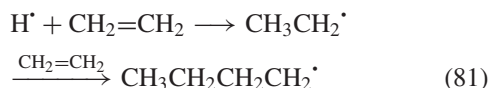


The name “spin trapping” was coined by Janzen,³⁶³ and derives from analogy with the use of stable nitroxyls as “spin labels” or “spin probes,” (see **Spin Labels and Spin Probes**), which provide spectroscopic information regarding their microscopic environment, a procedure pioneered by McConnell *et al.*³⁶⁸

9.8 Free-Radical Polymerization

Taylor³⁶⁹ in 1926 demonstrated that hydrogen atoms generated by the mercury-sensitized photodecomposition of hydrogen gas add to ethylene to form ethyl radicals, which were proposed to react with H_2 to give the observed ethane and another hydrogen atom. Evidence that polymerization could occur by free-radical reactions

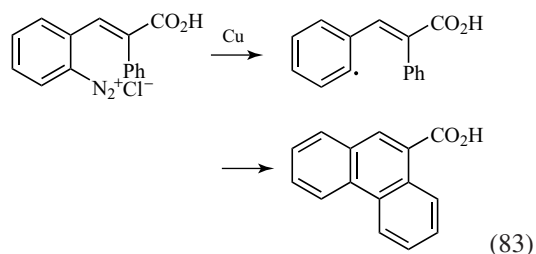
was found by the observation that ethyl radicals formed by the gas-phase pyrolysis of diethylmercury or tetraethyllead initiated the polymerization of ethylene,³⁷⁰ and this process was extended to the solution phase by Cramer (see **Kinetics of Polymerizations and Basic Concepts on Radical Chain Reactions**).³⁷¹ The mechanism, (81), (with participation by a third body) was presented for the reaction,^{369,370} which is in accord with current views, and a mechanism, (82), was shown for disproportionation. Staudinger in 1932 presented a mechanism for free-radical polymerization of styrene,³⁷² but just as did Rice and Rice in 1935,⁵⁸ showed the radical attack on the most substituted carbon (anti-Markovnikov attack). The correct orientation was shown by Flory in 1937.³⁷³ In 1935, Rice and Sickman reported that ethylene polymerization was also induced by methyl radicals generated from thermolysis of azomethane.³⁷⁴



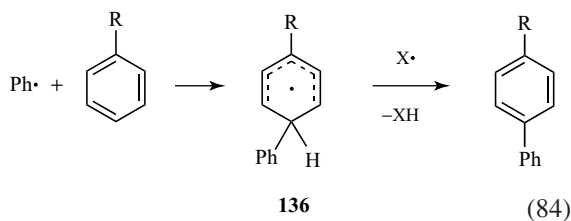
9.9 Free-Radical Aromatic Substitution

There are a number of processes for free radical substitution in aromatic systems, including the Pschorr

reaction, that involve intramolecular cyclization of an aryl radical with a side chain aryl group (see **Radical Arylations**). This was reported in 1896, although its radical character was not yet recognized (83).³⁷⁵



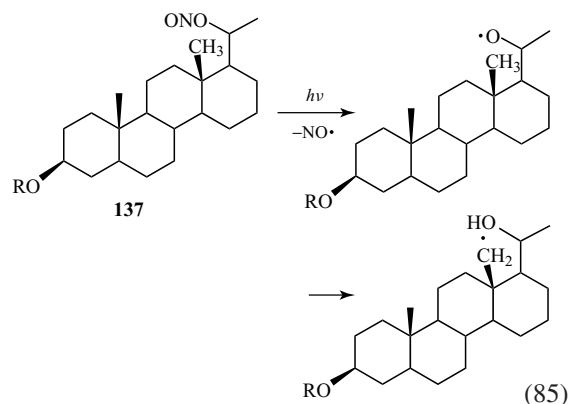
The formation of phenyl radicals by the thermolysis of diacyl peroxides was proposed by Hey, Waters, and coworkers,^{237,376} and these were proposed to give free-radical aromatic substitution via intermediate **136** (84). This mechanism was also applied to the formation of biaryls from diazonium ions in benzene,³⁷⁷ a conversion now known as the *Gomberg–Bachmann reaction*. Initially, such free radical substitutions on aromatic rings were suggested^{237,376} to involve displacement of hydrogen atoms, but it is currently accepted that these reactions are much more likely to involve intermediates from which hydrogen is abstracted by another radical (84). Kinetic and mechanistic studies of free-radical reactions of halogens with aromatics were also studied, as noted above.^{232,233}



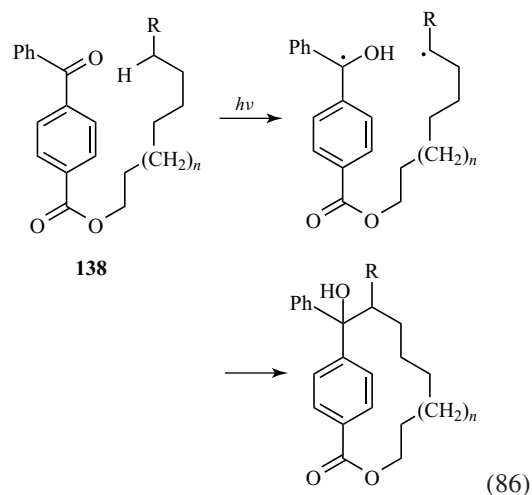
9.10 Remote Radical Functionalization

It was shown by Barton *et al.*³⁷⁸ that the photolysis of steroidal nitrites **137** proceeding by formation of alkoxy radicals could result in hydrogen abstraction from suitably situated methyl groups forming carbon-centered radicals which then reacted with the

nitric oxide generated to give oximes (85) (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**). This permitted the functionalization of the unactivated centers.



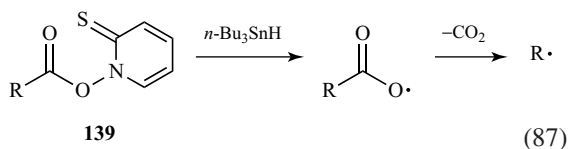
A comparable functionalization of remote centers was achieved by Breslow and Winnik,³⁷⁹ in which photolysis of hydrocarbons with a benzophenone moiety attached by a tether of suitable length (**138**) resulted in abstraction of hydrogen by the excited benzophenone from the hydrocarbon chain. This achieved functionalization of the hydrocarbon chain (86).



9.11 PTOC Esters

Pyridine-2-thione-*N*-oxycarbonyl (PTOC) derivatives of carboxylic esters **139** were developed by

Barton *et al.*, and serve as a convenient source of carboxy radicals, which upon decarboxylation provide specific routes to free radicals (87).^{380,381} This process can also proceed by a chain reaction. Acyl radicals also find many uses, and this has been reviewed.³⁸²



10 CONCLUSION

The history of free radicals in chemistry involved an uncertain beginning, and then two decisive moments arrived, when first triarylmethyl and then unstabilized aliphatic radicals became well-recognized intermediates. Then followed a sustained development of the subject, with some missteps, but free-radical chemistry is thriving today with a seemingly unlimited future. It is noteworthy that the two leading pioneers, Gomberg and Paneth, did not receive the Nobel Prize, while others such as Wieland, Ziegler, and Barton received the Prize for unrelated work, and individuals such as Zewail, Herzberg, Flory, Norrish, and Porter, who built on the original discoveries, were recognized for their later discoveries. It may be expected with confidence that further remarkable discoveries are still to come.

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Supramolecular Radical Chemistry

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1 INTRODUCTION

Supramolecular chemistry refers to the area of chemistry of "multicomponent" molecular assemblies in which the component structural units are typically held together by a variety of weak (non-covalent) interactions.¹ While traditional chemistry focuses on the covalent bond, supramolecular chemistry examines the weaker and reversible non-covalent interactions between molecules. These forces include hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π - π interactions, and electrostatic effects. Important concepts that have been demonstrated by supramolecular chemistry include molecular self-assembly, folding, molecular recognition, host-guest chemistry, mechanically interlocked molecular architectures, and dynamic covalent chemistry.¹

It must be underlined that supramolecular concepts have not aroused too much interest so far in the community of radical chemists. This is a logical consequence of the common idea that the reactivity and spectroscopic properties of free radicals cannot be significantly modified by weak forces such as those involved in supramolecular chemistry. A typical range for supramolecular intermolecular interaction comprises between circa 10 kcal mol^{-1} and much less than kT (circa 1 kcal mol^{-1}). In spite of the small value of these forces, it has been shown that, under specific conditions, they can control the reactivity of a free radical in an unexpected manner.

This article describes both the application of the concepts of supramolecular chemistry to control the

reactivity of organic free radical and how electron paramagnetic resonance (EPR) methods (see **Analysis of Radicals by EPR**) have been extensively used for detecting and identifying noncovalent assemblies in solution and for clarifying their structure and properties. Because of the many topics covered by supramolecular chemistry, this article describes only selected works that appeared in the literature. The readers are invited to consult review papers cited in this work to get a complete picture on each topic.

2 HYDROGEN BONDING

Hydrogen-bonding effects are important in modulating free radical properties. In spite of the tiny value of this force (a typical value for an individual intermolecular hydrogen bond is circa $4\text{--}6 \text{ kcal mol}^{-1}$),² it has been shown that it can control the spectroscopic, thermochemical, and kinetic properties of free radicals in a spectacular manner. In particular, oxygen-centered radicals are known to significantly change their properties on formation of a hydrogen-bonded complex on the oxygen atom retaining the unpaired electron.

The first successful EPR detection in a solution of a hydrogen-bonded radical complex showing hyperfine coupling with the hydrogen-bonded protons has been reported by Fukuzumi *et al.* in 2007 for a semiquinone radical anion deriving from 1-(*p*-tolylsulfanyl)-2,5-benzoquinone (TolSQ) hydrogen bonded with a protonated

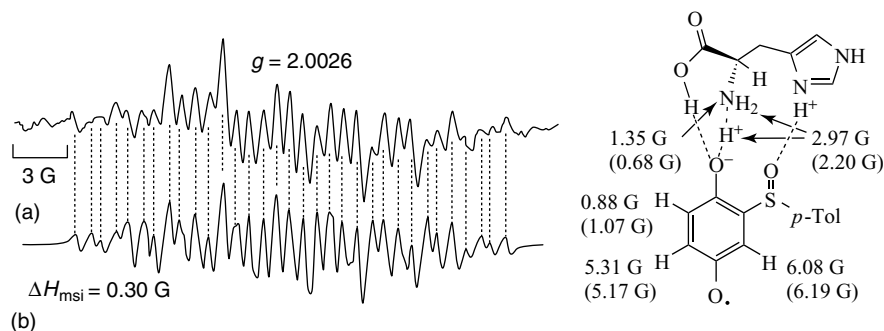
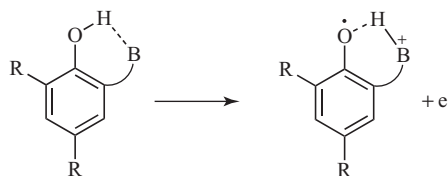


Figure 1 (a) EPR spectrum of TolSQ^{•-}/His·2H⁺ recorded in the presence of histidine and HClO₄ in deaerated MeCN at 298 K. (b) Spectrum simulated with the hfsc values of TolSQ^{•-}/His·2H⁺. [Yuasa *et al.* (2007). Ref. 3. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.]

histidine (His·2H⁺).³ The EPR spectrum of such hydrogen-bonded complex (TolSQ^{•-}/His·2H⁺) was detected after photoinduced electron transfer (ET) from 10,10'-dimethyl-9,9'-biacridine to TolSQ in the presence of His·2HClO₄ in acetonitrile at 298 K.⁴ The EPR spectrum is well reproduced by a simulated spectrum with hyperfine splitting constant (hfsc) values of $a_{3H} = 0.88$, 5.31, and 6.08 G and superhyperfine splitting due to one nitrogen atom and three equivalent protons ($a_N = 1.35$ G and $a_{3H} = 2.97$ G) of His·2H⁺ (Figure 1). Hydrogen bonds are found between the C=O oxygen atom of TolSQ^{•-} and the COOH proton as well as the NH₃⁺ protons of His·2H⁺, and also between the S=O oxygen atom of TolSQ^{•-} and the NH⁺ proton of the imidazole ring of His·2H⁺. Complete agreement of the observed EPR spectrum with the simulated spectrum (Figure 1) was considered as a clear indication of the formation of the TolSQ^{•-}/His·2H⁺ complex. Actually, the g value and the hfsc values of TolSQ^{•-}/His·2H⁺ are drastically changed from those of TolSQ^{•-} in the absence of His·2H⁺, which are $g = 2.0057$ and $a_{3H} = 2.00$, 2.20, and 3.35 G.

The strong hydrogen bonding between TolSQ^{•-} and His·2H⁺ is also responsible for the significant increase in the electron acceptor ability of TolSQ. Similar effects of hydrogen bonding on E_{red} of quinones have been previously reported.^{5–8}

Oxidation of phenols is facilitated by the presence of a proton-accepting group such as an amine, forming a hydrogen bond in the corresponding phenoxyl radical: these phenols (Scheme 1), having a pendant hydrogen-bonded base, are characterized by lower redox potentials with respect to other phenols.^{9–14}



Scheme 1 Oxidation of a phenol with a pendant base group.

The product of chemical and quasi-reversible electrochemical oxidations in each case is the phenoxyl radical in which the phenolic proton was transferred to the base, 'OAr-BH⁺, through a proton-coupled electron transfer (PCET) process and is hydrogen bonded to the oxygen atom retaining the unpaired electron.

Phenoxyl radicals are also known to change their thermochemical properties on formation of a hydrogen-bonded complex on the oxygen atom retaining the unpaired electron. In phenols, the O–H bond dissociation enthalpy, which in hydrogen-bond-accepting solvents (HBA) is larger than in hydrocarbons due to the preferential stabilization of the starting phenol with respect to the phenoxyl radical (see **Antioxidants in Chemistry and Biology**), is lowered in the presence of hydrogen-bond-donating (HBD) solvents because they preferentially stabilize the phenoxyl radical (Figure 2). For example, in the presence of strong HBD solvents such as 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP), the preferential stabilization of the phenoxyl radical results in a decrease in the measured BDE(O–H) in the *p*-methoxy phenol of about 1 kcal mol⁻¹.¹⁵

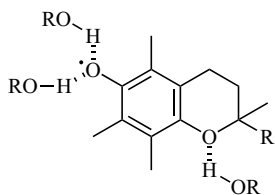
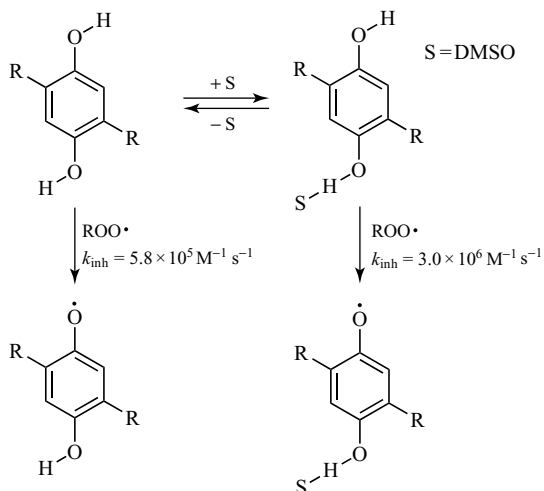


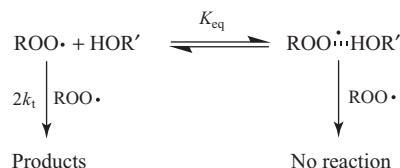
Figure 2 Hydrogen bonded α -tocopheroxyl radical.



Scheme 2 Reaction scheme for the reaction between a model hydroquinone and peroxy radicals in the presence of small amounts of DMSO.

The different strengths of the hydrogen bonds formed in the parent phenol and in the phenoxyl radical are also responsible for the unexpected reactivity increase of a model hydroquinone toward free radicals upon the addition of small amounts of HBA solvents.¹⁶ Actually, it has been observed that the addition of small amounts of DMSO results in a five times increase in the rate constant for the reaction of 2,5-di-*tert*-amylhydroquinone with peroxy radicals for the complexed hydroquinone with respect to the free hydroquinone. This behavior has been explained quantitatively in terms of the different strengths of the hydrogen bonds formed in the parent phenol and in the phenoxyl radical between the solvent and one of the hydroxyl groups (Scheme 2).

Complexation by HFP of phenoxyl radicals has important effects also on their persistency. Actually, the intensity of the EPR spectra is generally higher in the presence of the fluorinated alcohol, this effect



Scheme 3 Reaction scheme describing the kinetic solvent effects for the self-decay of secondary peroxy radicals observed in the presence of a strong hydrogen bond donor.

being particularly evident in the case of the radical derived from α -tocopherol, which is detectable by EPR at room temperature for several hours.¹⁵ Because the decay of α -tocopheroxyl radicals takes place by a bimolecular disproportionation reaction, to occur in the presence of HFP it requires the desolvation of at least one radical molecule with a consequent reduced reactivity. This behavior is similar to that found for the α -tocopheroxyl radical in the presence of magnesium ions by Nakanishi *et al.*¹⁷

Fluorinated alcohols such as HFP have also a significant effect on the persistency of peroxy radicals. Actually, the formation of a hydrogen-bonding complex between HFP and secondary peroxy radical resulted in a large increase in the lifetime of these radicals.¹⁸ This variation was accompanied by a decrease in the corresponding EPR *g*-value. The progressive reduction in the rate of termination by peroxy radical as the concentration of HFP increased was explained by invoking the simple kinetic model advanced by Ingold and coworkers to justify the solvent effect observed in the rate of hydrogen abstraction from phenol by alkoxy radicals (see Scheme 3 and **Antioxidants in Chemistry and Biology**).¹⁹

According to this model, EPR decay traces are due to the self-reaction of non-hydrogen-bonded peroxy radical in rapid equilibrium with nonreactive hydrogen-bonded radicals. Analysis of decay traces in the presence of different amounts of HFP afforded K_{eq} . From the measure of K_{eq} at different temperatures, an enthalpy change of $-3.4 \text{ kcal mol}^{-1}$ was estimated for the formation of the hydrogen-bonded complex.

Further, nitroxide radicals are good hydrogen-bonding acceptors.²⁰ This favorable property has been used to modulate their reactivity in nitroxide-mediated living polymerization (NMP; see **Nitroxide-Mediated Polymerization and its Applications**).²¹

For other examples describing the effect of hydrogen bonding on radical reactivity, see **Thermochemistry and Hydrogen Transfer Kinetics**, **Antioxidants in Chemistry and Biology**, and **Nitroxide-Mediated Polymerization and its Applications**.

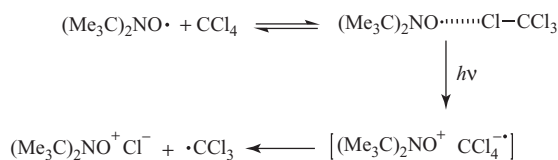
3 HALOGEN BONDING

The hydrogen atom is the most common electron acceptor site, and hydrogen bonding is the most frequently occurring noncovalent interaction in chemical and biological processes. Halogen atoms work equally well as acceptors and the interaction, which they give rise to, is characterized by several properties similar to those of the hydrogen bond.^{22–24} The term halogen bond (XB) is generally used for defining such noncovalent interactions involving halogens as electron acceptors. The general scheme $D \cdots X-Y$ thus applies to XB, in which X is the halogen (Lewis acid, XB donor), D is any electron donor (Lewis base, XB acceptor), and Y is carbon, nitrogen, halogen, etc.: halogen bonding to different XB donors can show a strength comparable to hydrogen bonding (in terms of equilibrium constants and other thermodynamic parameters).

Interest in molecular magnetic materials and emerging fields such as spintronics and quantum computing has inspired the study of X-bonding for directing the self-assembly of persistent nitroxide radicals to create supramolecular arrays with particular spin orientations.²⁵

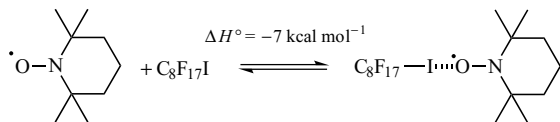
Morishima *et al.* provided the earliest reports of the interactions between nitroxides and halogenated molecules, describing the effect of the radicals on the NMR chemical shifts of halogenated molecules.^{26–28} The interaction was explained in terms of a spin delocalization, or charge-transfer interaction, with the assistance of molecular orbital calculations. In 1990, Ingold and coworkers reported the observation of charge-transfer absorption bands when nitroxides were dissolved in polyhalogenated solvents.²⁹ Laser irradiation at wavelengths within these bands ‘instantaneously’ yields the corresponding oxoammonium halide and a carbon-centered radical via a photoinduced electron transfer followed by the loss of a halide ion (Scheme 4).

More recently, complexes of chlorine dioxide with piperidine nitroxides have been reported.^{30,31} In all cases, it is reasonable to hypothesize the



Scheme 4 Reaction scheme for the photodecomposition of the halogen-bonded complex between a dialkyl nitroxide and a CCl_4 .

formation of XB pre-reactive complexes that spontaneously undergo electron transfer and transform into oxoammonium salts. A crystallographic and magnetic study of 2-halo-substituted nitronyl nitroxides³² provided the first direct observation of $\text{O} \cdots \text{I}$ distances consistent with nitroxide X-bonding, although this term was not used to describe the interaction. Similarly, one of the two polymorphs of 4-(4-iodobenzylidenamino) TEMPO was reported to exhibit structural characteristics consistent with X-bonding and antiferromagnetic behavior.³³ Schollhorn *et al.* recently described the first deliberate investigation of nitroxides as X-bond acceptors, reporting the single-crystal X-ray analysis of a one-dimensional coordination polymer in which the dominant intermolecular forces are XB, involving the nitroxide radical 4-amino-TEMPO.³⁴ This report was rapidly followed by an EPR study of X-bonding between TEMPO and aliphatic and aromatic iodoperfluorocarbons in solution.³⁵ Formation of an X-bonded TEMPO was manifested primarily as an increase in the isotropic nitrogen hyperfine coupling a_N and by the marked broadening of the EPR lines observed when the nitroxide spectra were recorded in iodoperfluorocarbon solvents. As expected, these effects were greater for iodoperfluorocarbons than for bromoperfluorocarbons and iodocarbons. On formation of the XB, the unpaired spin density is in part transferred from the nitroxide moiety to the iodine atom, and at the same time, its delocalization on the nitrogen atom increases, giving rise to an increase in the nitrogen splitting. The origin of the line broadening may result either from unresolved iodine (^{127}I ; $I = 5/2$) hyperfine coupling or/and an increase in the rotational correlation time, a consequence of the increased hydrodynamic radius of the X-bonded nitroxide species. A ΔH^0 value of -7 kcal mol^{-1} was measured for the formation of the TEMPO/*n*- $\text{C}_8\text{F}_{17}\text{I}$ complex (Scheme 5).



Scheme 5 ΔH° value for the formation of the TEMPO/*n*-C₈F₁₇I complex.

DFT and MP2 calculations have subsequently been utilized to investigate the physicochemical properties^{36,37} of X-bonded adducts of TEMPO, including interesting deshielding effects consistent with spin transfer observed in the ¹⁹F NMR spectra of TEMPO/haloperfluorocarbon systems.³⁷

More recently, Micallef and coworkers investigated the EPR behavior in the presence of pentafluoriodobenzene of another class of nitroxide radicals: the isoindoline nitroxides.³⁸ Also in this case, the EPR spectrum obtained in the X-bonding donor solvent exhibited a dramatic increase in the spectral line width.

All these studies clearly demonstrated that persistent nitroxides are effective electron donors for the formation of halogen bonds with iodoperfluorocarbons. It is expected that in the near future other classes of persistent radicals will be investigated in order to design and synthesize functional molecular materials with potential application in the fields of molecular magnetism (see **Physical Properties of Thiazyl Radicals Toward Conductive and Magnetic Materials**), spintronics, and quantum computing.

4 HOST-GUEST COMPLEXES

The substantial change in NMR shieldings that one usually observes upon formation of host-guest complexes is the major reason why this technique has become by far the most important method for the characterization of such complexes.³⁹ A limitation of NMR is that it operates at rather low frequencies and possesses a relatively slow “time scale”. In the case of fast exchange, which is most common for host-guest complexes, one observes only one sharp signal at an intermediate mean-weighted position between the signals of free and complexed molecules.

On the other hand, EPR spectroscopy, which is usually characterized by a shorter time scale compared to that of complexation processes, gives

rise to separate signals from free and complexed species when the radical used as a probe shows different spectroscopic parameters upon complexation.⁴⁰ In this way, it is possible to extend the time range accessible to resonance methods of supramolecular chemical kinetics into the microsecond region⁴¹ and to create a possibility of discriminating different modes of complexation, leading to usually indistinguishable (by NMR) microequilibria.

The inclusion of radicals by host systems has been studied from time to time by EPR spectroscopy during the last 40 years. The majority of these reports have been concerned with very persistent species such as sterically protected nitroxides or aromatic radical ions. Different types of water-soluble host molecules (Figure 3) such as cyclodextrins,^{42–54} calixarenes,^{55–61} cucurbiturils,^{62–66} cryptophane,⁶⁷ and octamethoxy-*p*-cyclophane⁶⁸ were investigated.

Evidence for the formation of a complex between nitroxide radicals and host species is generally obtained on the basis of the changes of the hyperfine *a*_N coupling constants. For a dialkyl nitroxide, the isotropic nitrogen hfsc (comprised between 13.5 and 18 G) is known to be very sensitive to the nature of the environment: the greater the polarity⁶⁹ and/or the hydrogen-bonding capability of the medium²⁰ the more favoured will be the dipolar structure, bearing larger electron density on the oxygen and spin density on the nitrogen atom (Figure 4).

The partitioning of nitroxide probes in the hydrophobic environment of the host gives rise to a reduction in the value of nitrogen splitting, with the result that the resonance fields for the free and included species are significantly different from those of the nitroxide dissolved in water. Double integration of the two EPR signals affords equilibrium constants for the formation of the complex.

From the analysis of spectroscopic parameters of the included species, it was also possible to distinguish different geometries of inclusion. Such a discrimination was accomplished for the inclusion of the diphenylmethyl *tert*-butyl nitroxide into β -cyclodextrin by Kotake and Janzen.^{70–73} The EPR spectrum, recorded in the presence of β -CD, showed three different signals with different hyperfine splittings that were assigned to the radical in water and to the radical included in the cavity of the CD either from the phenyl side or from the *tert*-butyl side.

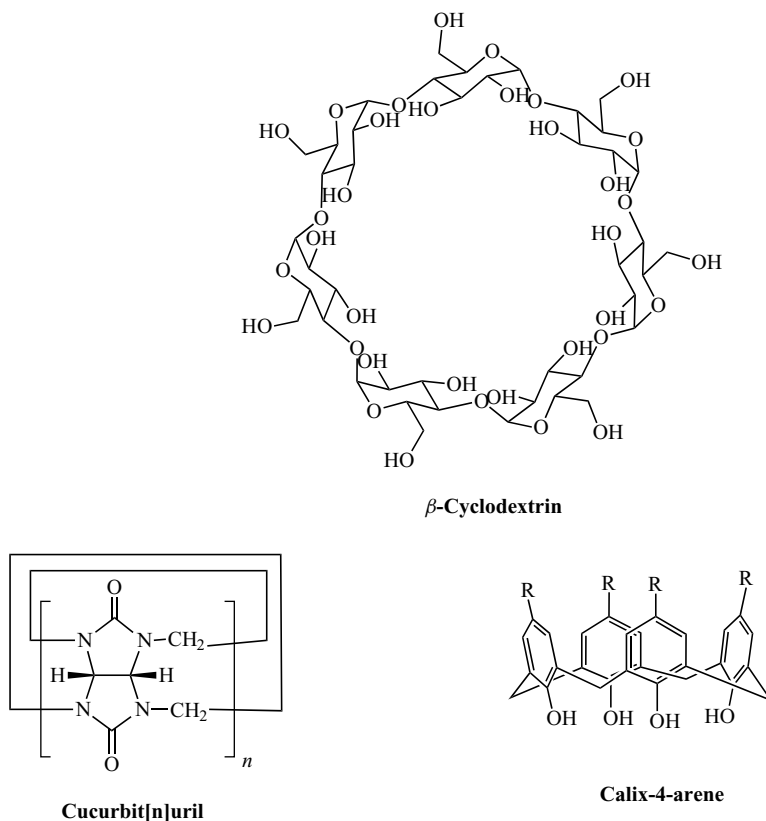


Figure 3 Some of the macrocyclic hosts investigated by EPR.

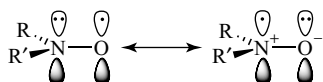


Figure 4 Resonance structures of dialkyl nitroxides.

By using the symmetric di-*tert*-amyl nitroxide, it was possible to demonstrate the formation of supramolecular structures with a higher level of organization in which the radical guest is able to template the formation of a complex with two molecules of β -cyclodextrin.⁷⁴

The persistence of the radical species made it possible to switch reversibly from 1:1 to 1:2 complexes many times by repeated acid–base treatments (as depicted in Figure 5) or by changing the temperature without occurrence of any side reaction. These 1:2 complexes represented the first examples of three-component, organic free radical

supramolecular entities, which can be reversibly formed by changing pH or temperature.

Benzyl *tert*-butylnitroxide and related nitroxides (reported in Figure 6) deserve a special mention. These radical probes, in the presence of different hosts, afforded easily including complexes, as indicated by the decrease in the nitrogen hyperfine splitting, a_N (due to the less polar environment of the host cavities), and from the change in the coupling to the benzyl protons, $a_{2H\beta}$ (due to conformational changes upon complexation).

Moreover, inclusion created a significant difference in the resonance field of the wing lines of each β -proton triplet ($M_1(H_\beta) = \pm 1$) of the included and free species with all kinds of host systems so far investigated, and in many cases the EPR spectra showed a strong linewidth dependence on temperature, indicating that the lifetime of formation and dissociation of the supramolecular complexes is in the range characteristic of the EPR spectroscopy.

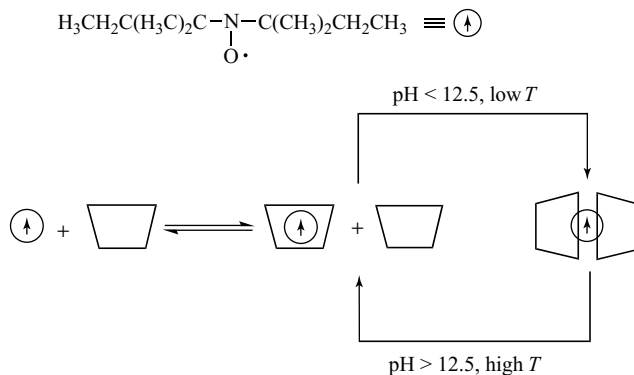


Figure 5 Schematic representation of the equilibria taking place in the presence of di-*tert*-amyl nitroxide and β -cyclodextrin.

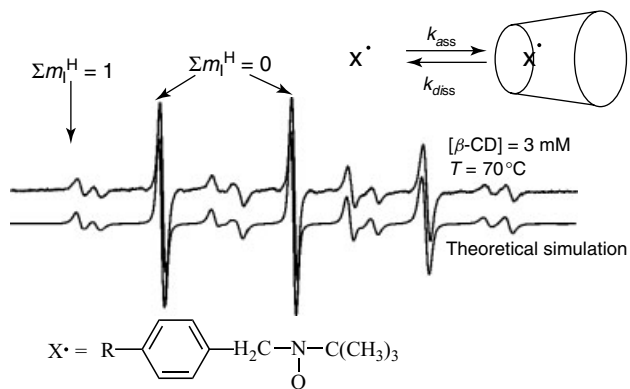


Figure 6 Schematic representation of the equilibrium taking place in the presence of β -cyclodextrin and EPR spectrum of benzyl *tert*-butyl nitroxide recorded in water in the presence of β -cyclodextrin with the corresponding theoretical simulation.

This favorable feature enabled measurement, by EPR, of the rate constants for the complex association (k_{ass}) and dissociation processes (k_{diss}) with different host systems.^{56,62,75–79}

In order to expand the use of EPR to study complexes of CDs with diamagnetic molecules, persistent nitroxide units have been covalently attached to cyclodextrin rims (Figure 7).^{80–84} In general, the aqueous solutions of spin-labeled CDs show typical nitroxide EPR spectra with the high field line broadened owing to restricted tumbling. Although the EPR parameters of these materials are not very sensitive to the complexation of small molecules, the formation of large host–guest complexes leads to substantial reduction in the rate of tumbling.

Spin-labeled CD containing two 4-carboxy-TEMPO groups attached to adjacent glucose units

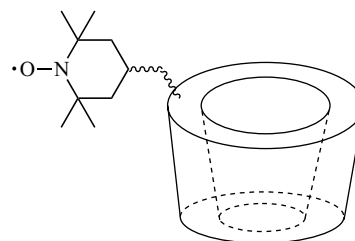


Figure 7 Schematic representation of a spin-labeled cyclodextrin.

or separated by two glucose units have also been reported and characterized by EPR.⁸⁵

Quite recently, spin trapping experiments have been performed in the presence of cyclodextrins or cucurbiturils.⁸⁶ A significant enhancement in adduct stability and a partial protection against glutathione peroxidase- and ascorbate anion-induced

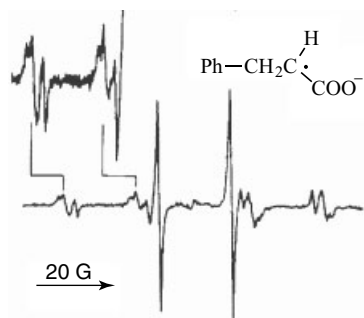


Figure 8 EPR spectrum of the reported α -carboxyl radical in the presence of 2-hydroxyl- β -cyclodextrin. [Lucarini *et al.* (1996). Ref. 87. Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/CC9960001577>.]

reduction are generally observed. The reader is invited to consult **Spin Labels and Spin Probes** for a complete discussion on this topic.

Although the majority of host–guest systems have been concerned with very persistent radicals, inclusion inside CD cavity of transient carbon-centered radicals as that shown in Figure 8 has been reported by using EPR spectroscopy.⁸⁷ This radical was generated in aqueous solution, using the flow technique, in which the solution passes through the microwave cavity about 60 ms after mixing the reagents. In the presence of CDs, the spectra of all radical species showed additional signals, which were assigned to the species included in CD.

Inspection of spectral parameters of the radical inside the hydrophobic cavity of CD shows that the values of the benzyl proton splitting, a_{2H} , of the included (27.9 G) and free species (23.1 G) are considerably different. These data demonstrate that inclusion leads to changes in the conformation adopted by the radical as reflected by the change in the hyperfine splitting of the hydrogen β atoms to the radical center, whose magnitude depends on the conformation adopted by the

radical. In general, the changes in conformation and unpaired-electron distribution that accompany inclusion of a transient radical could have significant effects on the regio- and stereochemistry of intramolecular reactions of guests, as compared with the same reaction of unbound radicals. With the only exception of a paper by Fukunishi *et al.* showing that inclusion inside cyclodextrin cavity promotes radical cyclization of *o*-(2-propenyloxy)- and *o*-(2-propynyloxy)benzenediazonium ions,⁸⁸ the monomolecular reactivity of free radicals inside cyclodextrins remains totally unexplored. However, it should be kept in mind that under free radical conditions the potential for a number of different cyclodextrin radicals to be formed exists and thus CDs cannot be treated as inert hosts.^{89–91}

Encapsulation inside the cavity of cucurbiturils or cyclodextrin can be used to increase the stability of aromatic radical cations. It has been shown by UV–Vis absorption, EPR, and electrochemical measurements that encapsulation by cucurbit[7]uril increases the thermodynamic and kinetic stability of the radical cation of the oligoaniline reported in Figure 9.⁹²

The stabilization is even more pronounced when many cucurbituril macrocycles are introduced onto a long radical cation polyaniline chain. This complexation leads to a slower attenuation rate and a smaller attenuation ratio of the radical cation, as well as lower first oxidation and reduction potentials compared to those of free polyaniline.⁹³

The effect of methylene blue (MB, Figure 10) encapsulation in cucurbit[7]uril on triplet excited-state behavior and singlet oxygen (1O_2) generation has also been recently studied by using laser flash photolysis and time-resolved near-IR luminescence spectroscopy. The lifetime of the triplet excited state of MB is longer in the cucurbit[7]uril cavity with respect to aqueous MB. Cucurbituril also protects the dye triplets from

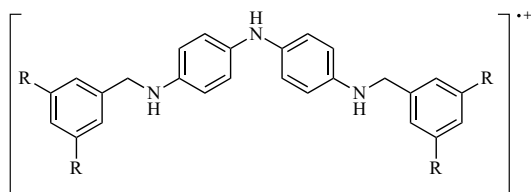


Figure 9 Radical cation deriving from a polyaniline.

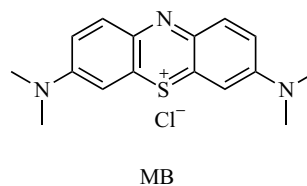


Figure 10 Structure of methylene blue (MB).

quenching by oxygen, reducing the quenching rate constant of circa one order of magnitude (from 2.6×10^9 to $0.2 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$).⁹⁴

5 SELF-ASSEMBLY

5.1 Self-Assembled Radicals

Self-assembly is generally defined as “the spontaneous and reversible organization of molecular units into ordered structures by noncovalent interactions”.⁹⁵ Because of these weak noncovalent interactions the amount of energy required for forming or destroying self-assembled structure is relatively small when compared to covalent interactions. Thus, one important feature of supramolecular self-assembly is its dynamic nature, which permits the preparation of functional materials, the physical properties of which can be reversibly modified by the action of appropriate external stimuli such as light or temperature.

Organic radicals that have no particular intermolecular interaction can be accommodated by self-assembled processes to give ordered structures in which two or more radical centers are enforced to be close to each other, inducing spin–spin interactions. Since in a self-assembled polyradical, the geometry of the radicals is fixed only by weak noncovalent interaction, in principle, the spin–spin interaction can be tuned and controlled by external stimuli.

Self-assembled polyradicals with unpaired electron spins in their frameworks have been prepared only very recently. This is mainly because of difficulties in introducing stable organic radicals at the core of the host frameworks. Fujita and coworkers reported the self-assembly of a radical cage containing multiple spin centers around a cavity suitable for guest inclusion.⁹⁶ They showed that persistent verdazyl radicals quantitatively self-assembled into the large spin cage shown in Figure 11 upon treatment with a Pd(II) complex. Similar to diamagnetic cages based on the triazine-cored complexes,⁹⁷ the reported spin cage is capable of binding neutral guests within the cavity in aqueous media.

A different example of open-shell moieties ordered by a supramolecular architecture showing new magnetic properties and based on lipophilic guanosines has been reported.^{98,99} Lipophilic

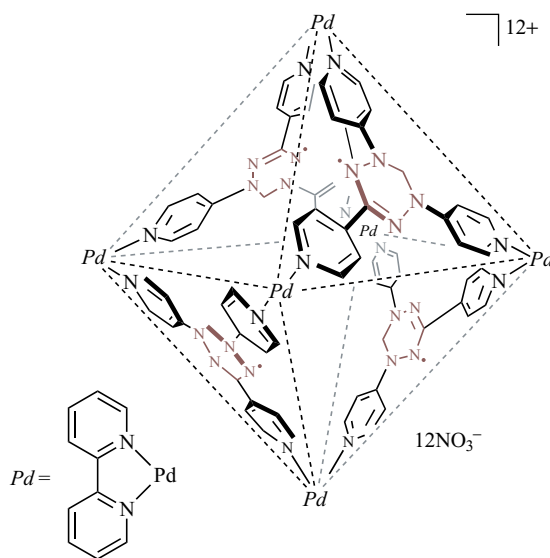


Figure 11 Self-assembled verdazyl-based spin cage.

guanosines are very versatile self-assembling units. In the presence of alkali cations, they spontaneously self-associate to give quartet-based columnar structures.¹⁰⁰ As it is possible to functionalize the guanosines in the eighth position and/or at the sugar hydroxy functions, they are ideal scaffolds to locate functional units in pre-programmed positions, inside highly ordered architectures. Graziano *et al.* showed that in the presence of K^+ , guanosine derivatives containing the persistent radical unit 4-carbonyl-2,2,6,6-tetramethylpiperidine-1-oxyl are able to self-assemble to give octameric species showing strong spin–spin interactions (Figure 12). Interestingly, it is possible to reversibly switch between discrete quartet-based assemblies and octamers by simply adding or removing metal cations. In this way, it is possible to reversibly control the intermolecular spin–spin interactions (Figure 12).

5.2 Spin Label to Investigate the Properties of Self-Assembled Monolayers Protecting Gold Nanoparticles

One of the most important nanosized materials is represented by metal nanoparticles (NPs) in the form of colloids and nanocrystals that are

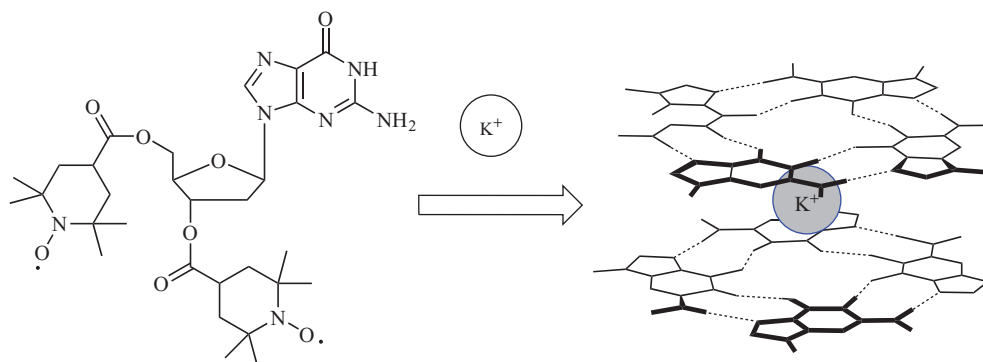


Figure 12 Assembly of a radical-armed guanosine derivative in the presence of alkali metal cations.

typically 1–50 nm in diameter.¹⁰¹ The surface of metal NPs may be passivated by organic ligands, forming a self-assembled monolayer (SAM) on a curved surface.^{102–105} These systems are usually named monolayer-protected clusters (MPCs). SAMs on NPs simultaneously stabilize the reactive metal and present organic functional groups at the particle–solvent interface. Tailored organic surfaces on metal NPs are useful for applications in nanotechnology, in different fields of material science, chemistry, biology, and medicine.

Persistent nitroxides radicals have been anchored to the surface of gold NPs. The first example has been reported in 1998 by Murray and coworkers who were able to couple 4-amino TEMPO with an MPC (see Figure 13) having ω -carboxylic acid groups. In this example, each gold cluster contained circa 13 nitroxide units.¹⁰⁶

AuNPs protected by weakly bound ligands such as phosphines, amines, or short alkyl thiolates can be transformed to spin-labeled NPs by simply mixing them with a disulfide diradical.^{107,108}

The first example of TEMPO being immobilized on magnetic NPs was reported in 2008.¹⁰⁹ TEMPO was covalently bonded to carbon-coated/Co FNPs, which have excellent magnetic properties. The NPs were shown to be highly active for the oxidation of alcohols using stoichiometric amounts of NaOCl and were cycled 14 times with no apparent loss of catalytic activity. More recently, TEMPO was immobilized on iron oxide (Fe_3O_4) superparamagnetic NPs by employing strong metal-oxide chelating phosphonates and azide/alkyne “click” chemistry.¹¹⁰ This simple preparation yields recyclable TEMPO-coated NPs with good TEMPO

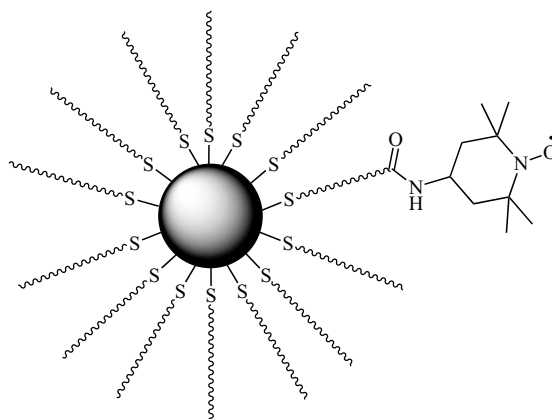


Figure 13 Schematic representation of TEMPO functionalized monolayer-protected metal nanoparticles.

loadings. They have excellent magnetic response and efficiently catalyze the oxidation of a wide range of primary and secondary alcohols to aldehydes, ketones, and lactones under either aerobic acidic Mn(II)/Cu(II) or basic NaOCl conditions (see **Nitroxides in Synthetic Radical Chemistry**).¹¹¹

By using nitroxide-labeled gold NPs and EPR spectroscopy Chechik and coworkers were able to investigate ligand dynamic on the gold surface and the ligand place-exchange reactions.^{112–115} The lateral mobility of the thiolate ligands on the surface of AuNPs has also been probed by EPR spectroscopy. This was achieved by using bisnitroxide ligands, which contained a disulfide group (to ensure attachment to the Au surface) and a cleavable ester bridge connecting the two spin-labeled

branches of the molecule.^{116,117} EPR spectroscopy has also been employed for accessing interfacial surface electrostatics of ligand-protected AuNPs.¹¹⁸

The properties of NPs can also be investigated by doping them with stable radicals not only in the form of covalently bonded compounds (spin labels) but also as added molecules (spin probes). Actually, EPR spectroscopy was employed for the investigation of the interaction between stable nitroxide radicals, such as TEMPO, TEMPOL, and unprotected AuNPs of various sizes.¹¹⁹ Unfortunately, the exchange interactions between the unpaired electrons of the adsorbed organic radicals and conduction-band electrons of the metallic particles were found to hide the EPR signal. However, in the presence of an organic monolayer covering the gold core of the NP, the addition of suitable spin probes gives rise to relatively persistent EPR signals that have been used to investigate the properties of self-assembled organic monolayers. These investigations rely on a series of nitroxide probes, obtained by *in situ* oxidation of amine precursors, based on the benzyl *tert*-butyl nitroxide moiety. With this family of probes the following systems were investigated:

1. Gold nanoparticles composed of an amphiphilic thiolate (C8-TEG) containing a hydrocarbon chain close to the gold surface and a poly(ethylene glycol) chain which provides high solubility in water and other polar solvents of different sizes.^{120,121}
2. Water-soluble AuNPs protected by a monolayer of fluorinated amphiphilic thiols (F8-PEG)

containing a perfluorinated portion and a short poly(ethylene glycol) unit.¹²²

3. Mixed monolayers composed of thiols that differ by an alkyl- or a perfluorinated chain.¹²³

These results have been recently reviewed.¹²⁴

5.3 Mechanical Interlocking of Free Radicals

Probably, one of the most attractive aspects of self-assembly is represented by the mechanical interlocking of molecules.^{125,126} Mechanical interlocking means that two or more species became connected to each other, not by chemical bonds, but rather are threaded through or around one another to form a single chemical species. The assemblies are generally sustained by supramolecular interactions between the individual, covalent components. Species that are linked in this way are said to be topologically connected. In order for compounds to be truly topologically connected, a chemical bond must be broken in order to extract the individual components of the assembly from each other. The great interest in such systems derives for the use as nanoscale molecular machines and molecular electronic devices.

One of the most important classes of interlocking structures is represented by rotaxanes. A rotaxane consists of a linear molecule which is threaded through a ring with the ends of the thread, or axle, capped in such a manner that the ring cannot slip off (Figure 14). Another example of topologically

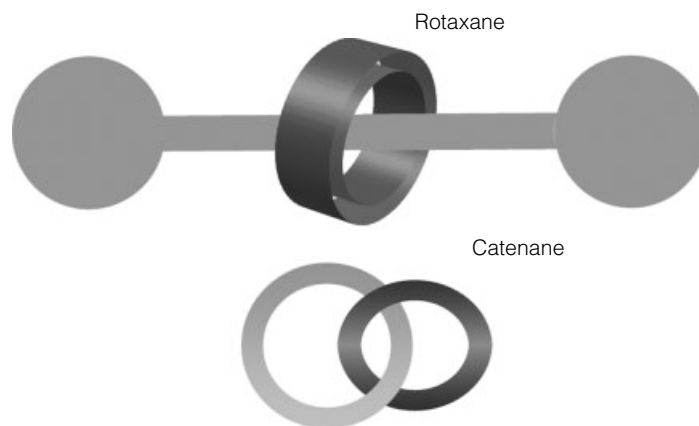


Figure 14 Schematic representation of a rotaxane and a catenane.

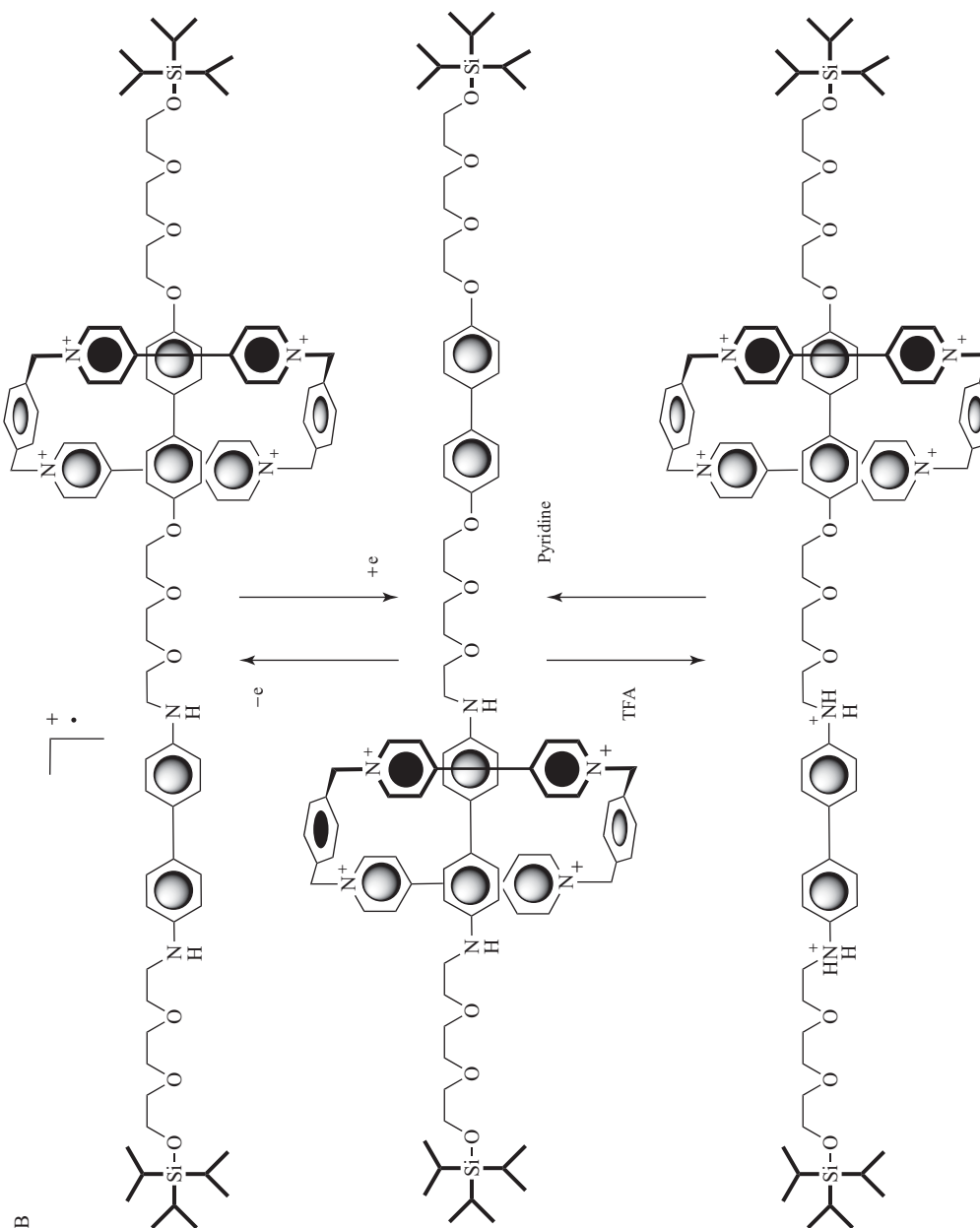


Figure 15 Structure of the switchable rotaxane reported in Ref. 134. [Bissell *et al.* (1994). Reproduced from Ref. 134. Copyright Macmillan Publishers Ltd, 1994.]

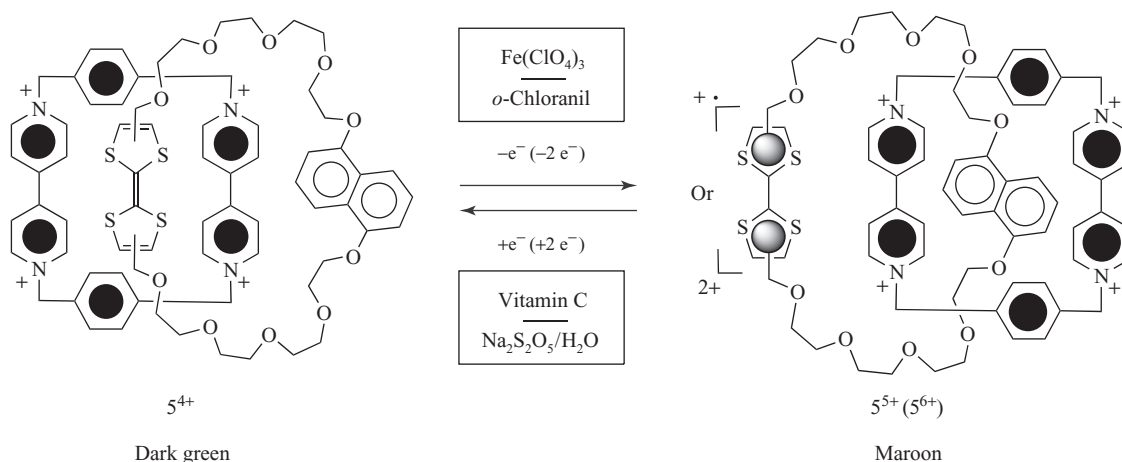


Figure 16 The chemically and electrochemically triggered redox switching of a catenane. [Asakawa *et al.* (1998). Ref. 135. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.]

connected species is represented by catenanes that are mechanically interlocked macrocycles akin to links in a chain.

Rotaxanes are not merely chemical curiosities but they also have the potential to act as molecular machines.^{127–129} Rotaxane threads can be designed in such a manner that they contain two different binding sites for the macrocycle. The preference for the macrocycle to bind to one site or the other can then be influenced by external factors, either chemically,¹³⁰ electrochemically,¹³¹ or photochemically.¹³² The ring can therefore be moved back-and-forth along the axle and such functional assemblies are known as molecular shuttles.

Persistent radical ions represent important functionalities that have been employed in different electrochemical-driven molecular shuttles. Macrocycles can be induced to move from one binding site to another of the axle by providing or subtracting an electron to the axle thus giving rise to the corresponding radical ion. A first example is provided by rotaxanes incorporating cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺)¹³³ as their ring component and two electron-rich aromatic units as the two different recognition sites on their axial component (Figure 15).¹³⁴

The preferred location of the wheel is in proximity to the benzidine part. Ring shuttling to the biphenol part can be induced electrochemically by oxidation of the benzidine part to its radical cation. In this case, charge repulsion with the fourfold positively charged wheel induces ring migration to the

biphenol station. The process is reversible, and the reduction of the benzidine radical leads back to the resting state.

Another example is provided by catenanes incorporating CBPQT⁴⁺ as their ring component and two electron-rich aromatic units tetrathiafulvalene (TTF) and 1,5-dioxynaphthalene (DNP) as the two different recognition sites (Figure 16).¹³⁵

One electron oxidation of the TTF moiety to the corresponding radical cation provokes circumrotation of the catenane rings leading to a structure where the cyclophane wheel with its two paraquat units is located in proximity to the DNP part of the crown ether ring. Again the process is reversible and the reduction of TTF to its normal form shifts back the ring to its resting state.

Electrochemically switchable molecular shuttles based on the reduction of the axle to the corresponding radical anion has also been reported.¹³¹ These rotaxanes contain succinamide and naphthalimide hydrogen-bonded stations for a benzylic amide macrocycle (Figure 17).

In its resting state, the rotaxane has the macrocycle hydrogen bonded to the succinamide unit. Electrochemical reduction of the naphthalimide station to the corresponding radical anion increases the HBA ability of the imide units to such a degree that translocation of the macrocycle is observed.

Very recently, Stoddart and coworkers introduced a new type of interaction based on viologen radical cations (V^{•+}) that paves the way to the preparation of very sophisticated molecular devices.^{136–138}

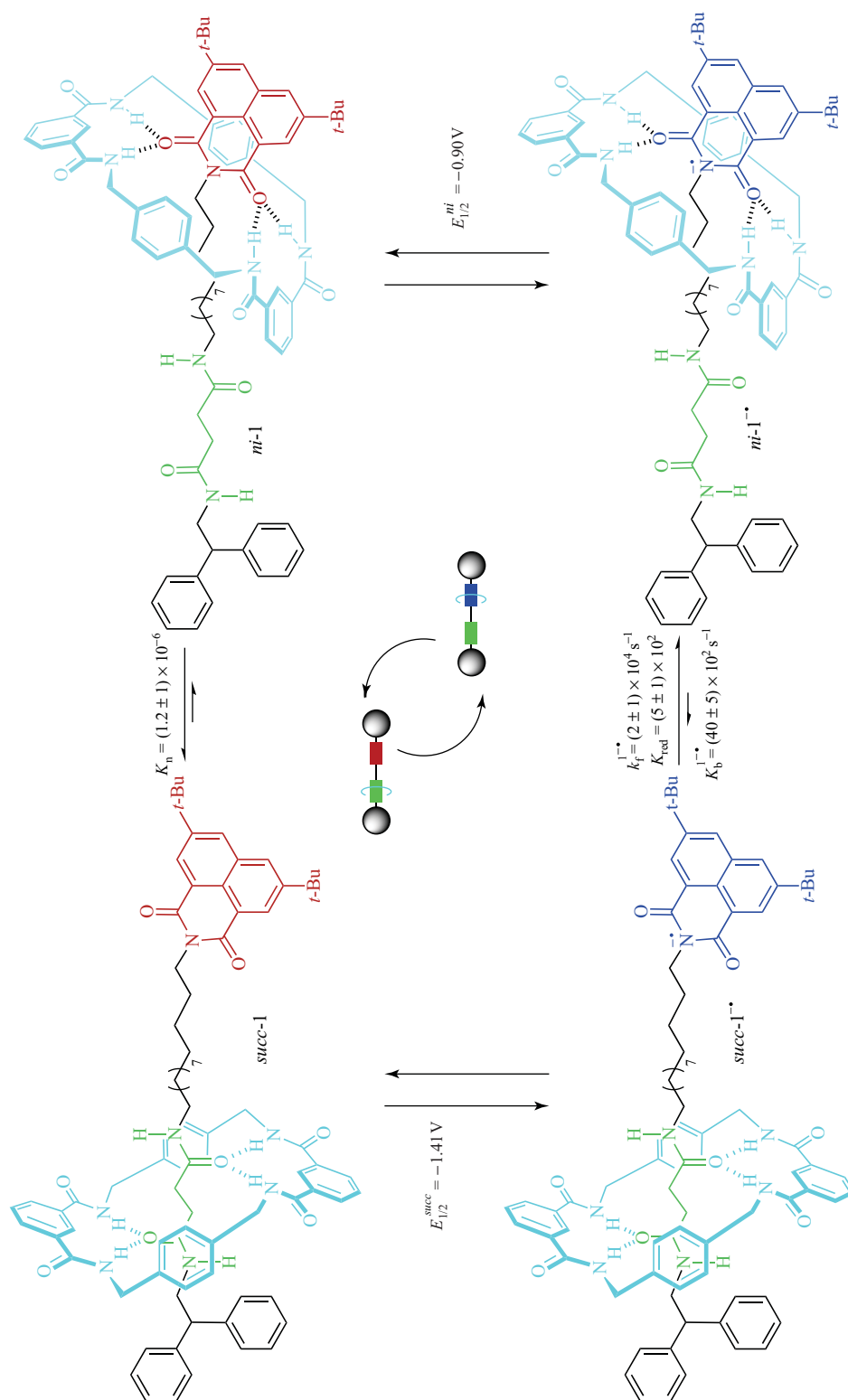


Figure 17 The electrochemically switchable, hydrogen-bonded molecular shuttle reported in Ref. 131. [Altieri *et al.* (2003). Reprinted with permission from Ref. 131. Copyright 2003 American Chemical Society.]

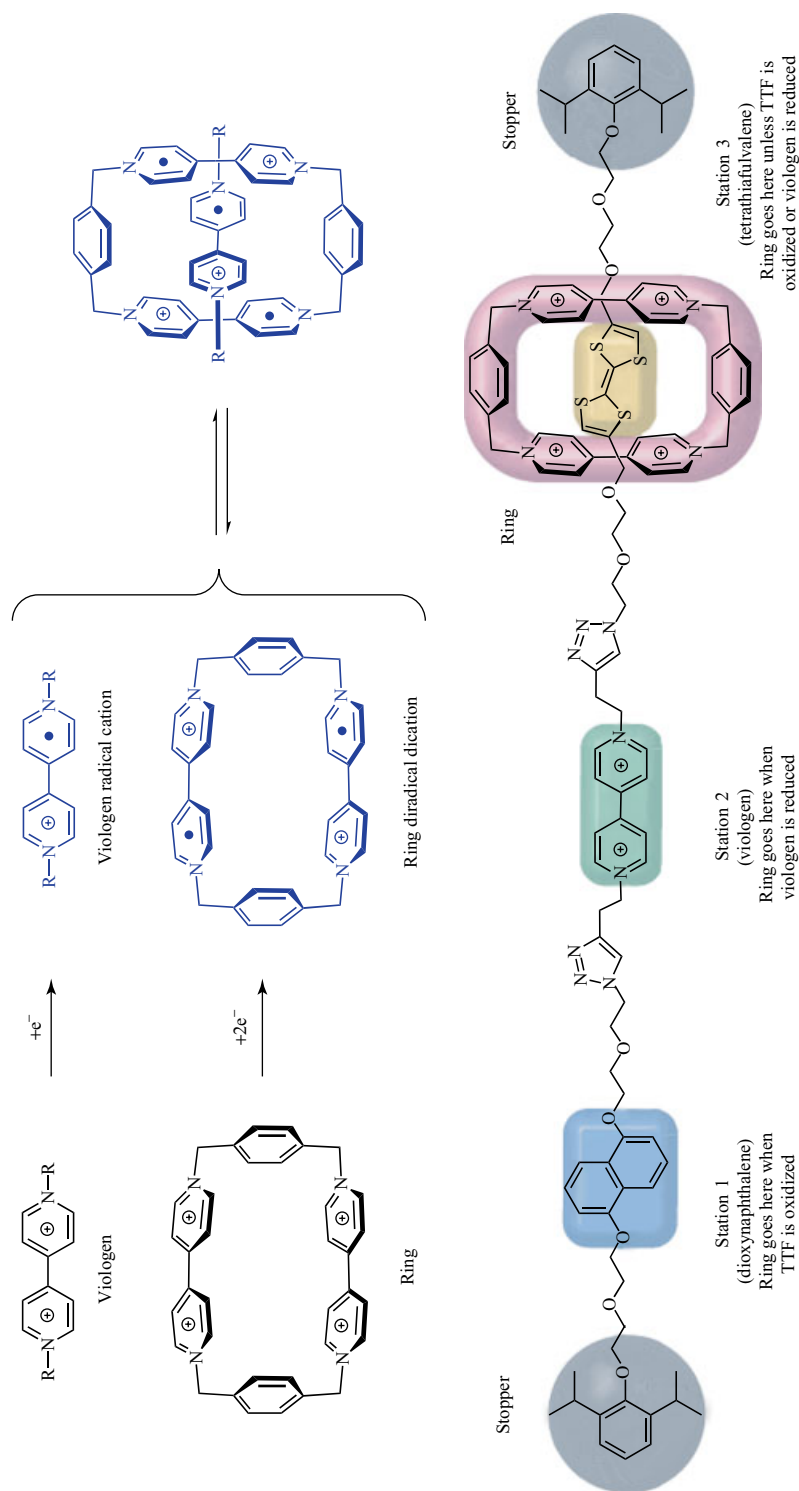


Figure 18 The attraction of positively charged radicals offers new opportunities for molecular machines made from interlocked molecules. Reduction leads to the formation of a stable complex between a viologen and the bis-viologen ring. [Anderson (2010). Reproduced from Ref. 137. Copyright Macmillan Publishers Ltd, 2010.]

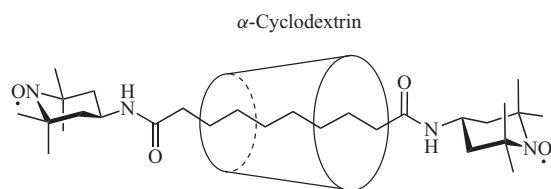


Figure 19 Schematic representation of the paramagnetic rotaxane containing α -cyclodextrin reported in Ref. 139.

Viologen radical cations are known to undergo dimerization and the formation of dimers $(V^{\bullet+})_2$ can be used as a new interaction for controlling switching between different states in switchable mechanically interlocked molecules. Stoddart and coworkers synthesized a molecule consisting of a ring threaded on a dumb-bell-shaped rod, such that the location of the ring along the length of the dumb-bell can be switched between three different positions just by changing the oxidation state of the compound. In the resting form, the ring prefers to sit around the most electron-rich TTF unit; oxidation of this TTF makes the ring prefer to sit on the naphthalene, whereas reduction makes the ring relocate to the central viologen. All these switching processes are fully reversible. The idea is summarized in Figure 18.

Sterically hindered nitroxides have been employed as bulky capping groups in the preparation of paramagnetic rotaxanes. In the first example,¹³⁹ the rotaxane is made from molecules having an alkyl chain flanked by 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) groups (Figure 19). Complexation of sebacoyl chloride by α -cyclodextrin followed by reaction with 4-amino-TEMPO resulted in the trapping of the cyclodextrin, threaded by the alkyl chain, thus generating the rotaxane structure. The room temperature EPR spectrum of the paramagnetic rotaxane (in water $a_N = 17.05$ G, $g = 2.0057$) consists of three lines as expected for a nitroxide

biradical in the extended conformation in which the TEMPO fragments behave as two single nitroxide radicals.

Very recently, the first example of paramagnetic rotaxane containing two cucurbit[6]urils (CB6) as the wheels has also been reported and characterized both by EPR and NMR spectroscopy.¹⁴⁰ Synthesis of the rotaxane was achieved using CB6 as the catalyst in the 1,3-dipolar cycloaddition between a nitroxide functionalized bearing an alkyne group and an aromatic chain containing azide functionalities to give 1,4-disubstituted triazole (Figure 20).

Lucarini and coworkers¹⁴¹ have recently synthesized a [1]rotaxane-type¹⁴² nitroxide-appended β -cyclodextrin with improved resistance to glutathione reduction (Figure 21). In this self-included molecule, the nitroxide functionality is mechanically trapped inside the cavity of CD by a covalent link with one of the CD rims. The TEMPO fragment has an approximately cylindrical shape whose diameter is about 8.5 Å, well above the internal diameter of the β -CD smaller rim (< 6.2 Å). On the basis of this, it was concluded that the barrier for the escape of the nitroxide moiety from the CD cavity must be significantly high, and the presence of a reversible equilibrium between the open and threaded forms of self-complex was excluded.

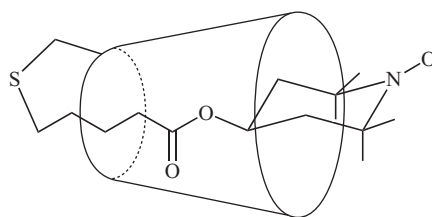


Figure 21 Schematic representation of the paramagnetic [1]rotaxane reported in Ref. 141.

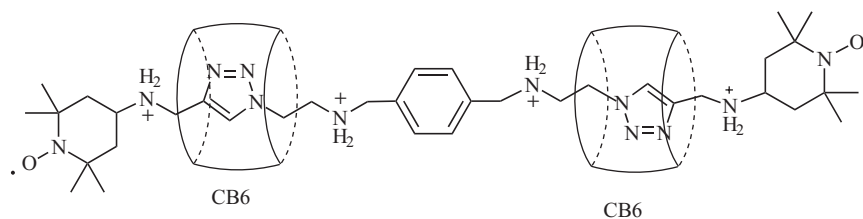


Figure 20 Schematic representation of the paramagnetic rotaxane containing cucurbit[6]uril reported in Ref. 140.

6 SUPRAMOLECULAR CONTROL OF RADICAL REACTIVITY INSIDE ZEOLITES

During the last years, zeolites have been largely examined as reaction media to control the product distribution of radical reactions.¹⁴³ Interest in the chemistry of radicals adsorbed on zeolites derives from the observation that the products of radical–radical reactions, which are nonselective in solution, can be made selective and can be controlled by supramolecular effects. Zeolites¹⁴⁴ are crystalline aluminosilicates constituted by oxygen (corner) sharing tetrahedral AlO_4 and SiO_4 groups that form a rigid three-dimensional network termed the zeolite framework. Their internal surface consists of an interconnected network of cylindrical channels (diameter circa 5.5 Å) and intersections (diameter circa 9 Å). The external surface is composed of a nonporous framework and pore openings. The pore openings on the external surface provide access to the channels and intersections of the internal surface. As a result, only molecules whose size/shape characteristics allow penetration into the holes and whose mobility allows diffusion inside the channels will be adsorbed efficiently on the internal surface.

The carbon radicals produced by photoexcitation are inert toward reaction with the zeolite framework. This feature allows the study of the effect of confined space on radical–radical reactions, which determines the observed products and radical persistence. The restricted mobility within zeolite pores limits the tendency of radicals, radical cations, or other reactive intermediates to undergo radical-destroying bimolecular reactions and prevents access to adventitious reagents (e.g., water and oxygen) that would cause their decay in solution. As a result, the trapped reactive intermediates can have lifetimes long enough to be studied by conventional spectroscopic techniques usually reserved for ordinary stable molecules. Carbon-centered radicals, for example, can live several hours and be studied by EPR or fluorescence on zeolite surfaces.^{145–148} In particular, the benzyl radical persists with a half-life of about an hour, whereas the diphenylmethyl radical is persistent for several days. The addition of air to a sample of DPM causes a peroxy radical spectrum to appear.^{145,146} Remarkably, when the sample

is vacuum degassed, the EPR signal of the diphenylmethyl radical reappears, showing that the addition of molecular oxygen is reversible.¹⁴⁵ Investigations of the photochemical reactions of molecules adsorbed on zeolites have provided insights into the supramolecular structure and dynamics of intermediates produced by photolysis.^{149–151}

Chemical transformation different from that observed in solution has also been observed. Actually, photolysis of aryl chlorides adsorbed gives rise to radical cations and the constraints imposed by the channels shift the reactivity from the C–Cl bond to the O–R bond.¹⁵²

7 CONCLUSION

The reported examples showed not only that supramolecular chemistry can be used to control the reactivity of organic free radicals but also that free radicals are important scaffolds to locate functional units in pre-programmed positions, inside highly ordered architectures. In particular, redox-active radical switches, which allow for direct and easily reversible control on reduction as well as on oxidation, could be forerunners to the development of molecular electronic devices.

At the same time, EPR spectroscopy has been extensively used for detecting and identifying non-covalent assemblies in solution and for clarifying their structure and properties. Although paramagnetic probes must be added to the samples, the reported examples provided considerable information on the properties of the noncovalent systems that are difficult to obtain with more common techniques. It is expected that this technique will significantly improve our ability to study more deeply supramolecular systems.

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Silanes as Reducing Reagents in Radical Chemistry

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1 INTRODUCTION

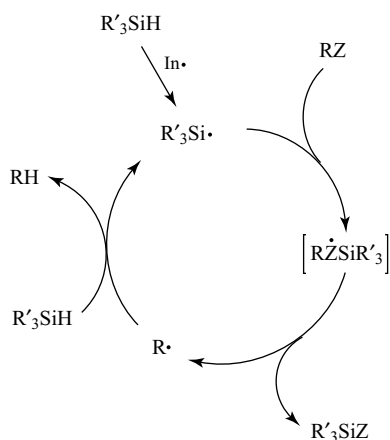
Silyl radical reactions can often be found as key steps of complex synthetic procedures oriented toward the construction of very different structures, spanning from natural products to silicon surfaces. In the late 1980s, Chatgililoglu introduced tris(trimethylsilyl)silane, (TMS)₃SiH, or TTMSS, as radical-based reducing agent for functional group modifications and mediator of sequential radical reactions. (TMS)₃SiH won the Fluka's reagent of the Year Prize in 1990 for its use in radical processes as a valid alternative to the toxic Bu₃SnH (see **Tin Hydrides and Functional Group Transformations**).¹ (TMS)₃SiH has found multiple applications in organic synthesis as well as in polymers and materials science.² Both its low toxicity and the mild reaction conditions rendered (TMS)₃SiH the reagent of choice for the reduction of organic halides, selenides, and activated hydroxy- and carboxy groups, also in aqueous media. The unique reactivity of (TMS)₃SiH has also been exploited in cascade reactions leading to complex molecular scaffolds in a single step. The entire radical chemistry of (TMS)₃SiH and related organosilanes has been the subject of periodical reviews^{1–6} and was summarized in the book *Organosilanes in Radical Chemistry*.⁷ The purpose of this article is

to give an overview of the relevance of organosilanes as radical-based reducing agents in organic synthesis.

2 SILANES AS RADICAL-BASED REDUCING AGENTS

The majority of radical reactions of interest to synthetic chemists are chain processes under reductive conditions (see **Basic Concepts on Radical Chain Reactions**).⁸ The reduction of a functional group by silicon hydride is shown in Scheme 1 as an example of a chain process.^{1,7} Initially, R'₃Si· radicals are generated by some initiation process. In the propagation steps, the removal of the functional group Z in the organic substrate (RZ) takes place by the action of the R'₃Si· radical via a reactive intermediate or a transition state represented by [RZ(·)SiR'₃]. A site-specific radical (R·) is generated, which then reacts with the silicon hydride and gives the reduced product (RH), together with “fresh” R'₃Si· radicals to reinitiate the chain. The chain reactions terminate by radical–radical combination or disproportionation reactions.

The hydrogen abstraction step from the Si–H moiety of silanes is fundamentally important for these reactions. Kinetic studies have been performed with a large variety of radicals toward (TMS)₃SiH



Scheme 1 Mechanism of the reduction of a functional group by silicon hydride.

(see **Radical Kinetics and Clocks**).⁹ In Figure 1, the scale of rate constants of hydrogen abstraction from a few group 14 hydrides by primary alkyl radicals at 80 °C is provided. The rate constant for (TMS)₃SiH is only ~5 times slower than that of Bu₃SnH. The contribution of TMS groups on the reactivity of (TMS)₃SiH can be appreciated in the analogous silane where one TMS group is replaced by Me,^{2,6} which results to have a 10 times slower rate constant. The couple (TMS)₃SiH/thiol functioning as a free-radical reducing system will be discussed later (Section 2.1.4).

2.1 The (TMS)₃SiH Reagent

2.1.1 Removal of Functional Group

(TMS)₃SiH is an effective reducing agent for the removal of a variety of functional groups. Several

examples are shown in Schemes 2–4. The most popular thermal initiator is azobisisobutyronitrile (AIBN), with a half-life of 1 hour at 81 °C. Other azo compounds are also used from time to time depending on the reaction conditions. Et₃B in the presence of very small amounts of oxygen is an excellent initiator for lower temperature reactions (down to –78 °C).

Examples of dehalogenation are shown for chloride **1**,¹⁰ bromide **2**,¹¹ and iodide **3**,¹² as well as for dichloride **4**.¹³ (Scheme 2). The reduction of dichloride represented the key step in the total synthesis of dactomelynes, a group of natural products isolated from a marine organism. The use of (TMS)₃SiH at room temperature allowed the monochloride to be obtained in high yield and stereoselectivity ($\beta : \alpha = 13 : 1$), whereas other radical-based reducing systems failed.¹³ In this respect, the stereoselective reduction of *gem*-dichlorides by (TMS)₃SiH or Bu₃SnH was previously reported, evidencing the different spatial shapes of the two reagents.¹⁴ This shows that the silane has a stronger preference than tin hydride to transfer a hydrogen atom from the less hindered side of the molecule.

The removal of functional groups is beyond dehalogenation. Reductive removal of chalcogen groups such as the selenide **5** can be obtained (Scheme 3).¹⁵ For the removal of a hydroxy group, the strategy starts from a thiocarbonyl derivative (e.g., *O*-arylthiocarbonate, *O*-thioxocarbamate, thiocarbonyl imidazole, or xanthate) or a selenocarbonate. Two examples of thiocarbonyl derivative are provided using the *O*-phenylthiocarbonate **6**¹⁶ and xanthate **7**.¹⁷ The latter is the last step of a multistep synthesis toward the natural product ventricos-7(13)-ene, a triquinane having a remote exo-methylene group. The authors reported that the Barton–McCombie reduction of xanthate **7** using

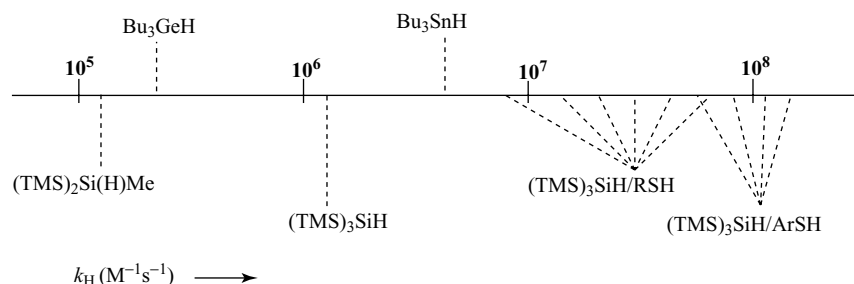
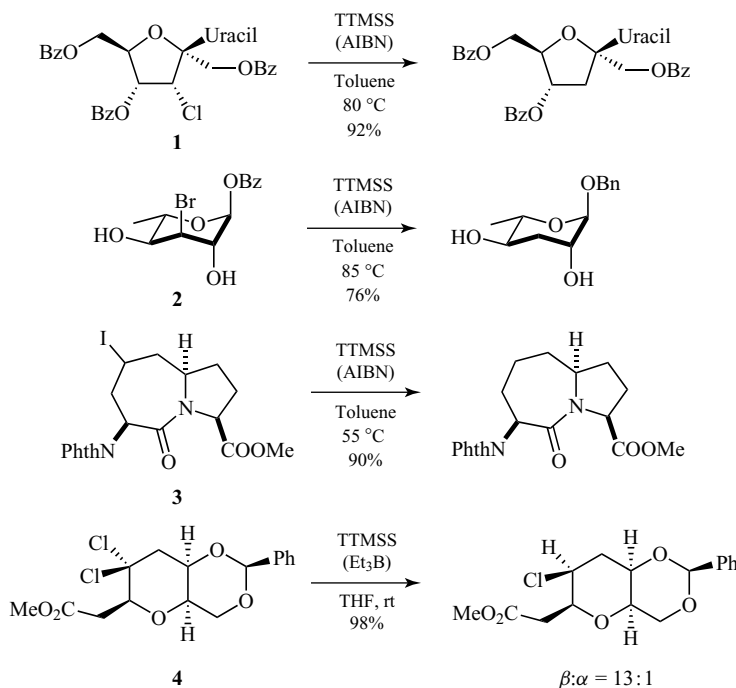


Figure 1 Rate constants for H-atom abstraction from a variety of reducing systems by primary alkyl radicals at 80 °C.²



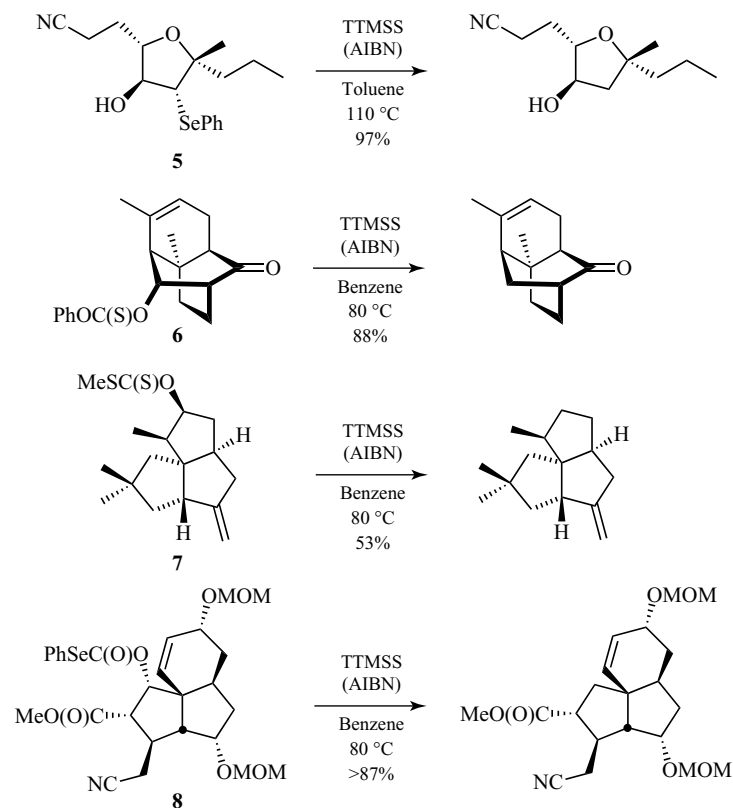
Scheme 2 Dehalogenation by reaction with $(\text{TMS})_3\text{SiH}$ (PhthN = *N*-phthalimido group).

TTMSS as the hydride source have proven to be critical: the silane by-products could be removed by treatment of the reaction mixture with tetrabutylammonium fluoride (TBAF), whereas they were unable to adequately purify the natural product when using the conventional organotin hydride reagent.¹⁷ Also for the selenocarbonate **8**, the deoxygenation was found effective, and it was achieved with an 87% efficiency from the alcohol.¹⁸

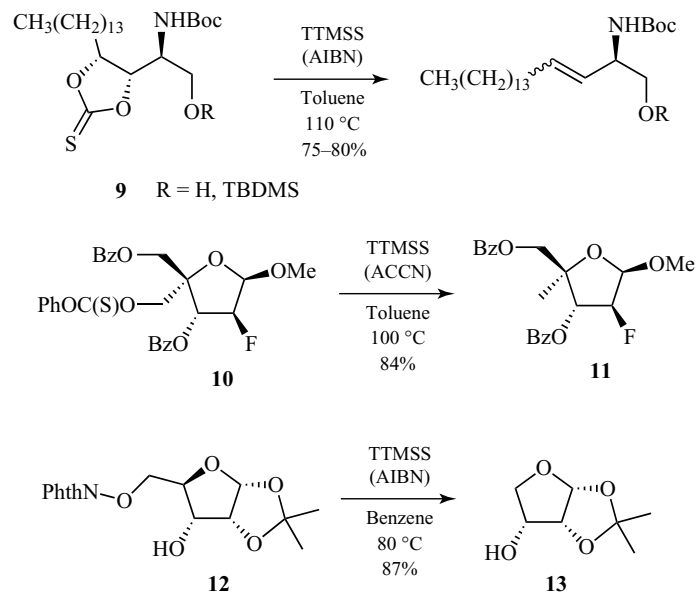
1,2-Diols can be transformed into olefins using the cyclic thiocarbonates or bisdithiocarbonate derivatives. Scheme 4 shows the olefination from cyclic thiocarbonate **9** where the *E*-isomer is more favored in the presence of the bulky *tert*-butyldimethylsilyl (TBDMS) group.¹⁹ The choice of functionalization of primary alcohols prior to the reaction with $(\text{TMS})_3\text{SiH}$ plays an important role. The hydroxyl group removal of primary alcohols can be achieved from a thiocarbonyl derivative such as the *O*-phenylthiocarbonate derivative **10**, using a slightly higher temperature than that for the deoxygenation of secondary alcohols (Scheme 3).²⁰ On the other hand, the phthalimido *D*-ribofuranose derivative **12** affords the *D*-erythrose **13** in good yield via the intermediacy of an alkoxyl radical

that undergoes a β -fragmentation prior to hydrogen abstraction.²¹ Similar reaction was obtained from the *D*-xylo to *L*-threose derivative.²¹

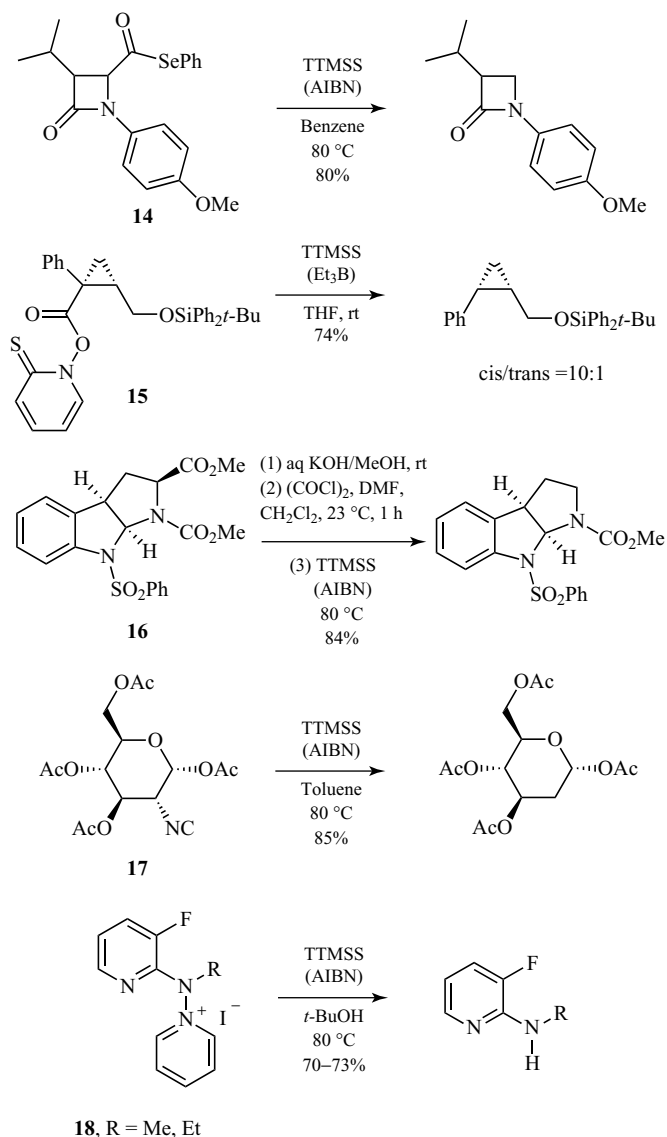
A variety of acyl derivatives (such as acyl chlorides, phenylseleno esters, or *N*-hydroxypyridine-2-thione esters) can be used for decarbonylation and reductive decarboxylation with $(\text{TMS})_3\text{SiH}$.²² The example of phenylseleno ester **14** afforded the decarbonylated β -lactam in good yield (Scheme 5).²³ The *N*-hydroxypyridine-2-thione ester **15** was used in the key step to construct the chiral *cis*-cyclopropane structure in compounds designed as antidopaminergic agents.²⁴ The observed high *cis* selectivity is due to the hydrogen abstraction from the sterically demanding $(\text{TMS})_3\text{SiH}$, which occurs from the less hindered site of the intermediate cyclopropyl radical. Hydrolysis of the methyl ester followed by decarbonylation at the C2 position of hexahydropyrroloindole (+)-**16**, afforded the desired tricyclic product in 84% yield and >99% ee.²⁵ The reduction of the isocyanide **17** is considered a smooth route for the deamination of primary amine obtained via formylation and dehydration.^{1,26}



Scheme 3 Removal of functional groups by reaction with $(\text{TMS})_3\text{SiH}$.



Scheme 4 Removal of functional groups by reaction with $(\text{TMS})_3\text{SiH}$.



Scheme 5 Removal of functional groups by reaction with (TMS)₃SiH.

Synthesis of secondary amines can be achieved either by replacement of a pyridinium moiety (**18**) with hydrogen²⁷ (Scheme 5) or by reduction of nitroxides.²⁸

The radical-based reductions with TTMSS have been expanded toward technological applications. Examples are the radical-based transformations in a microstructured reaction device in which deoxygenation and dehalogenation reactions

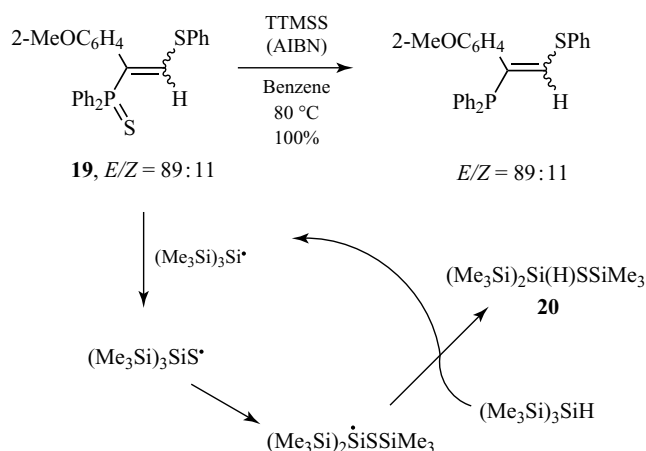
are found to be highly efficient (see **Radical Chemistry by Using Flow Microreactor Technology**),²⁹ the cleavage from resin-bound selenium and tellurium derivatives,³⁰ or the removal of terminal thiocarbonyl group from polystyrene.³¹

TTMSS is useful for the reduction of phosphine sulfides and phosphine selenides under free-radical conditions to give the corresponding phosphines or, after treatment with BH₃·THF (THF = tetrahydrofuran), the corresponding phosphine–borane

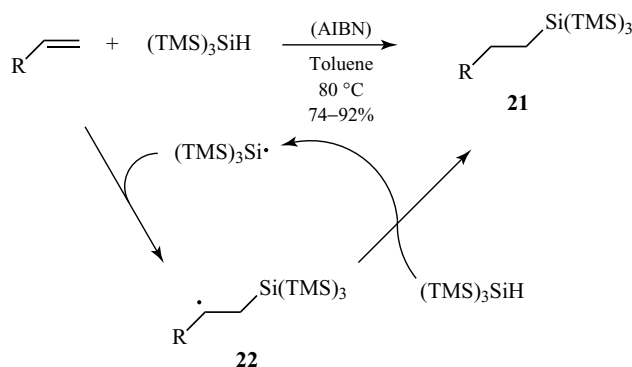
complex in good to excellent yields.³² Stereochemical studies on P-chiral phosphine sulfides showed that these reductions proceed with retention of configuration. This desulfidation protocol has recently been applied with success to the synthesis of bulky phosphines,³³ (Z)-1,2-diphosphino-1-alkenes,³⁴ and 1-thio-2-phosphino-1-alkenes.³⁵ An example of desulfidation of phosphine sulfide **19** is given in Scheme 6. During the desulfidation, no isomerization of the C–C double bonds took place. It is worth underlining that, in these reactions, the ejected silyl-ethyl radical undergoes a fast 1,2-migration of silyl group from silicon to sulfur, affording a new silyl radical, which either reacts with (Me₃Si)₃SiH to give **20**, completing the reaction cycle (Scheme 6), or replaces the (Me₃Si)₃Si• radical in the reaction sequence.³⁶

2.1.2 C–Si Bond Formation

The radical-based hydrosilylation of carbon–carbon double bonds by (TMS)₃SiH is an important class of reactions affording silanes **21** (Scheme 7).^{2,6,7} The initially generated silyl radical adds to the double bond to give a radical adduct **22**, which then reacts with the silicon hydride and gives the addition product, together with “fresh” silyl radicals to continue the chain. Rate constants for the reaction of (TMS)₃Si• radical with a variety of monosubstituted olefins were measured by laser flash photolysis techniques.^{26,37} Hydrosilylation of monosubstituted and *gem*-disubstituted olefins is an efficient process, which occurs with high regioselectivity (anti-Markovnikov) in the case of both electron-rich and electron-poor olefins.³⁸



Scheme 6 Desulfidation of phosphine sulfides.



Scheme 7 Hydrosilylation of alkenes by (TMS)₃SiH.

Analogous reactions were performed using tetrahydropyran as the solvent and 2,2'-azobis(dimethyl valeronitrile) as the initiator at 70 °C,³⁹ as well as in water using 1,1'-azobis(cyclohexane carbonitrile) at 100 °C (*vide infra*).⁴⁰ For cis- or trans-disubstituted double bonds, hydrosilylation was still an efficient process, although it requires slightly longer reaction times and an activating substituent.³⁸

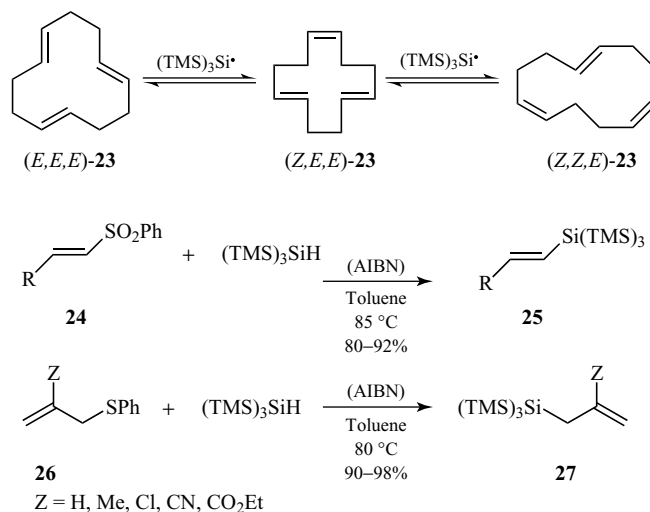
The addition of (TMS)₃Si• radical to 1,2-dialkyl substituted olefins is reversible. This radical behavior can be noteworthy also from a synthetic point of view. An example based on the isomerization of 1,5,9-cyclododecatriene (**23**) is shown in Scheme 8.⁴¹ The final isomeric composition of 78:20:2 for (*E,E,E*)-**23**:(*Z,E,E*)-**23**:(*Z,Z,E*)-**23**, which is independent of the starting isomer or isomeric mixture, was reached in 5 hours by using (TMS)₃SiH/*t*-BuOOBu-*t*/143 °C and the yield was ~80%.

Radical-mediated silyldesulfonylation of various (*E*)-vinyl sulfones **24** (R = alkyl or aryl) with (TMS)₃SiH provides access to (*E*)-vinyl silanes **25** (Scheme 8).^{42,43} These highly stereoselective reactions presumably occur via a radical addition followed by β -scission with the ejection of the PhSO₂• radical. Hydrogen abstraction from (TMS)₃SiH by the PhSO₂• radical completes the cycle of these chain reactions. Such silyldesulfonylation provides an alternative to the hydrosilylation of alkynes with (TMS)₃SiH that affords mainly (*Z*)-vinyl silanes

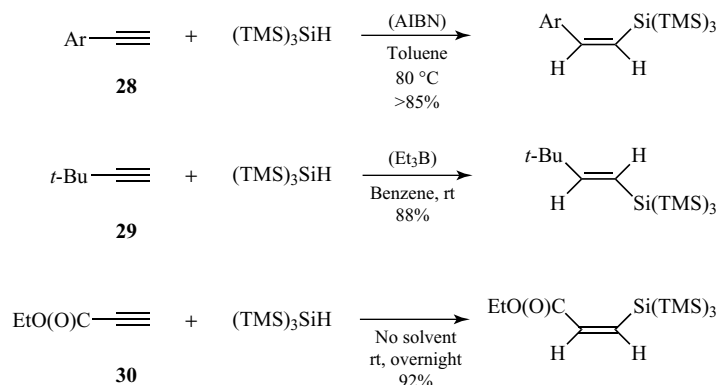
(*vide infra*). Upon oxidative treatment with hydrogen peroxide in basic aqueous solution, compound **25** undergoes Pd-catalyzed cross-couplings with aryl halides.^{42,43} In an analogous process, the reactions of unsubstituted and 2-substituted allyl phenyl sulfides **26** with (TMS)₃SiH give a facile entry to allyl tris(trimethylsilyl)silanes **27** in high yields (Scheme 8). In this case, the addition of (TMS)₃Si• radical to the double bond is followed by β -scission with ejection of a thiyl radical, thus affording the transposed double bond. Hydrogen abstraction from (TMS)₃SiH by PhS• radical completes the cycle of these chain reactions.⁴⁴

The addition of (TMS)₃SiH to a number of mono-substituted acetylenes was also studied in some detail.^{38,45} These reactions are highly regioselective (anti-Markovnikov) and give terminal (TMS)₃Si-substituted alkenes in good yields. High cis or trans stereoselectivity is also observed, depending on the nature of the substituents at the acetylenic moiety. For example, the reaction of the alkynes **28** and **29** with (TMS)₃SiH, initiated either by Et₃B at room temperature^{38,45} or by thermal decomposition of di-*tert*-butyl peroxide at 160 °C,⁴⁶ gave the same results (Scheme 9). These reactions proceed also without solvent as shown for the case of alkyne **30**.^{47,48}

The hydrosilylation reactions are of interest also because they represent a model reaction for the functionalization of silicon surfaces using radical chemistry.^{2,6} Indeed, radical reactions have



Scheme 8 Various reactions for which the key step is the addition of (TMS)₃Si• radical to the C–C double bonds.



Scheme 9 Hydrosilylation of alkynes by $(\text{TMS})_3\text{SiH}$.

been found to be most convenient for achieving organic modifications of hydrogen-terminated silicon surfaces. The two flat surfaces H-Si(111) and H-Si(100)-2 $\times$ 1 resemble $(\text{Me}_3\text{Si})_3\text{SiH}$ in that the three silicon atoms are attached at the SiH moieties.^{49,50} Therefore, it is not surprising that several $(\text{Me}_3\text{Si})_3\text{SiH}$ reactions, in particular activated alkenes and alkynes, have been adopted and applied to surfaces, and that mechanistic schemes are often proposed in analogy with $(\text{Me}_3\text{Si})_3\text{SiH}$ radical chemistry (see **Silicon Radical Surface Chemistry**).^{51,52}

2.1.3 Reaction with Molecular Oxygen

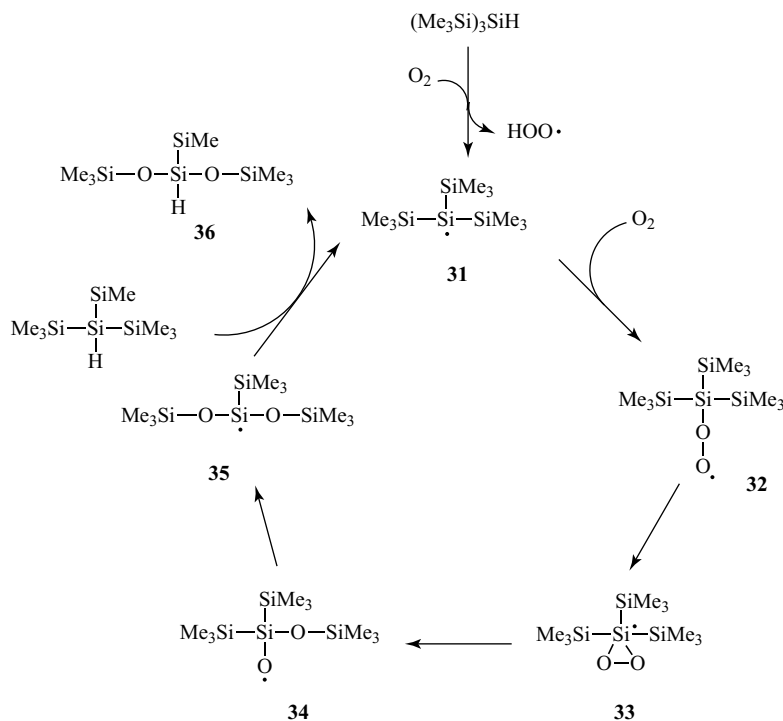
The reaction of $(\text{Me}_3\text{Si})_3\text{SiH}$ with oxygen is of considerable importance. From our initial studies, we found that this reaction occurs spontaneously and slowly at ambient temperature to form siloxane as the sole product.⁵³ When $(\text{TMS})_3\text{SiH}$ was treated with a mixture of $^{16}\text{O}_2$ and $^{18}\text{O}_2$ and the crude products were analyzed by mass spectrometry, similar label distributions were observed in the products as in the reactants for both cases, indicating an intramolecular mechanism: that is, two oxygen atoms in the final product arise from the same oxygen molecule. The mechanism of this unusual process was studied in some detail.⁵⁴ The absolute rate constant for the spontaneous reaction of $(\text{Me}_3\text{Si})_3\text{SiH}$ with molecular oxygen was determined to be $\sim 3.5 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at 70°C ⁵⁴ and theoretical studies elucidated the reaction coordinates.⁴⁷ The reaction sequence shown in Scheme 10 corroborates all findings.^{53,54} Silyl radical **31** adds

to oxygen to form the peroxy radical **32**. This silylperoxy radical undergoes three consecutive unimolecular steps: **32** $\rightarrow$ **33** $\rightarrow$ **34** $\rightarrow$ **35**. Hydrogen abstraction from $(\text{Me}_3\text{Si})_3\text{SiH}$ by radical **35** gives the final product **36** and another silyl radical **31**, thus completing the cycle of this chain reaction. There is strong evidence that the formation of the dioxirane-like pentacoordinated silyl radical **33** is the rate-determining step ($\sim 10^3 \text{ s}^{-1}$ at 70°C) of the three consecutive unimolecular steps.

A few aspects of the autoxidation of $(\text{Me}_3\text{Si})_3\text{SiH}$ are of interest to synthetic chemists: (i) in some cases oxygen can serve to initiate radical chain reactions, therefore no additional radical initiator is needed; (ii) the oxidized product **36** does not interfere with radical reactions; and (iii) GC analysis can be used for a titration of the reagent, thus giving the exact concentration of silane if necessary. A highly efficient air-initiated dehalogenation and hydrosilylation reactions with $(\text{TMS})_3\text{SiH}$ as a reducing agent has been established under solvent-free conditions (*vide infra*).^{40,55}

2.1.4 $(\text{TMS})_3\text{SiH}$ /Thiol Pair and Radical Reactions in Aqueous Medium

Earlier work from Roberts' laboratory showed that trialkylsilanes reduce alkyl halides to the corresponding hydrocarbons in the presence of alkanethiols (the so-called polarity-reversal catalysis in the radical chain reduction, see Section 2.2). He demonstrated that the key step in these reductions is the hydrogen transfer from silane to the thiyl radical, which is strongly endothermic and reversible.⁵⁶

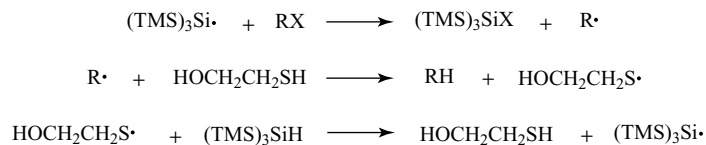


Scheme 10 Reaction mechanism for the autoxidation of $(\text{Me}_3\text{Si})_3\text{SiH}$.

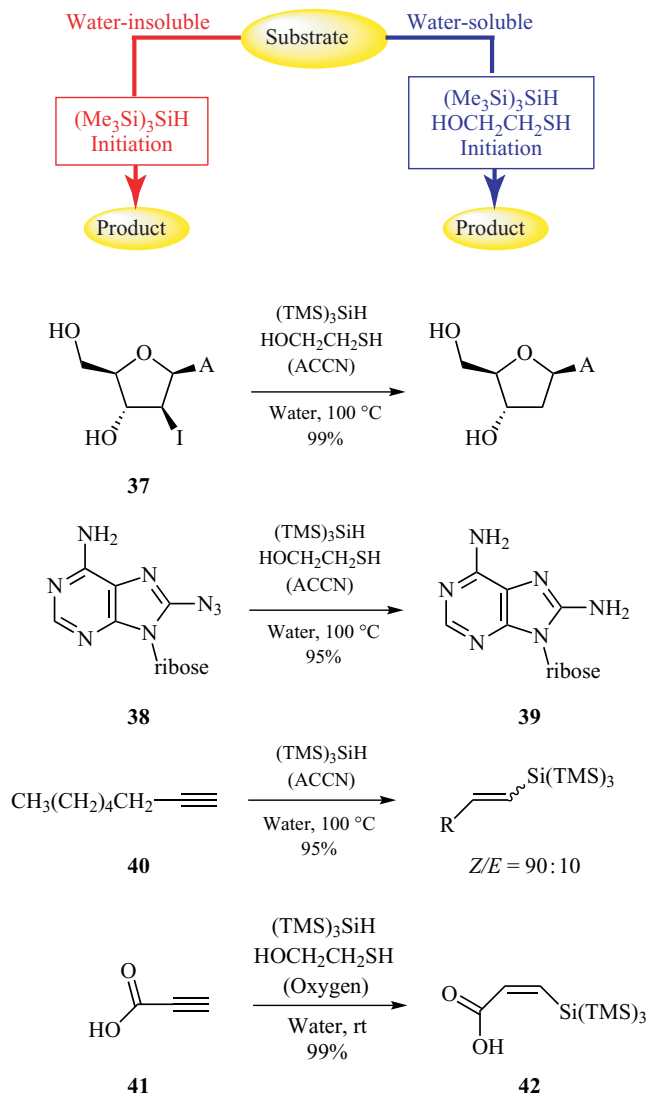
On the basis of this approach, the reactivity of $(\text{TMS})_3\text{SiH}$ could be expanded to fast trapping and reducing systems using the $(\text{TMS})_3\text{SiH}$ /thiol pair.⁵⁷ The mechanism in Scheme 11 illustrates the propagation steps with 2-mercaptoethanol as the thiol. Its role is to act as hydrogen donor and then to be regenerated by reaction of thiyl radical with silane. This reactivity can be employed to study the fast reaction of carbon-centered radicals with thiols, using the free-radical clock methodology.⁵⁷ The rate constants of primary alkyl radicals with $(\text{TMS})_3\text{SiH}/\text{RSH}$ and $(\text{TMS})_3\text{SiH}/\text{ArSH}$ are in the range of $0.9\text{--}8 \times 10^7$ and $0.75\text{--}1.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, respectively, at 80°C (Figure 1). Therefore, the role of thiol is to modulate the hydrogen donor ability of the system and allow the fast reaction

of carbon-centered radicals with the thiols to be studied.

Chemical reactions using water as a solvent have received considerable attention in organic synthesis from both practical and economic standpoints.⁵⁸ The use of water in organic reactions has the following significant advantages: low cost, abundance, safety (nonexplosive, nonflammable, and nontoxic), easily controlled reaction temperature due to the high heat capacity of water, and ease of phase-separation when water-insoluble products are formed. $(\text{TMS})_3\text{SiH}$ is not soluble in water and does not suffer from any significant reaction with water at 100°C for a few hours. This observation motivated our interest in applying it to radical reactions in water (Scheme 12).^{59,60}



Scheme 11 Removal of the X group from alkyl halides using the $(\text{TMS})_3\text{SiH}/\text{RSH}$ reducing system.



Scheme 12 Reduction⁶⁰ and hydrosilylation⁴⁰ reactions in water using (TMS)₃SiH or (TMS)₃SiH/HOCH₂CH₂SH for water-insoluble or water-soluble substrate, respectively.

Water-insoluble substrates, suspended with (TMS)₃SiH and the radical initiator ACCN (1,1'-azobis(cyclohexanecarbonitrile)), in aqueous medium at 100 °C under vigorous stirring can be reduced in good yields.⁶⁰ This procedure does not work with water-soluble substrates; however, when a catalytic amount of the amphiphilic 2-mercaptoethanol is coupled to (TMS)₃SiH, it becomes a very efficient system for the reduction of different organohalides (Scheme 12, upper part). Two examples of water-soluble nucleosides are

shown in Scheme 12, with the dehalogenation of iodide **37** and the reduction of 8-azidoadenosine **38** that afford the corresponding amino derivative **39**. The reduction of aliphatic and aromatic azides to the corresponding primary amines is analogous to that in Scheme 11: that is, after the addition of (TMS)₃Si· radical to the azide moiety, liberation of nitrogen, and formation of a silyl-substituted aminyl radical, the thiol serves as the hydrogen atom donor. Hydrolysis of the silylamine afforded the amine as the final product. Another example

is the hydrosilylation reaction C–C multiple bonds.³⁷ The water-insoluble alkyne **40** afforded the hydrosilylation product in good yield and in *Z/E* ratio of 90:10. Under dioxygen initiation at room temperature, the same reaction product is obtained in similar yield but in *Z/E* > 99 : 1. On the other hand, the water-soluble alkyne **41** afforded in quantitative yield the isomer **42** either under dioxygen initiation at room temperature or with ACCN at 100 °C. These procedures illustrate the flexibility of (TMS)₃SiH as the radical-based reducing agent of choice in different media, as well as additional benefits, including the possibility to work with unprotected substrates, ease of purification, and satisfactory environmental impact.

2.2 Other Organosilanes

Trialkylsilanes are not capable of donating their hydrogen atom at a sufficient rate to propagate the chain. Therefore, chain reactions are not supported under normal reaction conditions, although trialkylsilyl radicals are among the most reactive species toward various organic functional groups. For example, the reduction of thiocarbonyl derivatives by Et₃SiH can be described as a chain process under “forced” reaction conditions.⁶¹ However, Et₃SiH reacts with polyfluorinated halocarbons under free-radical conditions when initiated by thermal decomposition of peroxides.⁶² Phenyl or mixed alkyl/phenyl-substituted silicon hydrides show similar reactivities to trialkylsilanes. Indeed, by replacing one alkyl by a phenyl group, the effect on the hydrogen donating ability of SiH moiety increases only slightly.^{3,7} Although under canonical radical chain conditions these silanes are poor reducing agents, there are some interesting applications, in particular using Ph₂SiH₂.⁶³ The radical-based deoxygenation of bis-xanthate **43** is an example (Scheme 13). A variety of arylsilanes with hydrophilic groups have been prepared for testing radical dehalogenations in aqueous media.⁶⁴ Yields varied from poor to good depending on the substrate and the silicon hydride. The debromination of **44** is an example (Scheme 13). 9,10-Disilaanthracenes as an alternative silane for the reduction of halides and a Barton–McCombie type deoxygenation have also been proposed.^{65,66}

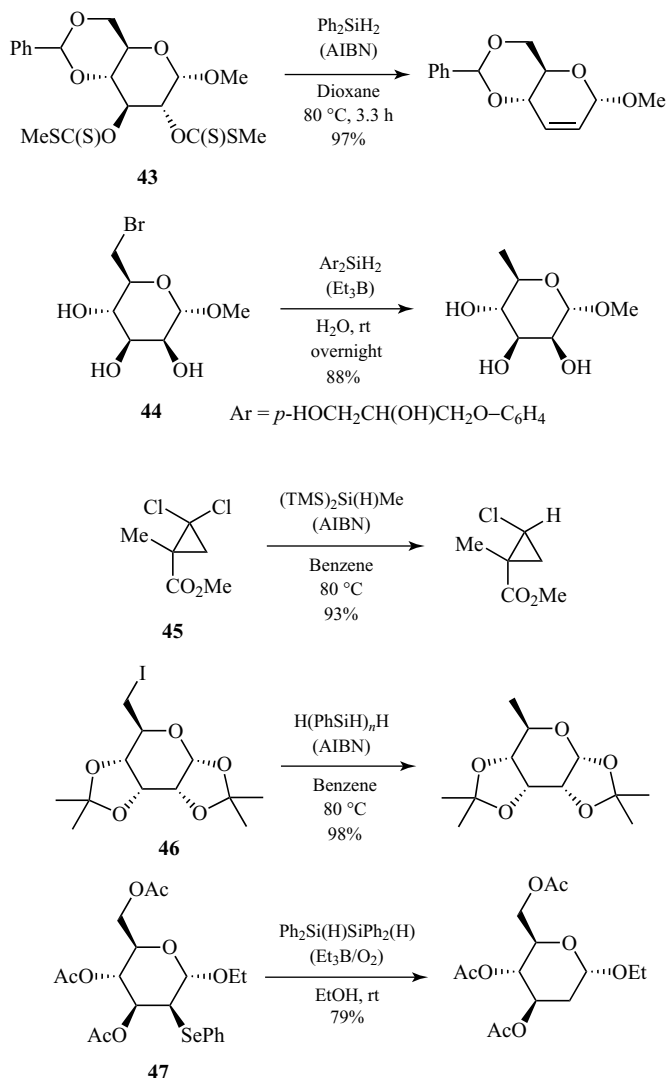
A systematic investigation of organosilanes having different silyl substituents at the SiH

moiety has been carried out with the aim of testing how to tune the reactivity by the choice of substituents. Reductions of a variety of organic derivatives were carried out using RSi(H)Me₂, where R = SiMe₃, SiMe₂SiMe₃, or Si(SiMe₃)₃, and the initiation was provided by benzoyl peroxide or *tert*-butyl perbenzoate (AIBN was found not to be efficient in these cases).⁶⁷ Reduction of a variety of organic derivatives was carried out by using (TMS)₂Si(H)Me under normal reaction conditions, as shown for the reduction of dichloride **45** in Scheme 13.⁶⁸ Although (TMS)₂Si(H)Me does not react spontaneously with oxygen at room temperature, a reaction takes place at 80 °C similar to the one described for (TMS)₃SiH in Scheme 10.⁶⁹ Poly(hydrosilane)s of the type H(RSiH)_nH, where R = *n*-hexyl or phenyl, rival the effectiveness of (TMS)₃SiH in radical chain dehalogenation reactions.⁷⁰ The reduction of iodine **46** is an example. Ph₂Si(H)SiPh₂(H) has been used in the reductions of alkyl bromides, phenyl chalcogenides (e.g., selenide **47**), and xanthates with AIBN in refluxing ethanol or Et₃B/O₂ at room temperature. Yields varied from moderate to excellent, depending on the experimental conditions.⁷¹

Substitution at the SiH moiety has been carried out with alkylthio groups, such as MeS and *i*-PrS. Tris(alkylthio)silanes, (RS)₃SiH, are radical-based reducing agents which can effect the reduction of bromides, iodides, xanthates, phenylselenides, and isocyanides in toluene, using AIBN as the initiator, at 85 °C.⁷²

Silylated cyclohexadienes have been prepared and utilized as radical transfer agents. Silylated 1,4-cyclohexadienes were introduced as reducing agents in radical chain reactions such as dehalogenation, deoxygenation via thionocarbonate ester, and deselenization, as well as hydrosilylating agents for some alkenes and alkynes.^{73–75} Two examples are given in Scheme 14, which show that these reactions also work well with different substituted silyl moieties.⁷⁴ The CH₂ moiety of cyclohexadiene acts as the H-donor with the formation of cyclohexadienyl radical as the intermediate, which rapidly ejects the silyl substrate. Silane-addition products of terminal alkenes are also reported in moderate yields. Two examples are given using the silylated cyclohexadiene **49** (Scheme 14).⁷⁵

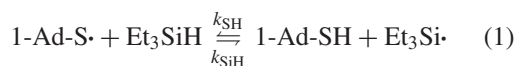
The low reactivity of alkyl- and/or phenyl-substituted organosilanes in reduction processes can be ameliorated in the presence of a catalytic

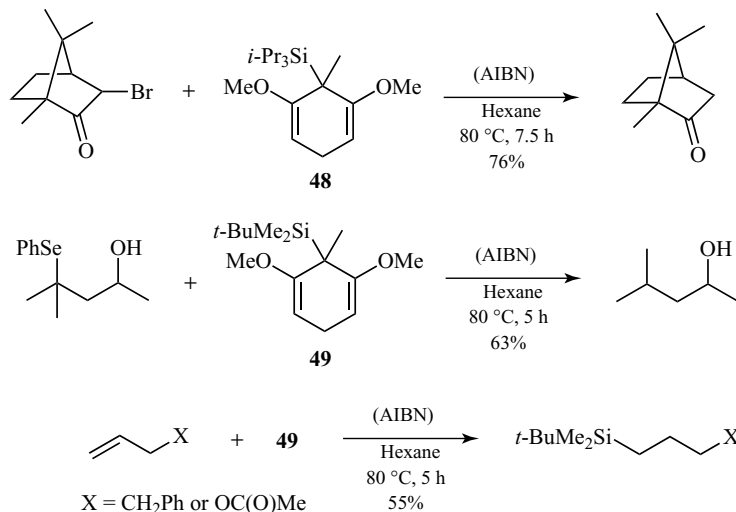


Scheme 13 Removal of functional groups by a variety of silicon hydrides.

amount of alkanethiols. The reaction mechanism is analogous to the one reported in Scheme 11 for $(\text{TMS})_3\text{SiH}$ /thiol pair and shows that alkyl radicals abstract hydrogen from thiols and the resulting thiyl radical abstracts hydrogen from the silane. For this procedure, the term *polarity-reversal catalysis* was coined, which has been applied to dehalogenation, deoxygenation, and desulfurization reactions.^{52,76} For example, 1-bromoadamantane is quantitatively reduced with 2 equiv of triethylsilane in the presence of a catalytic amount of *tert*-dodecanethiol. The reduction of aromatic azides affords anilinosilanes

and hence the corresponding anilines in virtually quantitative yields.⁷⁷ The reaction of thiyl radicals with alkyl-substituted silanes is the key step, being strongly endothermic and reversible. For example, the rate constants k_{SH} and k_{SiH} for the couple triethylsilane/1-adamantanethiol are 3.2×10^4 and $5.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, respectively, at 60°C (1). The equilibrium constant $K_{\text{eq}} = k_{\text{SH}}/k_{\text{SiH}}$ is 6.2×10^{-4} and hence ΔG° is $+20.4 \text{ kJ mol}^{-1}$.⁷⁶

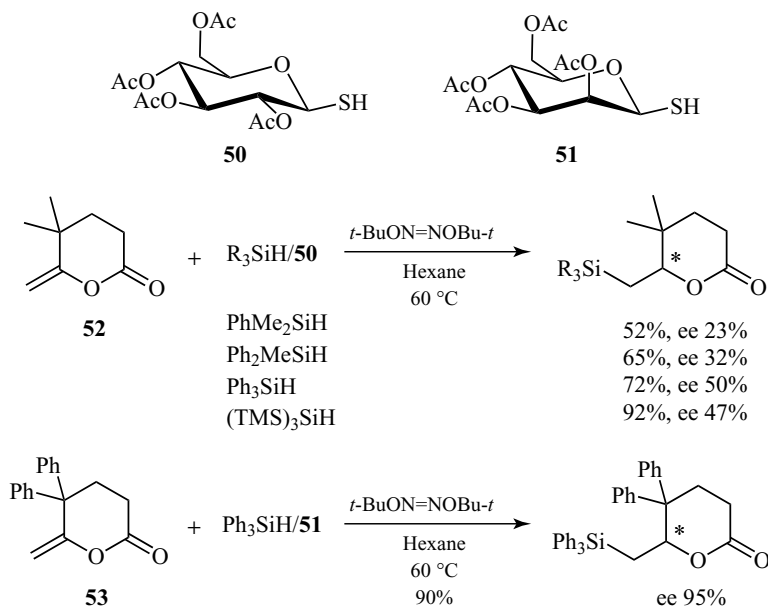




Scheme 14 Silylated cyclohexadienes as radical-based reducing agents.

Radical chain hydrosilylation of alkenes has been investigated in some detail.⁷⁵ Poor to moderate yields were obtained for the reaction of Et_3SiH with alkenes at $60\text{ }^\circ\text{C}$.⁷⁸ Thiol catalysis is more effective for the addition of arylsilanes than trialkylsilanes, presumably because the hydrogen abstraction by thiyl radical is more rapid from aromatic silanes.

This methodology has been extended to enantioselective hydrosilylation using optically active thiols as catalysts, such as the thioglucose tetraacetate **50** or the β -mannose thiol **51**.⁷⁹ Scheme 15 shows the hydrosilylation of methylenelactone **52** with various silicon hydrides and thioglucose tetraacetate **50** as the catalyst. Both yields and enantiomeric purities



Scheme 15 Hydrosilylation of C–C double bonds by various silicon hydride/thiol pairs.

increase with the degree of phenyl substitution at silicon. Thiols have also been shown to catalyze the addition of $(\text{TMS})_3\text{SiH}$ to alkenes. Higher enantioselectivities were generally found when β -mannose thiol **51** was used as hydrogen donor. The extra bulkiness provided by the *gem*- β -diphenyl groups in the alkene **53** compared to the alkene **52** is responsible for the high enantiomeric purity observed.

3 SILANES AS MEDIATORS OF CONSECUTIVE RADICAL REACTIONS

3.1 $(\text{TMS})_3\text{SiH}$ as Mediator

Synthetic strategies based on multistep radical reactions have steadily grown in popularity. Silanes, and in particular $(\text{TMS})_3\text{SiH}$, as mediators have contributed substantially to this area, often giving the best results, compared to other reducing reagents, by coupling reactivity with stereoselectivity.^{2,4,6,7} For example, Nicolaou and coworkers found $(\text{TMS})_3\text{SiH}$ to be a superior reagent in the radical-based approach toward the synthesis of azadirachtin, an antifeedant agent used as insecticide, as well as in other related systems.^{80,81}

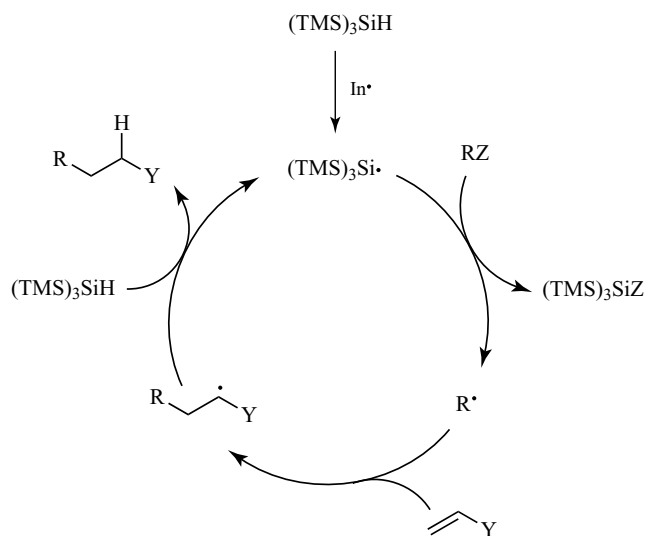
The carbon-centered radical $\text{R}^\bullet$, resulting from the initial atom (or group) removal by a silyl radical or

by addition of a silyl radical to an unsaturated bond, can be designed to undergo a number of consecutive reactions prior to H-atom transfer. The key step in these consecutive reactions generally involves the intra- or intermolecular addition of $\text{R}^\bullet$ to a multiple-bonded carbon acceptor. As an example, the propagation steps for the reductive alkylation of alkenes by $(\text{TMS})_3\text{SiH}$ are shown in Scheme 16.⁸ This sequence requires a radical reagent that is fast to abstract the group Z from the starting material but not too fast to reduce the corresponding $\text{R}^\bullet$ prior its addition to the multiple bonds. $(\text{TMS})_3\text{SiH}$ characteristics correspond well with these features, since the reagent is a slightly slower hydrogen donor than Bu_3SnH (Figure 1).

3.1.1 Intramolecular Reactions

The majority of sequential radical reactions deal with cyclization as the key step. The constructions of carbocycles, oxygen, and nitrogen heterocycles using $(\text{TMS})_3\text{SiH}$ as a mediator are numerous and represent the importance and expansion of this synthetic approach. Below, we have collected a number of reactions mostly from the recent work in the area of intramolecular reactions.

In the construction of carbocycles, five-membered ring formation has been used for preparing spiro-compounds starting from bromide **54** in



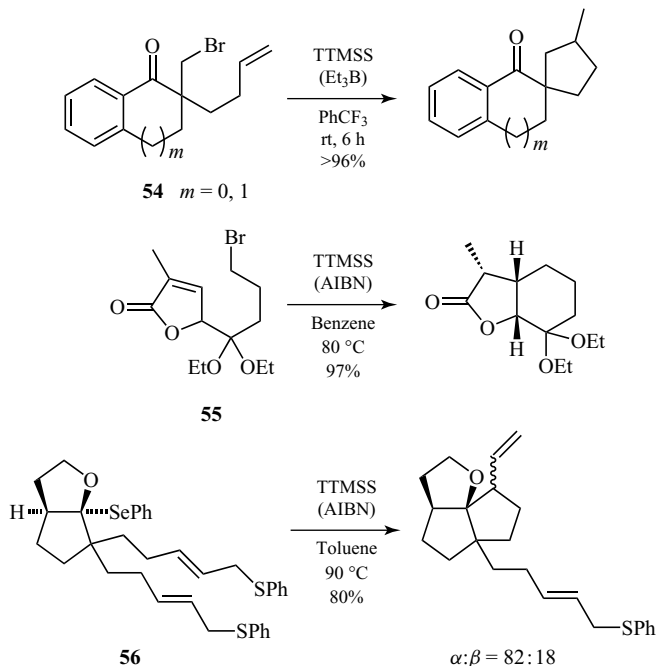
Scheme 16 Reductive alkylation of alkenes by $(\text{TMS})_3\text{SiH}$ ($\text{In}^\bullet$ is the radical derived from the initiator).

excellent yields (Scheme 17).⁸² Bromide **55** is the starting material of six-membered radical cyclization under standard reaction conditions.⁸³ It is worth underlining the complete diastereocontrol in which three contiguous stereocenters are generated in one step with >95% stereoselectivity. For preparing fused cyclic compounds such as functionalized diquinanes, the reaction of selenide **56** with (TMS)₃SiH furnished the expected product in 80% yield and in an $\alpha : \beta$ ratio of 82 : 18, as the result of a kinetic controlled reaction (Scheme 17).⁸⁴

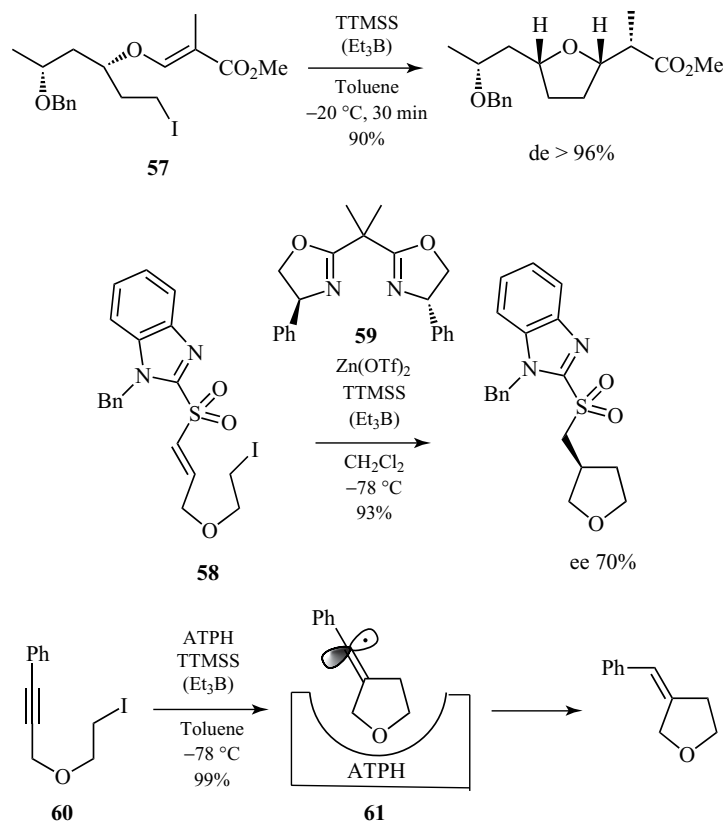
As a strategy for the construction of cyclic ethers, the radical cyclization of β -alkoxyacrylates was used for the preparation of *cis*-2,5-disubstituted THFs and *cis*-2,6-disubstituted tetrahydropyrans. An example is given with β -alkoxymethacrylate **57** as precursor for the cyclization of the optically active benzyl ether of (+)-methyl nonacate, exclusively formed as the threo product (Scheme 18).⁸⁵ Enantioselective radical cyclizations have been performed by using chiral Lewis acids together with (TMS)₃SiH as reducing agent. An example with 70% ee is given, in which the selective coordination of one of the enantiotopic sulfonyl oxygen in ω -iodoalkenyl sulfone **58** is achieved using Zn(OTf)₂-bis(oxazoline)-Ph **59**.⁸⁶ After the

5-*exo*-trig cyclization, the hydrogen atom transfer from silane proceeds with high enantioselectivity to give the cyclic ether in 90% yield. Similar asymmetric reactions were extended to 6-*exo*-trig cyclization as well as to 5-*exo*-trig cyclization of vinyl radicals, with good yields and enantioselectivity.⁸⁶ Another example of Lewis acid complexation that assists the radical cyclization is given by aluminum tris(2,6-diphenyl phenoxide) (ATPH).⁸⁷ The β -iodoether **60** can be complexed by 2 equiv of ATPH, which has a very important template effect, facilitating the subsequent radical intramolecular addition and orienting the (TMS)₃SiH approach from one face in radical **61**. The result is the formation of a cyclization product with *Z* selectivity and in quantitative yield (Scheme 18).

An example of acyl radical cyclization is given for substrate **62** (Scheme 19).⁸⁸ The careful choice of the configuration of the double bond, combined with conformational features of the pre-existing ring in the starting material **62**, can improve the poor diastereoselectivity of 6-*exo*-trig cyclizations. The (iodomethyl)cyclobutane derivative **63** undergoes ring-expansion with (TMS)₃SiH to afford the *cis*-oxepane in excellent yield (96%).⁸⁹ The higher selectivity of (TMS)₃SiH compared



Scheme 17 Construction of carbocycles using (TMS)₃SiH.

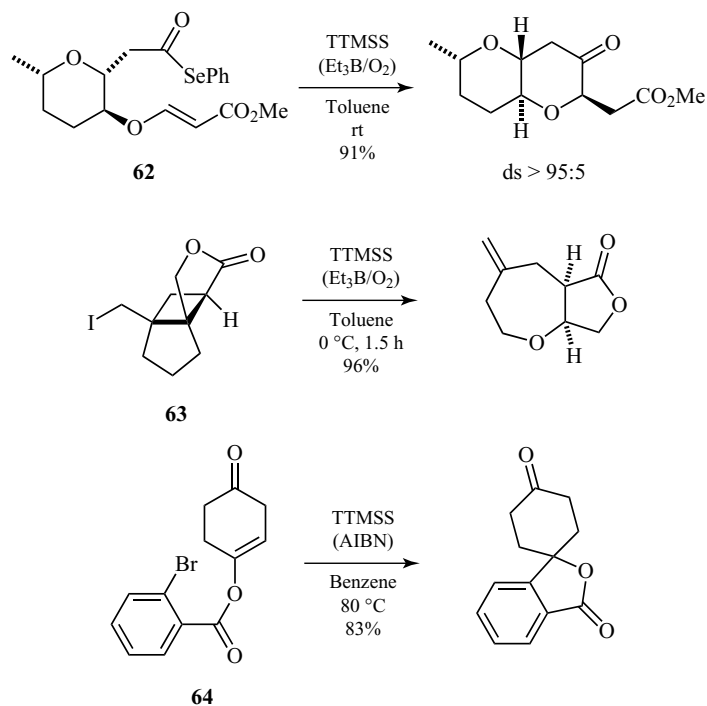


Scheme 18 Furan-ring construction using $(\text{TMS})_3\text{SiH}$.

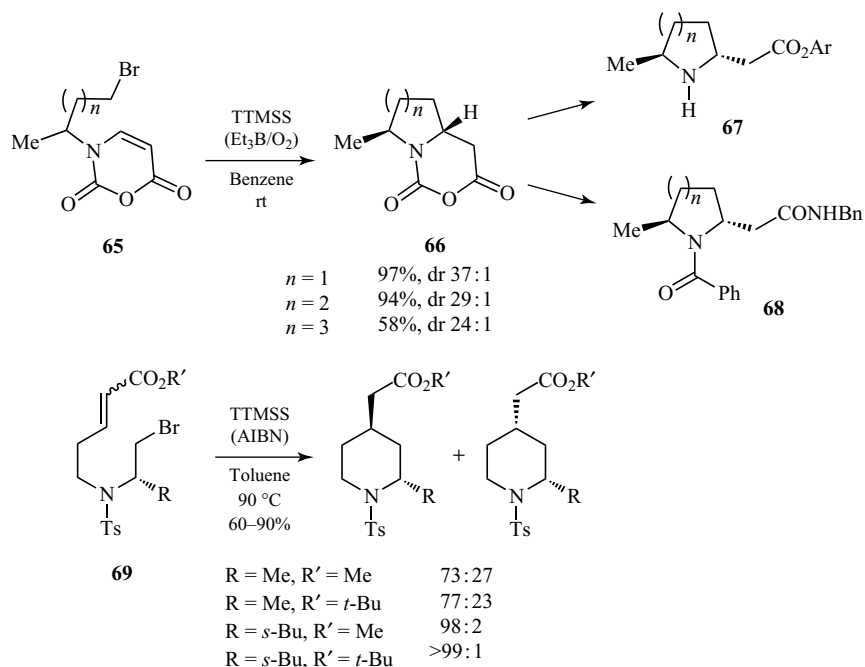
to Group 14 reducing agents was ascribed to the greater steric bulkiness of the silane. The cyclization strategy using $(\text{TMS})_3\text{SiH}$ as mediator has also been carried out for lactone formation. An example of appropriately designed *o*-bromobenzoate ester **64** allowed successful spirocyclization processes and lactone synthesis.⁹⁰ A series of keto spiro- γ -lactones, spirodilactones, spiro lactone-lactams, and spiro lactone-thiolactones have been prepared by this quite general route.^{90,91}

A synthetic strategy for the stereoselective construction of *trans*-2,5-disubstituted cyclic amines has been reported.⁹² The alkyl bromides **65** were prepared with an oxouracil moiety to function as the free-radical acceptor. The reaction with $(\text{TMS})_3\text{SiH}$ and Et_3B in the presence of air at room temperature provided the corresponding azabicycles **66** in high diastereomeric ratio, as the consequence of the stereoselective intramolecular addition of alkyl radical to the oxouracil acceptor, driven by the

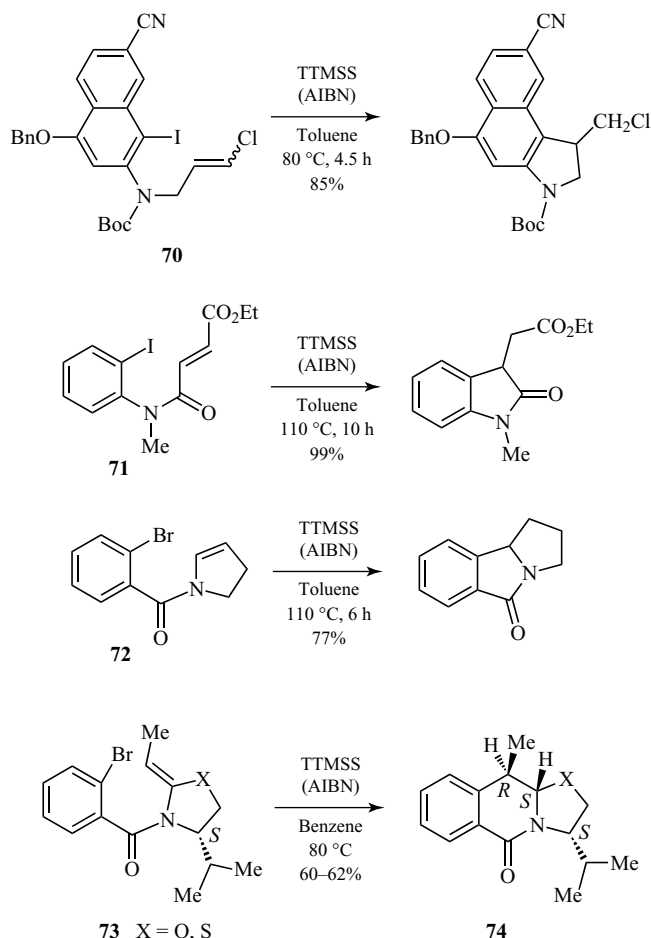
rotamer preference (Scheme 20). Similar results have been obtained by replacing the Me group with Ph in the chain. Further treatment of the azabicycles **66** afforded the amino esters **67**, using *p*-methoxyphenol, or the dipeptides **68**, by reaction with BnNH_2 and then $\text{Et}_3\text{N}/\text{PhC}(\text{O})\text{Cl}$. This synthetic strategy has also been adapted to the cyclization of acyl radicals.⁹² A diastereoselective radical route to 2,4-disubstituted piperidines has been achieved in good yields (60–90%) by cyclization of 7-substituted-6-aza-8-bromooct-2-enoates (**69**) using $(\text{TMS})_3\text{SiH}$ as the reducing agent.^{93,94} Four examples are given in Scheme 20, where the *trans/cis* diastereomeric ratios range from 73:27 for $\text{R} = \text{R}' = \text{Me}$ (90% yield) up to $>99:1$ for $\text{R} = s\text{-Bu}$ and $\text{R}' = t\text{-Bu}$ (60% yield). Although the bulkiness of the ester does not appear to have a significant effect on the stereoselectivity, the bulkiness of the 2-substituent increases the pseudo $\text{A}^{1,3}$ strain and favors the *trans* product.



Scheme 19 Construction of cyclic ethers and lactones using $(\text{TMS})_3\text{SiH}$.



Scheme 20 Construction of cyclic amines using $(\text{TMS})_3\text{SiH}$.



Scheme 21 Construction of nitrogen heterocycles using $(\text{TMS})_3\text{SiH}$.

The aryl radical cyclization has been successfully used for the preparation of a variety of indoline derivatives^{95–98} and polycyclic lactams^{99,100} (Scheme 21). Radical cyclization of **70** mediated by $(\text{TMS})_3\text{SiH}$ under standard reaction conditions worked well to afford the cyclic product in 85% yield.⁹⁷ Similar results are obtained for a benzothienopyridine analog.⁹⁶ Another example is shown in the cyclization of **71** mediated by $(\text{TMS})_3\text{SiH}$ and AIBN in refluxing toluene.⁹⁸ Starting from readily available substrates, a new one-pot procedure has been devised to prepare polycyclic lactams and sultams. 2-Pyrroline **72** was obtained from *N,N*-bisallylamide by ring-closure metathesis and subsequent isomerization promoted by ruthenium hydride complexes, and then underwent radical cyclization to furnish tricyclic lactam in good yield

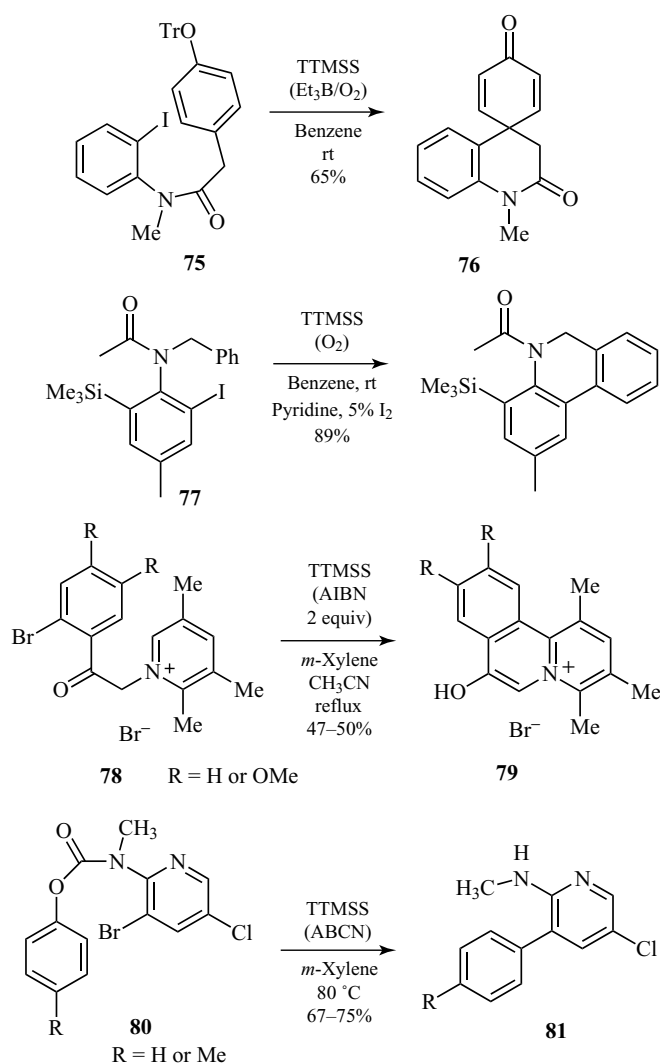
(Scheme 21).⁹⁹ The *N,O*- and *N,S*-heterocyclic fused ring products **74** were also synthesized under radical chain conditions (Scheme 21). Ketene acetals **73** readily underwent stereocontrolled aryl radical cyclization upon treatment with $(\text{TMS})_3\text{SiH}$ under standard reaction conditions to afford the central six-membered ring.¹⁰⁰ The tertiary *N,O*- and *N,S*-radicals formed upon aryl radical reaction at the ketene-*N,X*-acetal double bond ($\text{X} = \text{O}, \text{S}$) appear to have reasonable stability. The stereoselectivity in the hydrogen abstraction step by these intermediate radicals from $(\text{TMS})_3\text{SiH}$ was investigated and found to provide higher selectivities than Bu_3SnH .

$(\text{TMS})_3\text{SiH}$ and AIBN in toluene at 90 °C was used together with an aryl iodide for a

radical-induced transannular ring contraction, which is the key step in the first total synthesis of cavicularin.¹⁰¹ Cyclization of an aryl radical to the adjacent arene further evolved to the target of spirocyclohexadienone, a moiety common to various biologically active compounds.¹⁰² An example is shown in Scheme 22 for the synthesis of spirodihydroquinolone **76**. A solution of the appropriate trityl precursor **75** in benzene (0.15 M) was treated with 1.2 equiv of (TMS)₃SiH and 1.2 equiv of Et₃B, and the resulting mixture was stirred at room temperature open to air until the starting material was consumed (typically 3 hours). The

reactions proceed via ipso cyclization of aryl radicals to oxygen-substituted aromatic ring, followed by β -fragmentation of the trityl substituent to give the desired product (see **Radical Arylations**). The (TMS)₃SiH-mediated cyclization of aryl iodide **77** is facilitated by oxidative rearomatization with oxygen.¹⁰³ Actually, the AIBN is not necessary for the good performance of the reaction, and a mechanistic proposal is given below.

Synthesis of quinolinylum salt **79** was obtained in moderate yields by slow addition of a solution of 2 equiv of both TTMSS and AIBN in *m*-xylene to a solution, at reflux temperature, of pyridinium salt



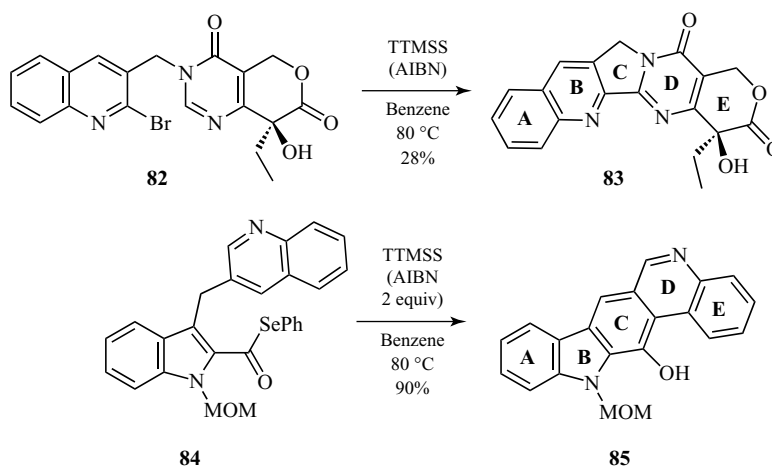
Scheme 22 Cyclization of an aryl radical to the adjacent arene mediated by (TMS)₃SiH.

78 in dry acetonitrile (Scheme 22).¹⁰⁴ Analogously, the reaction of bromopyridine **80** with TTMSS and azobis(cyclohexanenitrile) (ABCN) in *m*-xylene at 80 °C afforded the 3-aryl-2-aminopyridines **81** through an ipso-substitution of the initially formed aryl radical to the adjacent arene with formation of the carbamoyloxyl radical that affords the aminyl radical by decarboxylation and final reduction by TTMSS.¹⁰⁵

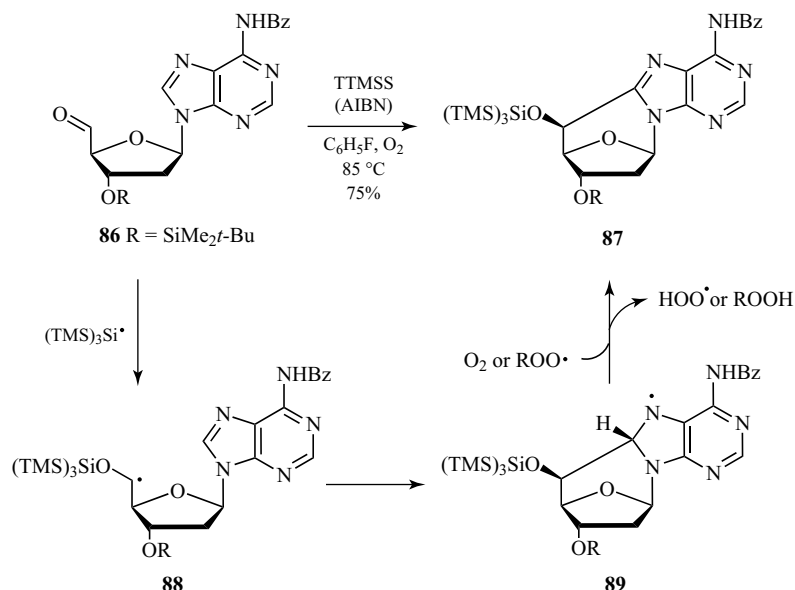
(TMS)₃SiH-mediated radical cyclization has been applied to the formation of ring **C** in two pentacyclic alkaloids (Scheme 23).^{106,107} After condensation of the **AB** and **DE** rings, the appropriate precursors, bromide **82** and seleno ester **84**, were treated with (TMS)₃SiH and AIBN in benzene to give the pentacycles **83** and **85**, respectively. In the reaction of **82**, AIBN was used in catalytic amount,¹⁰⁶ whereas in the reaction of **84** the initiator was in large excess.¹⁰⁷ The reactions are not radical chain reactions, because the radical derived from the decomposition of AIBN involved in some way in the oxidation or rearomatization of the intermediate radical after cyclization.

The (TMS)₃SiH undergoes addition to the carbonyl group of aldehydes and ketones to give the hydrosilylation products.¹⁰⁸ However, synthetically useful addition to carbonyl is limited.^{109–111} The most interesting example is the synthesis of (5′S)-5′,8-*cyclo*-2′-deoxyadenosine, a tandem-type lesion observed among the DNA modifications.¹¹² The reaction of aldehyde **86** with (TMS)₃SiH under typical reaction conditions, that is, 1.2

equiv of reducing agent and catalytic amount of AIBN at 80 °C, showed a low conversion of the starting aldehyde. However, when aldehyde **86** was treated with 5 equiv of (TMS)₃SiH and stoichiometric amount of AIBN at 85 °C under air, it was converted quantitatively in 2 hours to the cyclonucleoside **87** as the sole product in a 75% yield (Scheme 24).¹¹¹ From a mechanistic point of view, the addition of (TMS)₃Si• radical to aldehyde **86** affords the C5′ radical **88** which then attacks intramolecularly the adenine moiety to give **89**. The cyclization occurs with defined stereochemistry, affording exclusively the chair conformation in the forming rings. Oxygen has been suggested to facilitate subsequent rearomatization either directly¹¹³ or via a peroxy radical. It is worth mentioning that it has been reported that (TMS)₃SiCl can be used for the protection of primary and secondary alcohols.¹¹⁴ These (TMS)₃Si-protected alcohols can be deprotected by the usual reaction conditions employed in organic synthesis for the deprotection of other silyl groups. The deprotected alcohols were obtained in 62–95% yields by using photolysis at 254 nm. Indeed, exposure of **87** to UV irradiation for 30 min at room temperature in CH₂Cl₂/CH₃OH (8:3) mixture afforded the 5′-*O*-desilylated compound in 54% yield.¹¹¹ Although a simple hydrosilylation/deprotection combination is formally equivalent to the ionic reduction of carbonyl moieties, the use of an aldehyde functional group in consecutive radical reactions followed by photodeprotection is a new approach for the formation



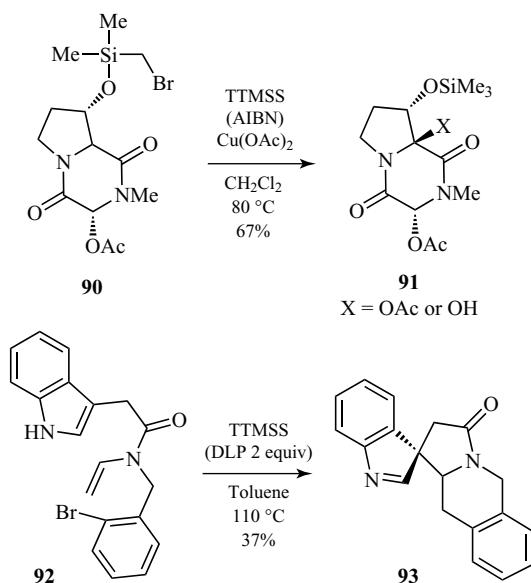
Scheme 23 Construction of pentacyclic alkaloids using (TMS)₃SiH.



Scheme 24 Reaction mechanism for the synthesis of (5'*S*)-5',8-cyclo-2'-deoxyadenosine.

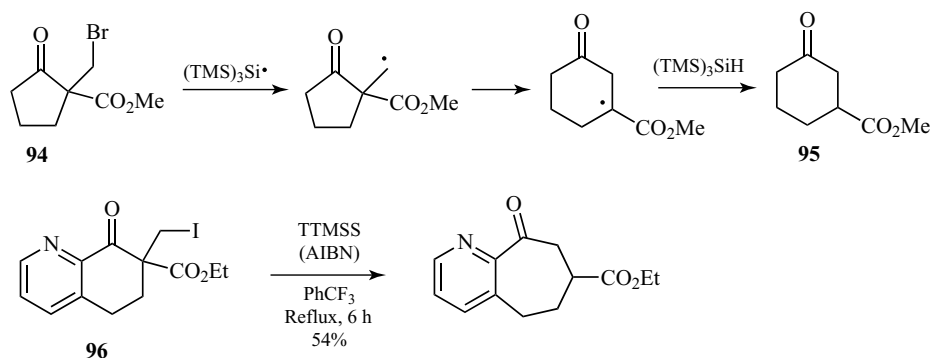
of new stereogenic centers based on the hindered properties of the (TMS)₃Si-group.

Another interesting example of radical translocation followed by oxidation, where (TMS)₃SiH proved to be the best radical mediator, is illustrated in Scheme 25.¹¹⁵ In particular, the radical-promoted functionalization of the angular carbon was developed with the readily available bromomethylsilyl acetal **90**. A large excess of Cu(OAc)₂ (10 equiv) and AIBN (3 equiv) is required together with (TMS)₃SiH (3 equiv). The electron-rich captodative radical produced after the 1,5-hydrogen atom transfer is readily oxidized by Cu(OAc)₂ to afford the desired acetate **91** in 42% yield, together with the corresponding alcohol in 25% yield. Such a procedure for selective oxidation of the angular methane carbon of hydroxyproline-derivatives should be useful for oxidative elaboration of analogous molecules. On the other hand, when bromide **92** is treated with (TMS)₃SiH and 2 equiv of dilauroyl peroxide (DLP), the spiro-derivative **93** was obtained in one step and 37% yield. The organic peroxide appears to act as the initiator and the oxidant. In this case, the 6-endo cyclization of aryl radical onto an enamide double bond is followed by a consecutive oxidative-ionic spirocyclization at C-3 of an indole nucleus.¹¹⁶

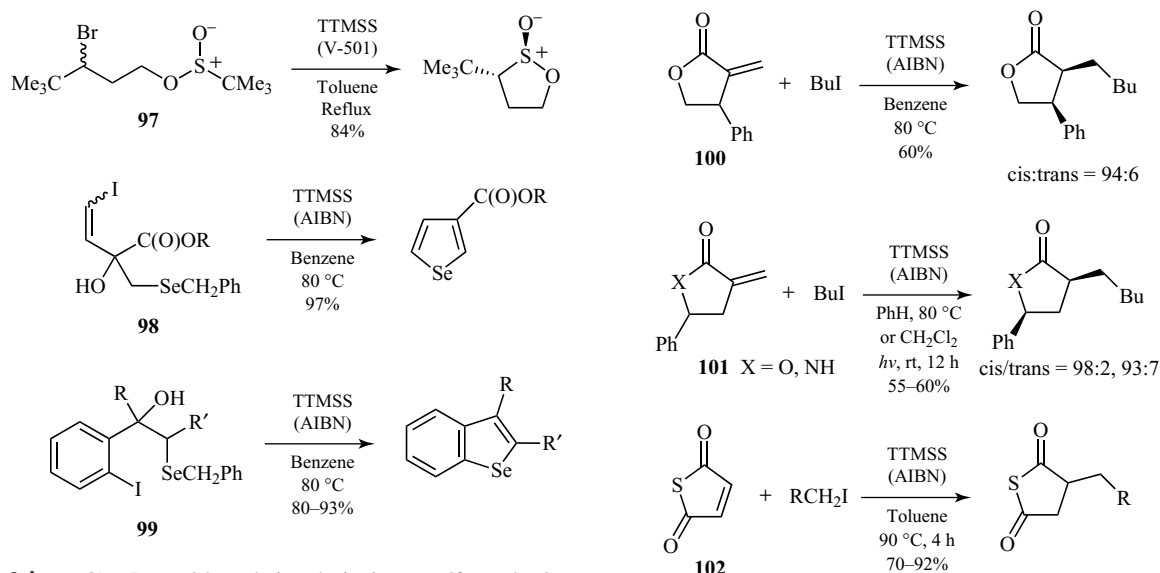


Scheme 25 Examples of unimolecular radical processes followed by oxidation.

A general method of one-carbon ring-expansion of cycloketones was introduced in the late 1980s and proved to be a powerful synthetic tool.^{117,118} (TMS)₃SiH has been used for studying in details the mechanism of ring-expansion of cyclopentanone **94**



Scheme 26 Ring-expansion mediated by $(\text{TMS})_3\text{SiH}$.



Scheme 27 Internal homolytic substitution at sulfur and selenium mediated by $(\text{TMS})_3\text{SiH}$.

Scheme 28 Intermolecular C–C bond formation using TTMS as mediator.

to cyclohexane **95** as shown in Scheme 26.^{118,119} This protocol has been successfully applied to the iodo derivative **96** with the formation of a seven-membered ring in 54% yield.⁸²

A method for the synthesis of cyclic sulinates based on the intramolecular homolytic substitution at sulfur by alkyl radicals was found to be effective.¹²⁰ An example is illustrated for the reaction of di-*tert*-butyl-substituted sulfinate **97** with TTMS and 4,4'-azobis(4-cyanovaleric acid) (V-501) in refluxing toluene which affords exclusively the *trans* isomer in good yield. C–Se and C–Te bonds are formed by an internal homolytic substitution of vinyl or aryl radicals at selenium or tellurium with

the preparation of selenophenes and tellurophenes, respectively (see **Intramolecular Homolytic Substitutions in Synthesis**).¹²¹ Two examples are shown in Scheme 27, where $(\text{TMS})_3\text{SiH}$ was used in the cyclizations of vinyl iodides **98** and aryl iodides **99** that afford (after concomitant dehydration) the selenophene-3-carboxylates and benzene-selenophenes in good yields.^{121,122} The presence of $(\text{TMS})_3\text{SiH}$ after the reductive cyclization to give 3-hydroxylselenophenes induced also the dehydration, presumably through an intermediate silyl ether.

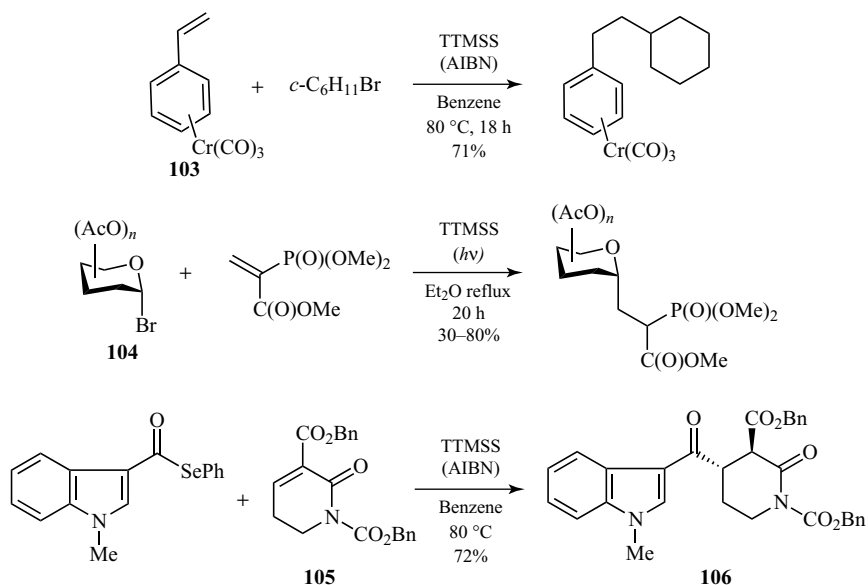
3.1.2 Intermolecular Reactions

Intermolecular C–C bond formation mediated by $(\text{TMS})_3\text{SiH}$, which is illustrated in Scheme 16, has been the subject of several synthetically useful investigations. The effect of the bulky $(\text{TMS})_3\text{SiH}$ can be appreciated in the example shown in Scheme 28. The reaction of α -methylenebutyrolactone **100** with n -BuI affords of α,β -disubstituted lactone in good yield and diastereoselectivity.¹²³ The analogous reaction of lactone or lactam **101** having γ -phenyl with n -BuI gives the corresponding α,γ -disubstituted derivatives also with high *cis* selectivity.^{123,124} The *anti*-rule can be successfully applied for the prediction of stereochemistry: that is, H-donation preferentially occurs in the *anti* fashion to the substituents in the cyclic radical intermediate, in order to reduce steric interference with bulky silicon hydride. Indeed, for the analogous reactions of β - or γ -alkyl substitution were found to be less selective.¹²³ A variety of iodoalkyl derivatives undergo clean free-radical addition to thiomaleic anhydride **102** to give substituted thiosuccinic anhydrides in high yield under standard reaction conditions.¹²⁵

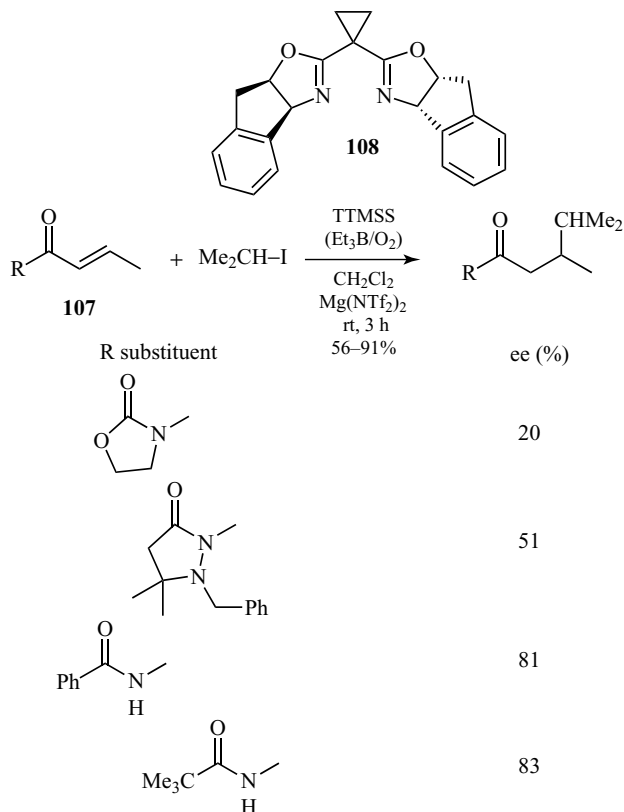
Alkyl radical addition reactions to styrene chromium tricarbonyl **103** can be accomplished

using alkyl halides (10 equiv) and TTMSS (5 equiv) in the presence of AIBN in refluxing benzene.¹²⁶ As an example, the addition of cyclohexyl radical is given in Scheme 29. These reactions are believed to proceed through intermediates in which the unpaired electron is interacting with the adjacent arene chromium tricarbonyl moiety since the analogous reaction with styrene affords only traces of addition products. Another interesting case of C–C bond formation is the radical reaction at the anomeric center of carbohydrates with vinylphosphonate derivatives.^{127,128} Indeed, the highly stereoselective preparation of α -substituted C-glycosyl phosphonates in an $\alpha:\beta$ ratio of 98:2 was achieved by reductive addition of bromide **104** to α -phosphonoacrylate. Yields (in parenthesis) depend on the sugar configuration: D-galacto (80%), D-manno (47%), D-glucos (30%), and L-fuco (62%).¹²⁸ The use of $(\text{TMS})_3\text{SiH}$ with acyl selenides can also yield new C–C bond formation with the α,β -unsaturated lactam ester **105**. The resulting ketone **106** can be envisaged as potentially useful for the synthesis of 2-acylindole alkaloids.¹²⁹ The combined effects of H-donating ability and steric hindrance by the silicon hydride are evident in the stereochemical outcome.

Schemes 30 and 31 show two classes of intermolecular C–C bond formation carried out



Scheme 29 Intermolecular C–C bond formation using TTMSS as mediator.

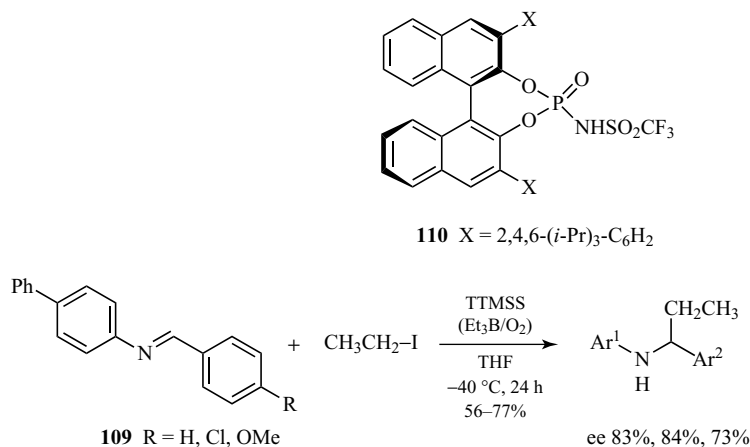


Scheme 30 Enantioselective radical reactions using TTMSS as mediator.

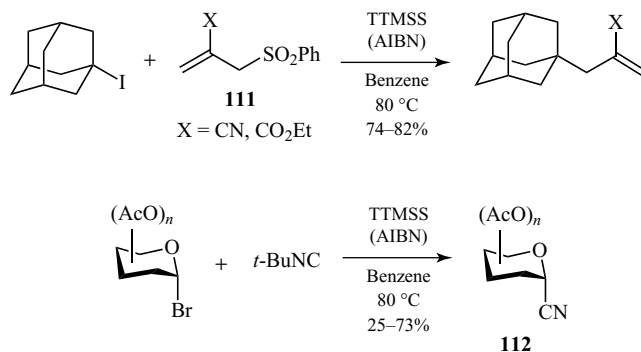
by Lewis acid-mediated enantioselective radical reactions.^{130,131} Conjugated radical additions to a variety of α,β -unsaturated imides **107** were performed at room temperature using 3 equiv of the hydrogen donor TTMSS and $\text{Et}_3\text{B}/\text{O}_2$ as initiator in CH_2Cl_2 .¹³⁰ The chiral Lewis acid derivative from magnesium triflimide and bisoxazoline **108** was used. Modest enantioselectivities of 20% and 51% were obtained for oxazolidinone-derived and pyrazolidinone-derived crotonate, respectively. However, substituted imides were found to give the best yields and enantioselectivities. Phenyl, 4-Cl-phenyl, and *tert*-butyl imide substituents provided enantioselectivity enhancement, the last one giving 83%. On the other hand, binaphthol-derived chiral phosphoric acid catalysts were applied to radical addition reactions of imines, which provided chiral amines in good yields and good enantioselectivities.¹³¹ Three examples are shown in Scheme 31. The highest enantiomeric excess was obtained for the addition of ethyl radical to imine **109** using the

catalyst **110** in THF at -40°C . The enantioselectivities were not affected by the electronic properties of imines.

Intermolecular formation of C–C bond can also be coupled with β -elimination process. In this case, the reaction partners are designed to generate the alkyl radicals $\text{R}^\bullet$, which gives the addition to unsaturated bonds. The radical adducts obtained so far do not terminate by H donation from $(\text{TMS})_3\text{SiH}$, but give the β -elimination process with loss of radical $\text{X}^\bullet$ that abstracts hydrogen from silicon hydride in order to complete the radical chain. This strategy can be successfully carried out by the proper choice of the X group (that can give a stabilized radical species) and the hydrogen donor. Examples are given in Scheme 32, which formally represent an allylation and a cyanation protocol, respectively. Radical allylation with $(\text{TMS})_3\text{SiH}$ as the mediator and 2-functionalized allyl phenyl sulfones **111** occurred with moderate to good yields, depending on the nature of the starting materials.¹³² The reaction



Scheme 31 Enantioselective radical reactions using TTMSS as mediator.

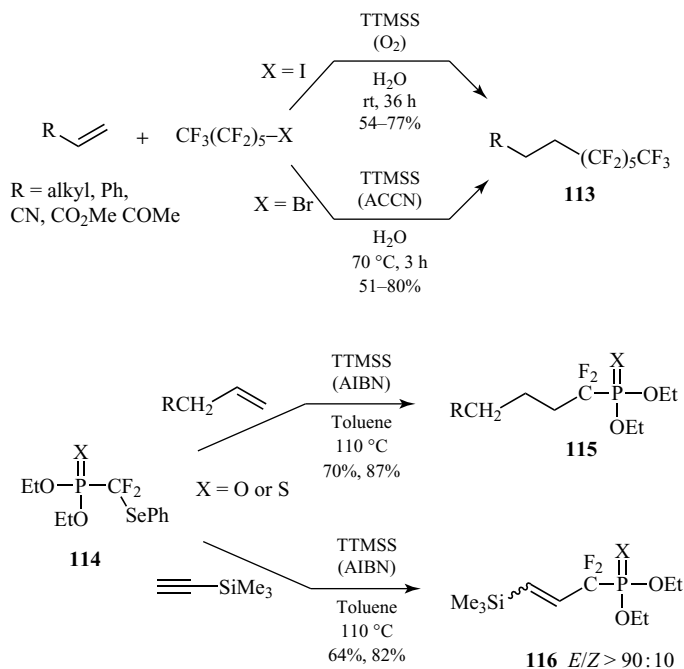


Scheme 32 Allylation and cyanation protocols mediated by TTMSS.

proceeds via addition of the adamantyl radical to the double bond, giving rise to an intermediate that undergoes β -scission to form $\text{PhSO}_2^\bullet$ radical, which abstracts hydrogen from the silane to regenerate $(\text{TMS})_3\text{Si}^\bullet$ radical. The glycosyl radical cyanation yielded α -cyanoglycosides **112** in variable yields, depending on the configuration of sugar: D-galacto (73%), D-manno (40%), D-gluco (71%), and L-fuco (25%). Only α -cyano anomers were formed.¹³³ The key propagation steps for these transformations are the addition of glycosyl radical to the carbon atom of the isocyanide moiety, followed by a fragmentation yielding a *tert*-butyl radical and the desired glycosyl cyanide. *tert*-Butyl radical abstracts hydrogen from the silane to complete the chain.

The $(\text{TMS})_3\text{SiH}$ -mediated addition of fluoroalkyl radicals to alkenes have also been reported.^{134,135} The addition of perfluoroalkyl iodides or bromides to a variety of alkenes afforded the expected adducts

113 with moderate to good yields in water as the solvent (Scheme 33).¹³⁴ Two versatile and convenient methodologies were individuated depending on the nature of the starting materials: that is, with iodides the initiation step with molecular oxygen was sufficient to ensure smooth reaction at room temperature, whereas with bromides the azo-initiation at 70 °C was necessary. Phenylseleno derivatives **114** are found to be good precursors of phosphonodifluoromethyl and phosphonothiodifluoromethyl radicals under normal reaction conditions: that is, refluxing toluene and AIBN as initiator (Scheme 33). Moreover, when generated by the $(\text{TMS})_3\text{Si}^\bullet$ attack on **114** and in the presence of alkenes or alkynes, they gave access to α,α -difluorinated derivatives **115** and β,γ -unsaturated adducts **116**, via carbon–carbon bond formation. The phosphonothio derivatives are obtained in higher yields than phosphonates in both reactions.¹³⁵

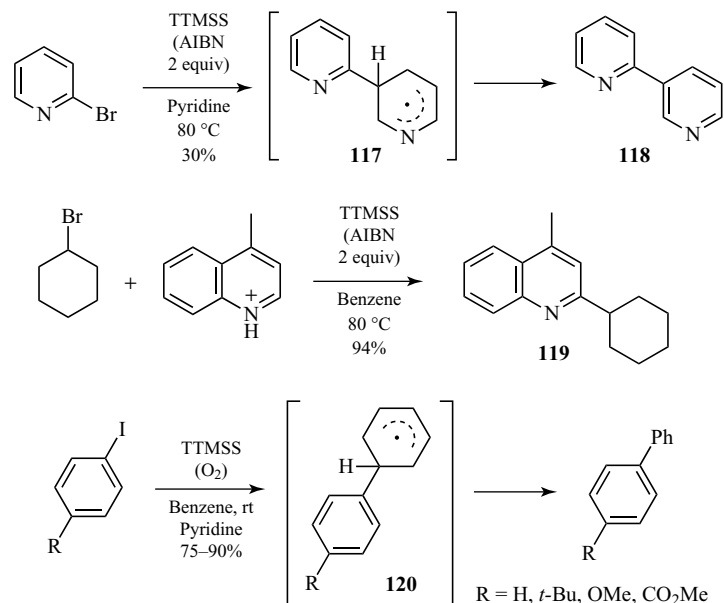


Scheme 33 Fluoroalkyl radicals addition to C–C multiple bonds mediated by TTMSS.

Homolytic aromatic substitution often requires high temperatures, high concentrations of initiator and long reaction times, and typically occurs in moderate yields (see **Radical Arylations**).¹³⁶ Such reactions are often conducted under reducing conditions with $(\text{TMS})_3\text{SiH}$, even though the reactions are not reductions and often finish with oxidative rearomatization. The reaction of 2-bromopyridine with pyridine is an example where a solution containing silane (2 equiv) and AIBN (2 equiv) is slowly added over 8 hours (Scheme 34).¹³⁷ The synthesis of 2,3'-bipyridine **118** presumably occurs via the formation of the cyclohexadienyl radical **117** and its rearomatization by disproportionation with the alkyl radical derived from AIBN.¹³⁶ Heteroaromatic bases activated by protonation with trifluoroacetic acid react with alkyl bromides or iodides and $(\text{TMS})_3\text{SiH}$ under thermal conditions (in the presence of 1–2 equiv of AIBN in benzene), affording the desired product in moderate to good yields.¹³⁸ An example is the reaction of protonated lepidine with cyclohexyl radical to give **119** in 94% yield (Scheme 34). Here again, the stoichiometric quantity of AIBN ensured the rearomatization of the stabilized cyclohexadienyl-type radical intermediate, which reaches a stationary concentration

suitable for intercepting the α -cyanoisopropyl radical, thus leading to the substitution product. Similar examples are the $(\text{TMS})_3\text{SiH}$ -mediated addition of aryl iodides to benzene, which are facilitated by oxidative rearomatization of **120** with oxygen.¹⁰² Here, AIBN is not necessary for good performance of the reaction. The reaction proceeds well in both inter- and intramolecular (*vide supra*) versions.

An interesting methodology for the synthesis of *N*-alkoxylamines mediated by $(\text{TMS})_3\text{SiH}$ has also been developed.¹³⁹ The method consists of the trapping of alkyl radicals generated *in situ* by stable nitroxide radicals. To accomplish this simple reaction sequence, an alkyl bromide or iodide was treated with $(\text{TMS})_3\text{SiH}$ in the presence of thermally generated *t*-BuO $\cdot$ radicals. The reaction is not a radical chain process and stoichiometric quantities of the radical initiator are required. This method allows the generation of a variety of carbon-centered radicals such as primary, secondary, tertiary, benzylic, allylic, and α -carbonyl, which can be trapped with various nitroxides. Examples of the intermolecular phosphorous–carbon bond formation are numerous. The $(\text{TMS})_3\text{SiH}$ -mediated addition of phosphorus-centered radicals to a number of alkenes



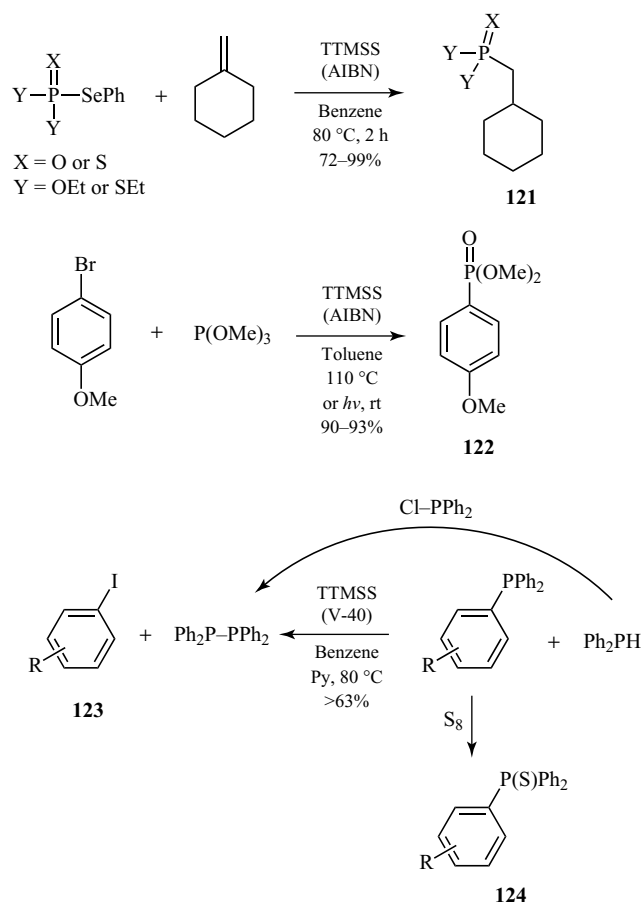
Scheme 34 Homolytic aromatic substitution mediated by TTMSS.

has been investigated in some detail.¹⁴⁰ The synthesis of **121** is an example using four structurally different phenylseleno derivatives with 3 equiv of (TMS)₃SiH and AIBN in refluxing benzene for 2 hours (Scheme 35). Comparative studies on the reaction of the four phosphorus-centered radicals have been obtained. Although the reaction with 1-methylene cyclohexane is efficient with all four derivatives, different selectivities are observed with electron-rich or electron-poor alkenes.¹⁴⁰ Intermolecular C–P bond formation by means of radical phosphonation¹⁴¹ and phosphination¹⁴² has been achieved by reaction of aryl halides with trialkyl phosphites and chlorodiphenylphosphine, respectively, in the presence of (TMS)₃SiH under standard radical conditions (Scheme 35). The phosphonation product **122** was obtained either under UV irradiation at room temperature or in refluxing toluene. The phosphination procedure of iodides **123**, which involves *in situ* formation of tetraphenylbiphosphine from Ph₂PCl, required pyridine in boiling benzene for 20 hours. Phosphinated products were handled as phosphine sulfides **124**. This approach was extended to the phosphination of alkyl halides and sequential radical cyclization/phosphination reaction.¹⁴²

3.1.3 Tandem and Cascade Reactions

The increasing popularity of radical reactions is certainly due to the so-called tandem or cascade reaction: that is, the ability of forming and breaking several bonds in a one-pot procedure (see **Radical Cascade Reactions**). Carbonylation procedures have been successfully used for radical strategies of C–C bond formation. Alkyl halides were carbonylated under moderate pressure of CO in benzene at 80 °C in the presence of (TMS)₃SiH and AIBN.^{22,143} An example of carbonylation of a primary alkyl bromide is shown in Scheme 36. This radical chain reaction proceeds by the addition of the alkyl radical onto carbon monoxide, which generates an acyl radical intermediate **125**, which, in turn, abstracts hydrogen from the silane to give the corresponding aldehyde. Examples of three-component coupling reactions are also given in Scheme 36. The cascade proceeds by the addition of an alkyl or a vinyl radical onto carbon monoxide with formation of an acyl radical intermediate, which can further react with electron-deficient olefins to lead to the polyfunctionalized compounds **126** and **127**, respectively.^{22,143}

Supercritical carbon dioxide (scCO₂) is an emerging reaction medium for free-radical reactions for



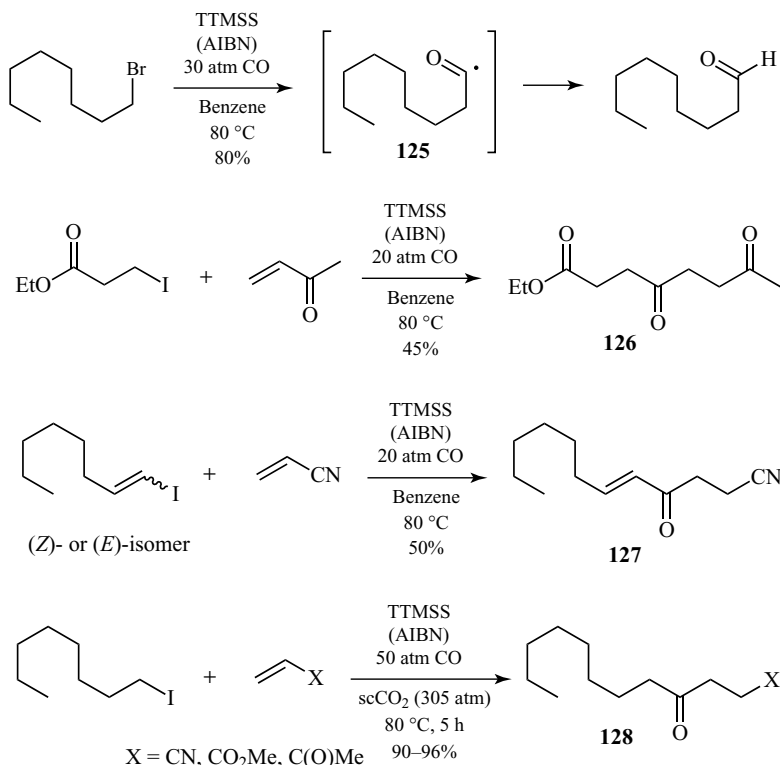
Scheme 35 Intermolecular C–P bond formation using TTMS as mediator.

a number of reasons, such as the pressure-tunable cage effect, the absence of radical chain transfer to the medium,¹⁴⁴ and unique properties such as high diffusivity and high miscibility of the reactant gases.¹⁴⁵ Since $(\text{TMS})_3\text{SiH}$ does not react with CO_2 and CO is highly soluble in scCO_2 , it is thought that radical carbonylation in scCO_2 should be characterized by high tenability of product distribution.¹⁴⁶ Indeed, the extension of the three-component coupling reaction in this reaction medium gave excellent results, as shown in Scheme 36 for the reaction of alkyl iodide with a variety of alkenes to give **128** in excellent yields.

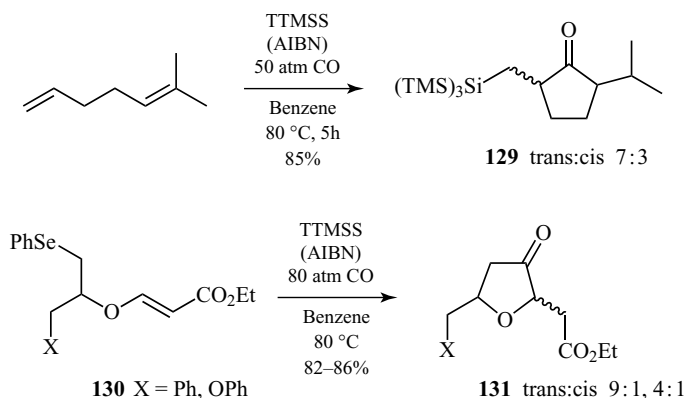
The addition of $(\text{TMS})_3\text{SiH}$ to the substituted 1,5-dienes in the presence of CO is an intramolecular version of the above-mentioned strategy and represents an example of $(4 + 1)$ radical annulation process to give the cyclic ketone

129 (Scheme 37).¹⁴⁷ Indeed, the initial addition of silyl radicals to the least substituted terminus is followed by carbonylation and acyl radical cyclization prior to hydrogen abstraction. This methodology has been further developed for the preparation of cyclic ethers. An example is given for compound **130**, derived from the easy regioselective ring-opening of appropriate epoxides with benzeneselenoate followed by hetero-Michael addition to ethyl propiolate, which underwent radical tandem carbonylation/cyclization reaction in the presence of $(\text{TMS})_3\text{SiH}$ and CO (80 atm) to give **131**.¹⁴⁸

Barton–McCombie deoxygenation of 7-azabenzonorbornanols via xanthate derivatives such as **132** afforded the corresponding 2-azabenzonorbornanes in 64–90% yields.^{149–152} These compounds are not



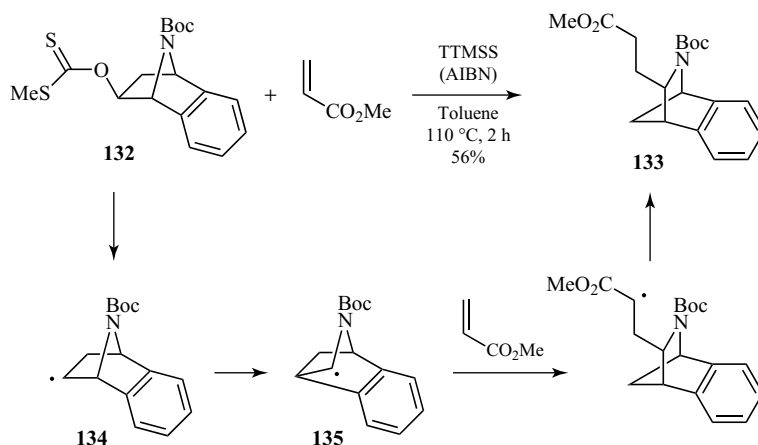
Scheme 36 Three-component coupling reactions mediated by TTMSS.



Scheme 37 Tandem reactions mediated by TTMSS for the construction of cyclic ketones.

readily accessible by other means. The reaction proceeds through the neophyl-type radical rearrangement **134** $\rightarrow$ **135** with a rate constant of $\sim 10^5\text{ s}^{-1}$ at 111°C (Scheme 38).¹⁵⁰ It was also found that the slow addition of silane in the presence of

methyl acrylate (or other electron-deficient alkenes) gave good yields of the rearranged trapped azacycle **133**. Extension of these processes to provide enantio-enriched products was successfully applied after desymmetrization of the starting materials.¹⁵¹

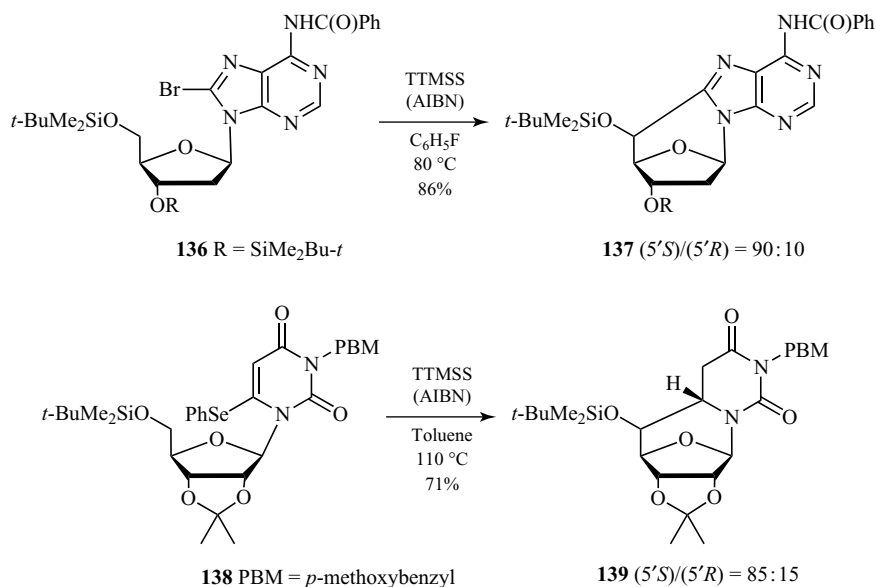


Scheme 38 Synthesis of 2-azabenzonorbornanes via neophyl-type rearrangement.

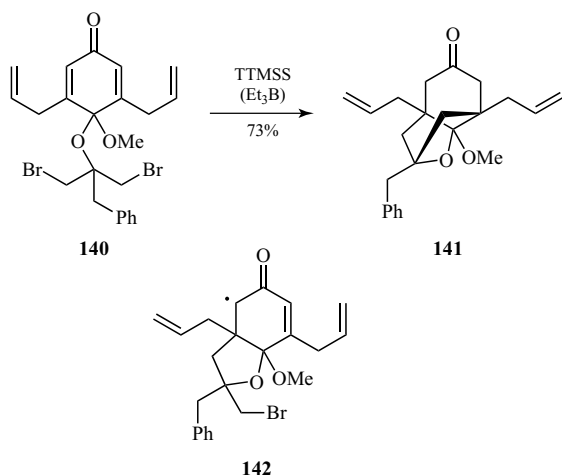
Substituted 5',8-cyclopurine and 5',6-cyclopurimidine nucleosides have been synthesized by combining radical translocation/cyclization steps.^{153,154} Two examples are shown in Scheme 39. Treatment of the 8-bromo derivative **136** or 6-phenylseleno derivative **138** with $(\text{TMS})_3\text{SiH}$ and AIBN in benzene at 80 °C for 4 hours resulted in the cyclonucleosides **137** and **139**, respectively. The initially generated radical on the base moiety by Br or PhSe abstraction translocates to C5' position of sugar by

hydrogen atom transfer followed by cyclization on the base moieties (cf. Scheme 14). Rearomatization or hydrogen abstractions complete the cycle, affording the cyclonucleosides in good yields and diastereomeric ratio in favor of the (5'S) isomer.

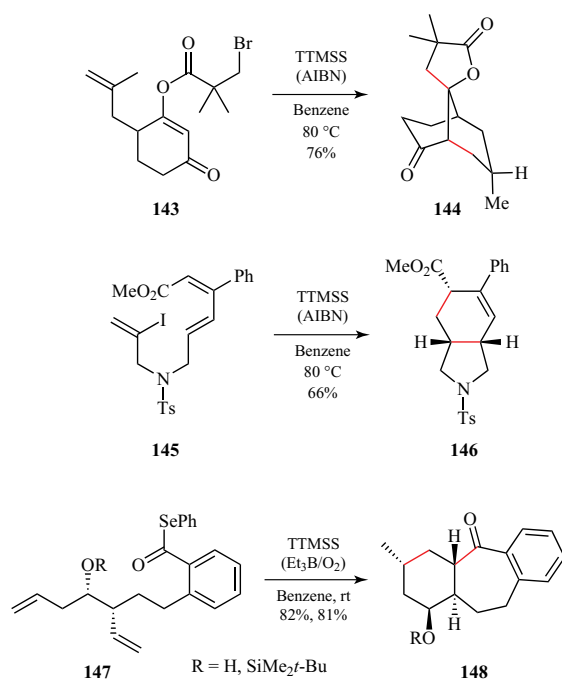
Radical-based tandem cyclizations favor the application of TTMSS over other reducing agents, owing to the absence of toxicity and high chemoselectivity. A nice example of two consecutive 5-exo cyclizations in a one-pot reaction is illustrated



Scheme 39 Synthesis of cyclonucleosides mediated by TTMSS.



Scheme 40 Two consecutive reductive cyclizations mediated by TTMSS.

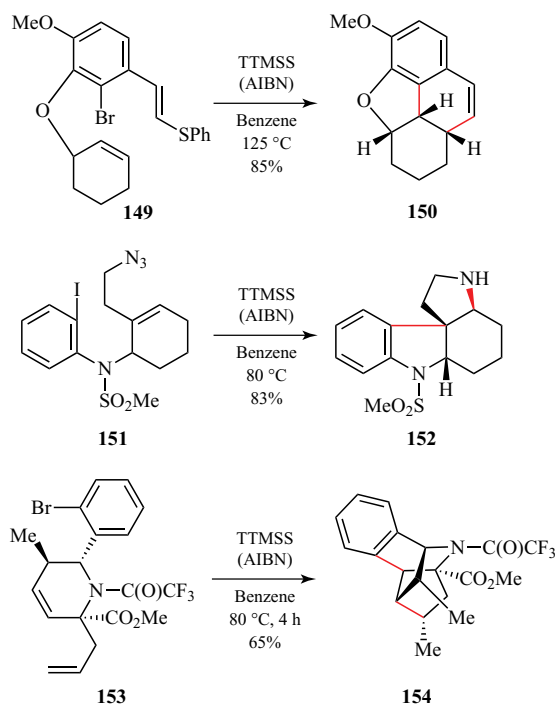


Scheme 41 Tandem cyclizations mediated by TTMSS (the new C–C bonds are shown in red).

in Scheme 40. Starting from dibromide **140**, the first cyclization via the radical **142** affords the desymmetrization of the molecule, whereas the second cyclization provides the bicyclic core **141**, which is common to the guttiferone family of natural products.¹⁵⁵ Bridged spirolactones **144** have

been synthesized via tandem radical cyclizations of enol ether **143**, where the first 5-exo spirocyclization is followed by a 6-endo cyclization to give the bridged derivative as a single diastereoisomer (Scheme 41).¹⁵⁶ Free-radical reaction of vinyl iodides having dienolate function in the presence of $(\text{TMS})_3\text{SiH}$ and AIBN in refluxing benzene caused tandem cyclization reactions to produce (4 + 1) and (4 + 2) annulated compounds.¹⁵⁷ The transformation **145** → **146** resulted from a tandem 5-exo, 6-endo cyclization to give the isoindole skeleton where the stereogenic centers are highly controlled. Reactions that feature a 7-exo acyl radical cyclization followed by a 6-exo or 5-exo alkyl radical cyclization proceed with very good yields and diastereoselectivities.¹⁵⁸ As an example, the treatment of **147** with $(\text{TMS})_3\text{SiH}$ at room temperature provided the tricycles **148** in excellent yields as a single diastereomer. Interestingly, the bulky silyl ether moiety is not required to achieve stereoselectivity in this process.

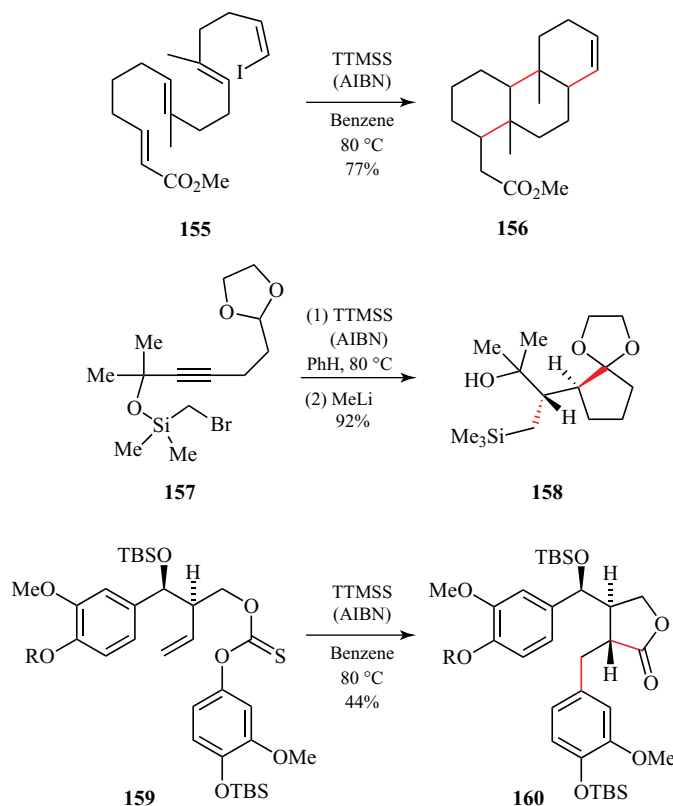
Tandem strategies have been successfully applied to the synthesis of alkaloids starting from aryl



Scheme 42 Tandem cyclizations mediated by TTMSS (the new C–C bonds are shown in red).

radical generation. The plan for tandem cyclization as the key step in the synthesis of morphine alkaloids has been successfully implemented.¹⁵⁹ For example, the initially formed aryl radical, generated by bromine abstraction from compound **149**, underwent a tandem cyclization to construct the desired carbocyclic skeleton followed by elimination of thiyl radical and formation of **150** (Scheme 42). The reaction of iodoarylazide **151** with $(\text{TMS})_3\text{SiH}$ under standard experimental conditions and after washing with dilute acid afforded the amine **152** in an overall 83% yield.¹⁶⁰ The skeletons of a variety of alkaloids such as $(\pm)$ -horsfiline, $(\pm)$ -aspidospermidine, and $(\pm)$ -vindoline have been achieved by this route.^{160–162} Radical cyclizations of tetrahydropyridine scaffolds have been used to access diverse skeletal frameworks.¹⁶³ Treatment of the allylated tetrahydropyridine **153** with $(\text{TMS})_3\text{SiH}$ and AIBN in refluxing benzene resulted in a single diastereomer **154** in a 65% isolated yield (Scheme 42).

As model studies and radical reactivity control have improved, the so-called cascade (or domino) reactions have emerged as a very powerful method for natural product synthesis, since it offers a unique route to the preparation of complex backbones from appropriately designed but quite simple precursors. A few selected reactions are presented here. Treatment of the iodo derivative **155** with $(\text{TMS})_3\text{SiH}$ starts a cascade of 6-endo, 6-endo, and 6-exo cyclizations to afford exclusively **156** in 77% yield (Scheme 43).¹⁶⁴ An analogous cascade involving 5-exo, 5-exo, and 5-exo modes of cyclization afforded a linear fused five-membered carbocycle.¹⁶⁵ Radical cascade starting from bromomethyldimethylsilyl propargyl ethers has been utilized in a remarkable way.^{166–168} Reduction of the bromide **157** in the presence of $(\text{TMS})_3\text{SiH}$ and subsequent treatment with MeLi produced the functionalized cyclopentanone precursor **158** as a single diastereomer (Scheme 43). The formation of **158** has been explained by a series of reactions, involving a

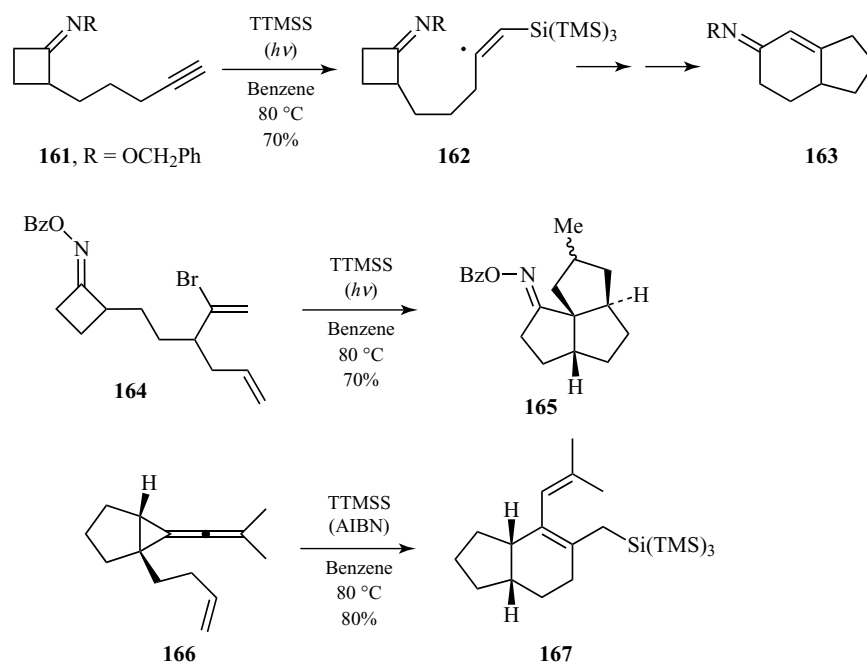


Scheme 43 Domino reactions mediated by TTMSS (the new C–C bonds are shown in red).

5-exo cyclization of the initial α -silyl alkyl radical, followed by a [1,5]-radical translocation of the generated σ -type vinyl radical onto the proximal acetal function, and a final 5-exo cyclization process. Stereoselective hydrogen abstraction, dependent on the steric bulkiness of the hydrogen donor, followed by MeLi-induced opening of the Si–O bond, afforded the final product. The introduction of different substituents on the skeleton resulted in a completely different reaction pattern.^{167,168} A radical carboxyarylation approach is also introduced as the key step in the total synthesis of several biologically important natural products.^{169,170} Treatment of thiocarbonate derivatives **159** (R = Me or TBS) with 1.1 equiv of (TMS)₃SiH in refluxing benzene and in the presence of AIBN (0.4 equiv added over 6 hours) as radical initiator, produced compound **160** in 44% yield. This remarkable transformation resulted from a radical cascade, involving (TMS)₃Si $\cdot$ radical addition to a thiocarbonyl function and 5-exo cyclization and intramolecular 1,5-*ipso* substitution, with the final ejection of (TMS)₃SiS $\cdot$ radical.

The number of consecutive reactions in some radical cascade processes can be really astonishing.^{171,172} Three representative examples

are illustrated in Scheme 44. Treatment of the acetylene derivative **161** with (TMS)₃SiH leads, in one pot, to the bicyclic compound **163** in 70% yield. The proposed mechanism involves (TMS)₃Si $\cdot$ radical addition to the triple bond to form a vinyl radical **162**, followed by a remarkable cascade of radical 6-exo cyclization, ring-opening, transannulation, ring-expansion, and termination via ejection of the (TMS)₃Si $\cdot$ radical, to afford the bicyclic product **163**. When a solution of vinyl bromide **164** was irradiated with a sunlamp in the presence of (TMS)₃SiH, it gave the corresponding triquinane oxime **165** as a 1:1 mixture of α - and β -methyl diastereomers resulting from a cascade of radical 6-exo cyclization, aminyl radical fragmentation, 5-exo radical transannulation, and 5-exo cyclization sequence. Treatment of the butenyl-substituted allenecyclopropane **166** with (TMS)₃SiH/AIBN resulted in facile radical cyclizations into the cyclopropane–carbon centers of the allene moieties, followed by cyclopropane ring-opening and allene isomerization, leading to the bicyclic 1,3-diene **167**.¹⁷³ Desilylation of **167** with TBAF in THF gave the corresponding bicyclic 5,6-ring-fused 1,3-diene in 71% yield.



Scheme 44 Radical cascade processes mediated by TTMSS.

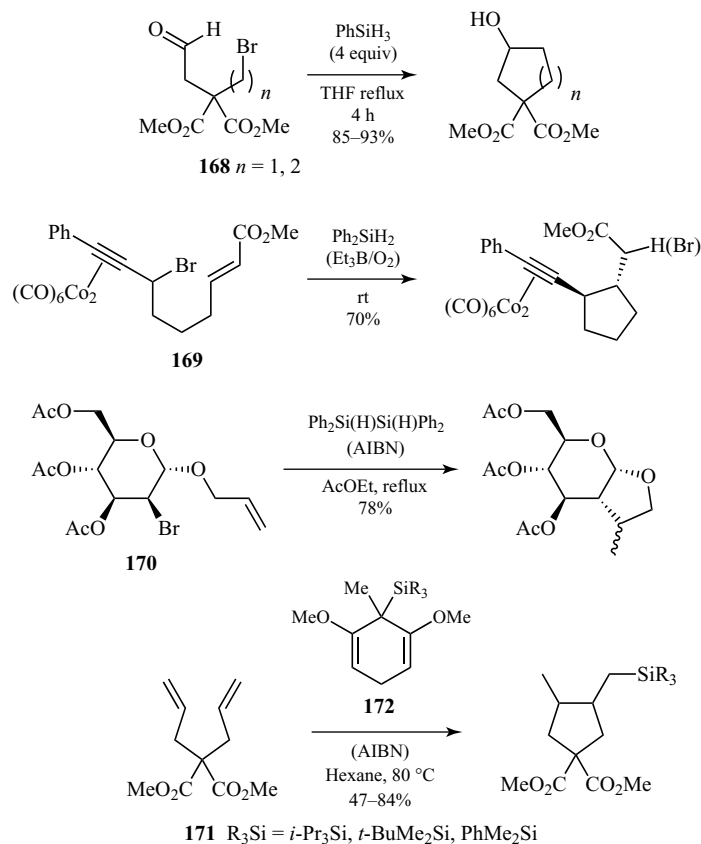
3.2 Other Organosilanes

The use of silanes other than $(\text{TMS})_3\text{SiH}$ in sequential reactions has been limited. A few selected examples are shown in Scheme 45. Taking advantage of the high reactivity of alkoxy radicals toward organosilanes, which is 2–3 orders of magnitude higher than that of primary alkyl radicals, cyclization can start from halocarbonyl compounds **168** using PhSiH_3 .¹⁷⁴ Both 6-*exo*-trig and 5-*exo*-trig cyclizations of alkyl radicals to the carbonyl moieties can be accomplished, with aldehydes working better than ketones. The thermally unstable propargyl bromide cobalt complex **169** afforded the cyclization product using Ph_2SiH_2 as reducing agent and $\text{Et}_3\text{B}/\text{O}_2$ as the radical initiator at room temperature.¹⁷⁵ However, a mixture of reduced and bromine atom-transfer products (1:1.8 ratio) was also isolated owing to the low hydrogen-donating ability of

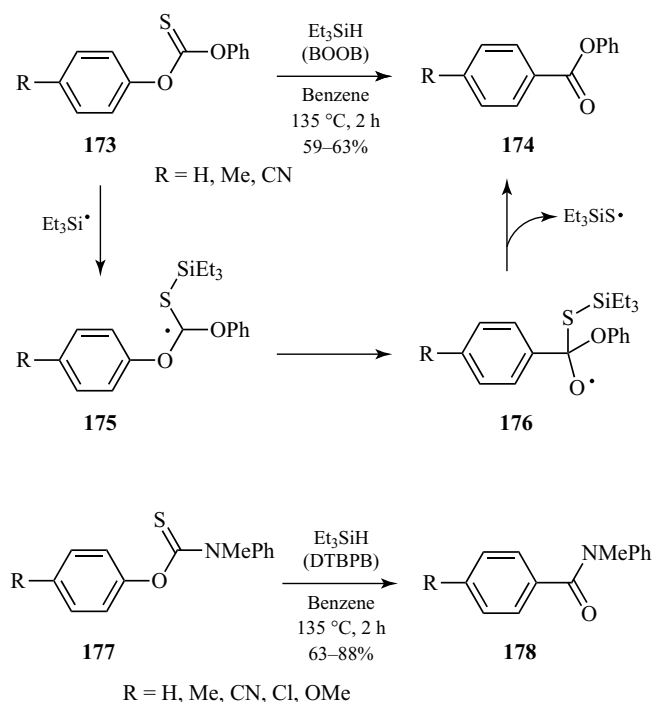
the employed silane. Fused cyclic ethers have been derived from appropriately substituted sugars using 1,1,2,2-tetraphenyldisilane.¹⁷⁶ An example is given with the stereoselective 5-*exo* radical cyclization of allylic 2-bromo-2-deoxysugar **170**, in the presence of silane and AIBN in refluxing ethyl acetate (Scheme 45).

A few examples of the hydrosilylation/cyclization of dienes are given by using the silylated cyclohexadienes **172** as reagents (Scheme 45). The cyclization of 1,6-diene **171** shows how flexible this methodology is to introduce any type of silyl group in the reaction products.¹⁷⁷ Yields are moderate to good, and the *cis*:*trans* ratio of ~4:1 does not change substantially by the nature of the silylating group, as expected.

Procedures for the transformation of thiocarbonates **173** and thiocarbamates **177**, available in a single high-yielding step from phenols, into esters **174** and amides **178** of benzoic acid mediated by Et_3SiH



Scheme 45 Intramolecular C–C bond formation mediated by a variety of silanes.



Scheme 46 Transformation of phenol derivatives into esters and amides of benzoic acid mediated by Et_3SiH .

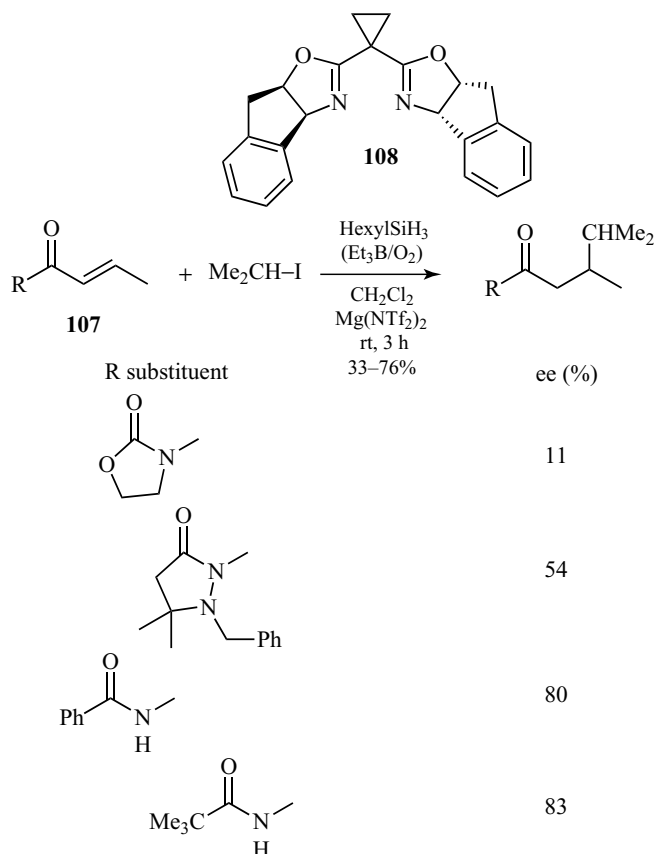
have also been discovered (Scheme 46).^{178–180} The initiation step is the thermal generation of the *tert*-butoxyl radical from the decomposition of di-*tert*-butyl peroxide (BOOB) or 2,2-bis(*tert*-butyl peroxy)butane (DTBPB), which reacts with Et_3SiH . The $\text{Et}_3\text{Si}^\bullet$ radical adds at the sulfur atom of the $\text{C}=\text{S}$ moiety in analogy to the first step of the Barton–McCombie reaction, producing the carbon radical **175** in the case of thiocarbonates, which undergoes 1,2 $\text{O} \rightarrow \text{C}$ transposition through an *O*-neophyl rearrangement to give alkoxy radical **176**. This metal-free preparation of benzoic acid derivatives from phenols provides a potentially useful alternative to metal-catalyzed carbonylation of aryl triflates.¹⁸⁰

Scheme 47 shows the use of hexyl SiH_3 as reducing agent in the intermolecular C–C bond formation, which is analogous to Scheme 30 reported for TTMSS. In particular, the reactions carried in the presence of chiral Lewis acid derivative from magnesium triflimide and bisoxazoline **108** were used.¹²⁹ The enantioselectivities and yields are similar to those reported for TTMSS. Substituted imides

of **107** were found to give the best yields and enantioselectivities, and the study of *tert*-butyl imide substituent has been extended, providing enantioselectivity up to 94%.

4 CONCLUSIONS

The synthetic application of silyl radical reactivity in the last decade has expanded considerably. $(\text{TMS})_3\text{SiH}$ has become popular among organic chemists and its arrival on the scene has resulted in a great advancement for radical chemistry. Unique transformations are possible, allowing one to generate structures that would otherwise be very difficult to synthesize. The scope and breadth of $(\text{TMS})_3\text{SiH}$'s utility as a mediator of consecutive radical reactions is spectacular, and we are convinced that much more diverse applications are yet to come. The need for nontoxic reagents such as $(\text{TMS})_3\text{SiH}$ to achieve these steps is evident, since chemical and biological issues are satisfied simultaneously. It seems pertinent to suggest a significant role of $(\text{TMS})_3\text{SiH}$ or the $(\text{TMS})_3\text{SiH}$ /thiol couple in



Scheme 47 Enantioselective radical reactions using hexylSiH₃ as mediator.

aqueous or heterogeneous media in future research. We trust that this article will serve as a platform to expand silicon radical chemistry with new and exciting discoveries.

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Unusual Radical Acceptors

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1 INTRODUCTION

When chemists think about radical reactions, and in particular about applications of radical reactions to organic synthesis, the mind of even the more acquainted ones runs immediately to additions to carbon–carbon multiple (mostly double) bonds: maybe also to aromatic compounds (see **Radical Arylations**), one of the first types of radical traps ever studied. People more experienced with radical chemistry are definitely familiar with addition to other moieties such as carbon–heteroatom multiple bonds and the consequent generation of heteroatom-centered radicals (see **Main-Group Elements in Radical Chemistry**). Nevertheless, there are plenty of other unusual traps that are becoming more and more important in the field of radical chemistry, but these are often not taken into consideration by synthetic organic chemists due to either the opinion that they are unstable, not easy to make and sometimes hazardous, or even the unawareness of their ability to act as selective radical acceptors. Among the assortment of uncommon moieties, in this article we will deal with three particular classes of radical acceptors, namely, azides, isonitriles, and heterocumulenes. The choice was primarily dictated by the outstanding results obtained with those acceptors in the domain of radical addition. Moreover, those traps are among the ones that suffer to the maximum extent from instability and/or hazard prejudices. Quite the opposite, we will show that their respective radical adducts are easily accessible and actually give rise to a mine

of stunning synthetic applications that are probably far from being exhausted.

2 AZIDES

2.1 Introduction

Organic azides are long known as extraordinarily useful intermediates for the construction of cyclic and acyclic nitrogen compounds owing to their ability to give rise to a large number of important reactions basically enabled by the 1,3-dipolar nature of the azido group and the inherent aptitude of this functional group for elimination of molecular nitrogen under thermal and photochemical conditions.^{1–4} In spite of the often irrational fear of organic azides caused by their potential explosive features, over the years interest in these nitrogen compounds has continued to increase tremendously owing to a plethora of novel applications.⁴ Since the 1980s, additional interest in their radical reactivity has been revealing that organic azides form a very special family of radical acceptors. Aliphatic and aromatic azides undergo efficient intra- and intermolecular additions of carbon- and heteroatom-centered radicals, leading to ultimate aminyl radicals which are involved in numerous synthetic processes often yielding aza-heterocycles through carbon–nitrogen bond formation. Electron-poor sulfonyl azides readily accept nucleophilic radical species, leading to azido group transfer products by release of a sulfonyl radical. As a result, sulfonyl azides find excellent use as azido

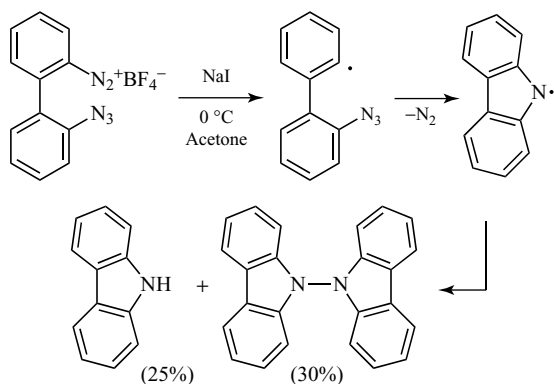
group transfer reagents in homolytic azidation processes. A review appeared in 2009 has exhaustively surveyed the radical chemistry of aliphatic and aromatic azides up to 2008.⁵ In that review, sulfonyl azides were additionally surveyed, but less thoroughly, since their distinctive radical chemistry had already been covered in an earlier comprehensive monograph.⁶ In this article, we shall deal particularly with those mechanistic and synthetic studies that allow more significant insights into the fascinating radical world of the azide family, including not only organic but also inorganic members.

2.2 Organic Azides

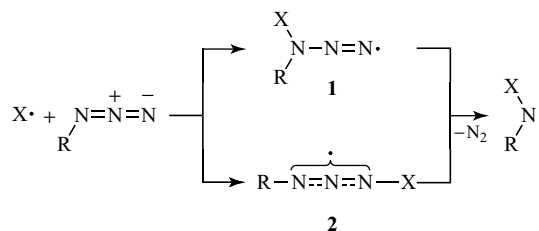
2.2.1 Aliphatic and Aromatic Azides as Acceptors of Carbon Radicals

The first documented example of radical addition to an azide dates back to 1978, when we discovered that 2'-azido-2-biphenyl radicals, available from the corresponding diazonium salt by reduction with iodide ion in acetone at 0 °C, gave rise to significant amounts of carbazole products clearly ascribable to carbazolyl radicals arising from cyclization (i.e., intramolecular addition) onto the azido group, accompanied by elimination of molecular nitrogen (Scheme 1).⁷

In spite of that promising chemical information, soon substantiated by Robert's electron paramagnetic resonance (EPR) spectral data,^{8,9} the radical chemistry of azides remained essentially ignored up to the 1990s, when the appearance of further pioneering works stimulated a deep theoretical and



Scheme 1 Cyclization of aryl radical onto an aromatic azide.

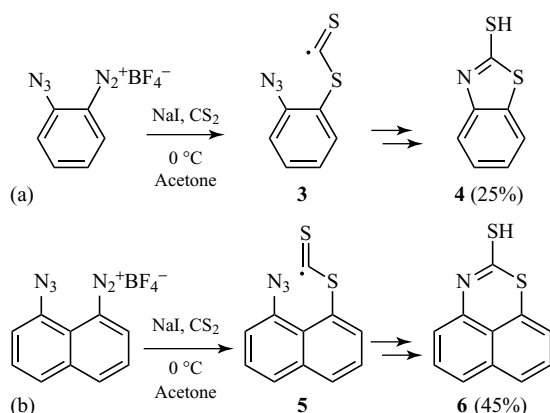


Scheme 2 Aminyl radicals from homolytic addition to aliphatic and aromatic azides.

synthetic interest in radical azide reactions, which has virtually seen no interruption. Overall spectral and chemical evidence provided by the reported studies clearly suggests that the azido function of an aliphatic or aromatic azide can undergo homolytic attack at both/either the R-substituted and/or the terminal nitrogen, giving rise to a 3,3-triazenyl (1) and/or a 1,3-triazenyl radical (2), respectively, depending on the structural/polar features of both the attacking radical and the azide substrate (Scheme 2). It is sometimes not clear to which end of the azido moiety addition occurs, because ultimate aminyl radicals could plausibly arise from either triazenyl radical adduct by extrusion of molecular nitrogen.^{8–10}

Aliphatic and aromatic azides are rather modest acceptors of carbon radicals: as a consequence, their *intermolecular* reactions with carbon radicals are of no practical interest. However, the *intramolecular* reactions with typical carbon radicals such as alkyl, vinyl, aryl, carbonyl, and dithiocarbonyl usefully lead to six- and/or five-membered cyclic aminyl radicals that are crucial intermediates in the radical production of a variety of interesting azaheterocycles.

A few years after our original discovery of aryl radicals (Scheme 1), dithiocarbonyl radicals furnished additional instances of intramolecular carbon radical addition to an aromatic azido function.¹¹ Azidodithiocarbonyl radicals **3** and **5** were produced in acetone at 0 °C by the addition of the respective azidoaryl radicals to carbon disulfide. Under these conditions, the dithiocarbonyl **3** gave mercaptothiazole **4**, though to a modest extent, through five-membered cyclization onto the adjacent azide (Scheme 3a), whereas the dithiocarbonyl **5** afforded mercaptotiazine **6** in a notably better yield by a corresponding six-membered cyclization process (Scheme 3b).¹¹

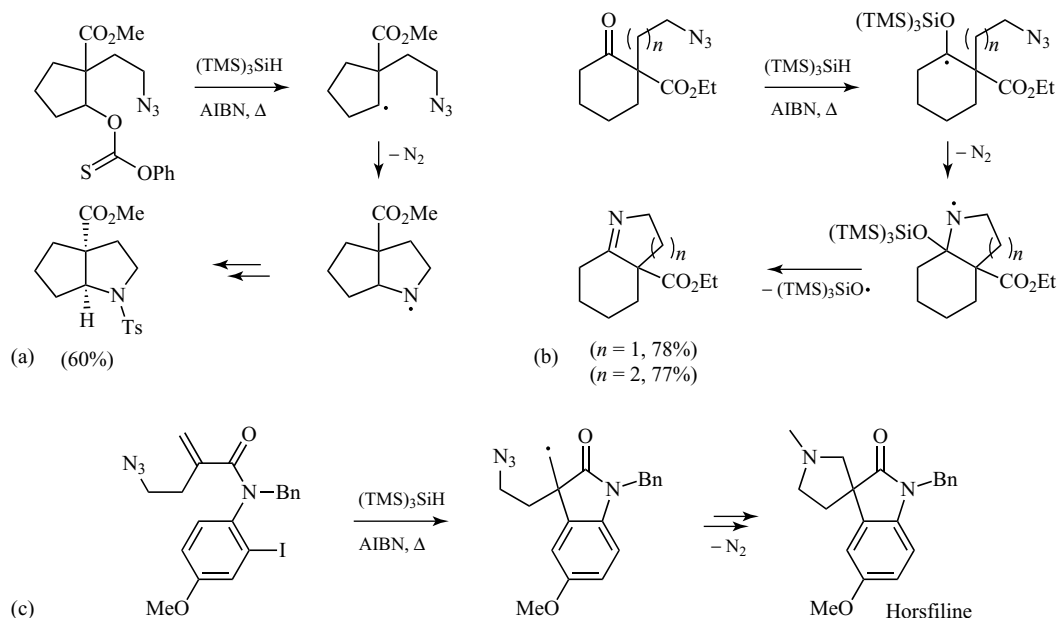


Scheme 3 Cyclizations of dithiocarbonyl radicals onto aromatic azides.

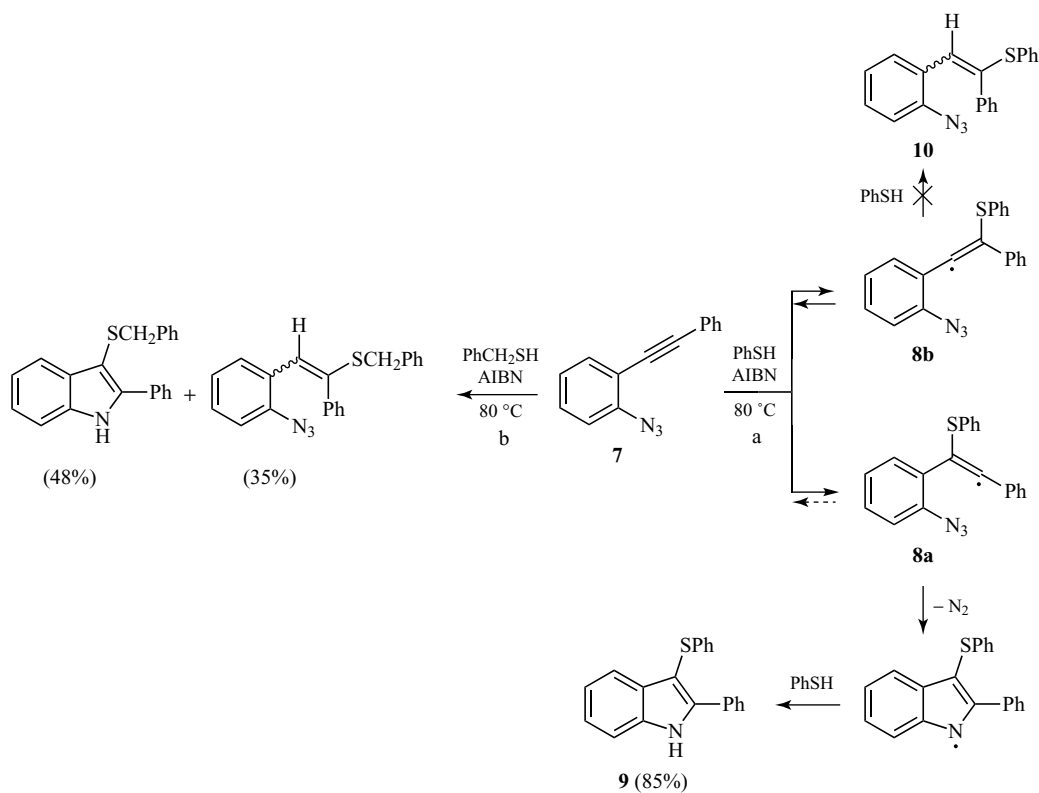
Kim *et al.* subsequently demonstrated that the intramolecular reaction of aliphatic azides with alkyl radicals offers a powerful synthetic access to *N*-heterocycles through the intermediacy of cyclic aminyl radicals.¹² Indeed, various aliphatic azido-iodides and azido-thionocarbonates reacted with tris(trimethylsilyl)silane [(TMS)₃SiH]/AIBN (see **Silanes as Reducing Reagents in Radical Chemistry**) in refluxing benzene giving rise to

good to very good yields of simple/fused pyrrolidines and piperidines via five- and six-membered cyclizations of derived alkyl radicals onto the internal azido substituent (Scheme 4a).¹² In those azide cyclizations, suitable adoption of (TMS)₃SiH reagent was dictated by the original observation that, with iodide and thionocarbonate moieties, the tris(trimethylsilyl)silyl radical strictly forms the alkyl radical even in the presence of an azido substituent. Similarly effective azide cyclizations to pyrrolines and tetrahydropyridines occurred with α -silyloxyalkyl radicals arising from the addition of the oxyphilic tris(trimethylsilyl)silyl radical to the carbonyl groups of azidoketones and azidoaldehydes (Scheme 4b).¹² The fair intramolecular reactivity of alkyl azide with alkyl radical has been next exploited in the synthesis of several important natural products, such as the elegant Murphy's synthesis of Horsfiline (Scheme 4c).^{13–16}

A later work disclosed that aromatic azides can also exhibit easy intramolecular addition of vinyl radicals.¹⁷ Upon reaction with benzenethiol (PhSH)/AIBN in refluxing benzene, azidoacetylene **7** gave a high yield of cyclized indole **9** only, which was clearly due to five-membered cyclization of the derived (benzenesulfanyl)vinyl radical **8a** onto the aromatic azido group. The exclusive occurrence of



Scheme 4 Cyclizations of alkyl radicals onto aliphatic azides.

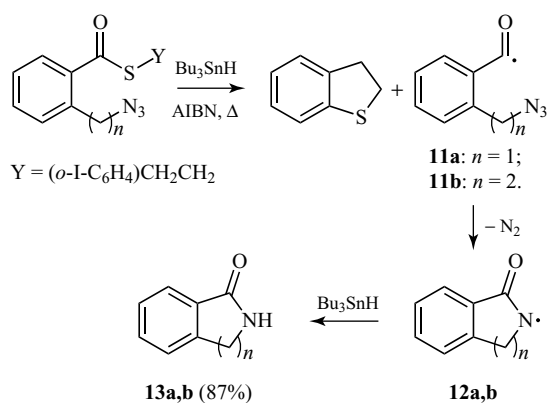


Scheme 5 Cyclizations of vinyl radicals onto aromatic azides.

indole **9** plausibly arose from fast cyclization of vinyl radical **8a** as well as by reversible production of the regioisomeric vinyl radical **8b**: both factors would explain the absence of any possible vinyl sulfide adduct **10** (Scheme 5, route a).¹⁷ The corresponding reaction with benzylthiol similarly gave the indole analog, but in a moderate yield. The more reactive benzylsulfanyl radical could undergo nearly irreversible addition to the acetylene **7**, thereby leading to the concomitant formation of vinyl benzyl sulfide adduct to a fairly comparable extent (Scheme 5, route b).¹⁷

Aliphatic azides have been last found to form cyclic amidyl radicals upon intramolecular five- and six-membered addition of acyl radicals.^{18,19} Aryl-derived azidoacyl radicals **11a,b** arising from reaction of 2-(*o*-iodophenyl)thiol esters with Bu₃SnH/AIBN and/or (TMS)₃SiH/AIBN actually furnish excellent yields of five- and six-membered lactams **13a,b** via H transfer to the corresponding amidyl radicals **12a,b** (Scheme 6). When

allyltriphenylstannane is used as tin radical precursor, the azidoacyl radical interestingly affords a satisfactory yield of the *N*-allylated lactam by allyl transfer reaction of the cyclized amidyl radical with the allylstannane.¹⁸



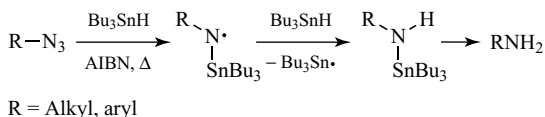
Scheme 6 Cyclizations of acyl radicals onto aliphatic azides.

Analogous cyclizations to lactams are somewhat less feasible with alkyl-derived azidoacyl radicals, owing to the fair tendency of alkanoyl radicals to undergo decarbonylation.¹⁸

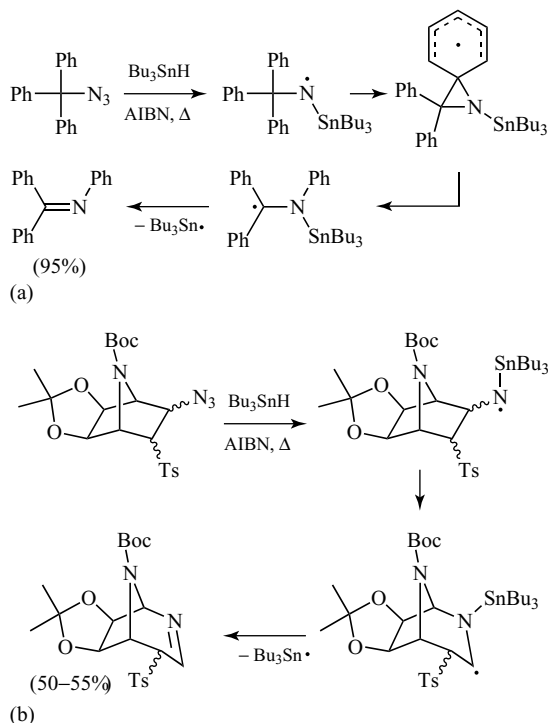
2.2.2 Aliphatic and Aromatic Azides as Acceptors of Heteroatom-Centered Radicals

Alkyl and aryl azides are notably better radical acceptors of tin than carbon radicals. Indeed, the intermolecular reactions of these azides with tributyltin radicals smoothly lead to *N*-(tributylstannyl)aminyl radicals, which actually are the key intermediates in numerous very useful azide processes mediated by Bu₃SnH/AIBN. Tin-bound aminyl radicals are a more appealing species than “ordinary” aminyl analogs since, besides being easily accessible, they display increased nucleophilic character and hence, often, increased reactivity.^{20–22} Computational studies reported by Kim *et al.* actually show that the *N*-(trimethyltin)-substituted methylaminyl radical has higher singly occupied molecular orbital (SOMO) energy, as well as higher electron density at nitrogen, than the dimethylaminyl and methylaminyl counterparts.²² Aromatic and aliphatic azides react with Bu₃SnH/AIBN, typically in refluxing benzene, usually yielding excellent yields of amines through a radical chain mechanism entailing H transfer from tin hydride to the derived *N*-(tributylstannyl)aminyl radical (Scheme 7).^{23–27} Until very recently, the AIBN-initiated reaction with Bu₃SnH, first documented by Samano and Robins in 1991,²³ provided the only radical method for the reduction of azides to primary amines among a plethora of the reported nonradical ones.²⁸

Stannylaminyl radicals produced from α -aryl/heteroaryl-substituted aliphatic azides cleanly form rearranged imines through 1,2-migration (see **Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**) of the aryl/heteroaryl group from the α -carbon to the



Scheme 7 Radical reductions of aromatic and aliphatic azides via stannylaminyl radicals.

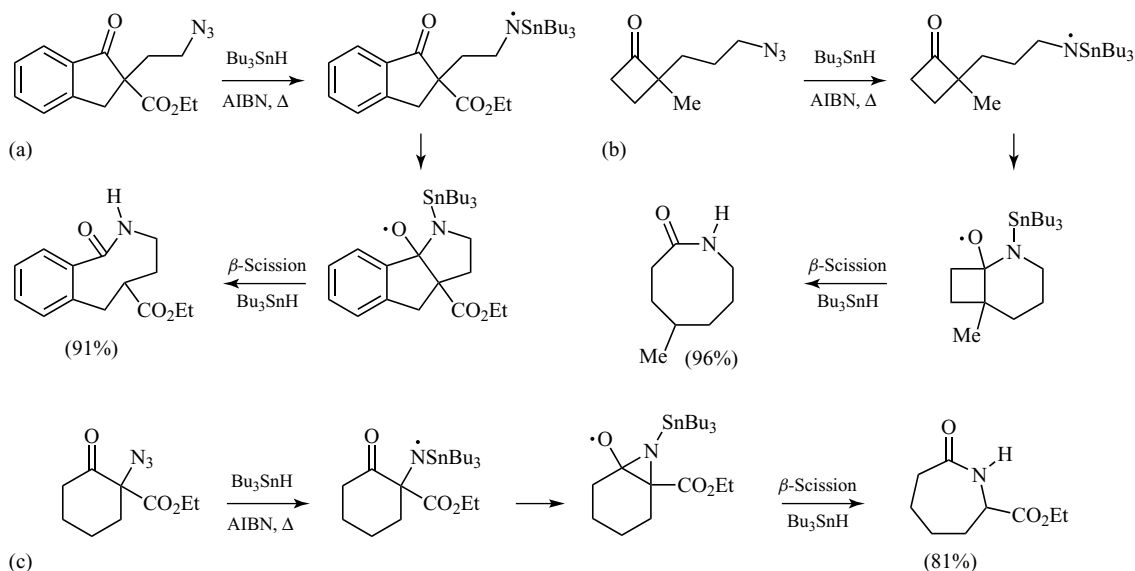


Scheme 8 Radical rearrangements with stannylaminyl radicals derived from aliphatic azides.

aminyl nitrogen (Scheme 8a).²⁹ Analogous radical migrations are quite unusual with other aminyl radicals. Such stannylaminyl radical rearrangement has been usefully applied to a radical synthesis of phenanthridine compounds from readily available 6-fluorenyl azides.²⁹

Moreover, under standard conditions, stannylaminyl radicals arising from certain 2-azido-substituted 7-azabicyclo[2.2.1]heptanes strikingly rearrange to the corresponding ring-expanded diazabicyclooctenes, which are valuable synthetic precursors of some α -mannosidase inhibitors (Scheme 8b).³⁰ Such a radical rearrangement was originally claimed to occur via 1,2-migration of a bridgehead alkyl carbon atom. However, since radical 1,2-shifts of alkyl carbons are virtually unknown, a ring-opening/ring-closure sequence should be more likely involved.

Cyclic ketones and ketoesters bearing 2-azidoethyl or 3-azidopropyl α -substituents form ring-expanded lactams by very efficient 5- or 6-exo-cyclizations of nucleophilic stannylaminyl radicals onto the ketone carbonyl groups (Scheme 9a,b).^{31,32}



Scheme 9 Cyclizations of stannylaminyl radicals onto carbonyl groups.

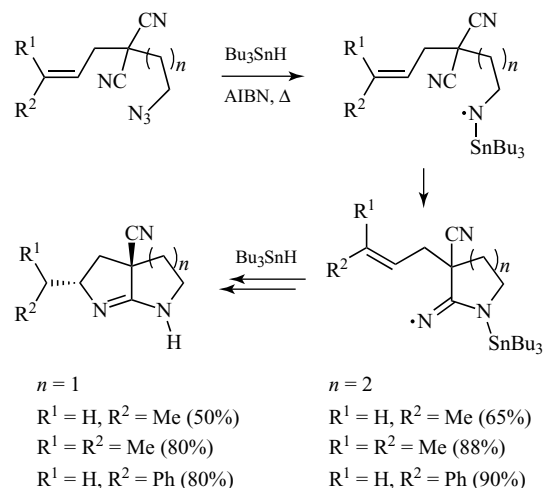
These peculiar stannylaminyl cyclizations enable facile access to otherwise poorly accessible medium-sized lactams. Similarly efficient 3-exo cyclizations of stannylaminyl radicals onto adjacent ketone groups offer a valuable entry to *N*-acyl-protected α -amino esters from easily available cyclic (and also acyclic) α -azido- β -keto esters (Scheme 9c).^{33,34}

It has been established that stannylaminyl radicals derived from aliphatic azides can also perform easy intramolecular addition to electrophilic cyano group in both 5-exo and 6-exo fashion.³⁵ Upon usual treatment with Bu_3SnH /AIBN, α -(2-azidoethyl) and α -(3-azidopropyl)-substituted malononitriles bearing an additional α -allylic substituent furnish good to very good yields of bicyclic hexahydropyrrolopyrroles and hexahydropyrrolopyridines. These bicyclic products are the result of fast 5- and 6-exo cyclization of stannylaminyl radicals onto either malononitrile cyano group, followed by 5-exo cyclization of the cyclized aminoiminyl radicals onto the alkene moiety (Scheme 10).³⁵

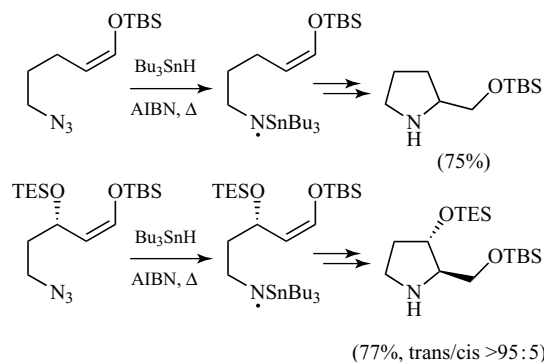
Furthermore, in 2009 Sammis *et al.* reported some unprecedented instances of intramolecular addition of stannylaminyl radical to alkenes.³⁶ Despite enhanced nucleophilic character, stannylaminyl radicals produced under typical conditions from 1-silyloxy-substituted 5-azido-1-penten-1-ones and

Bu_3SnH /AIBN were nevertheless fairly able to perform 5-exo cyclization onto the electron-rich silyl enol ether moiety yielding good yields of isolated 2-silyloxymethylpyrrolidines. Two representative examples are shown in Scheme 11.³⁶

These rather surprising stannylaminyl radical cyclizations opened the way to an easy access to 2-hydroxymethylpyrrolidine compounds, which are

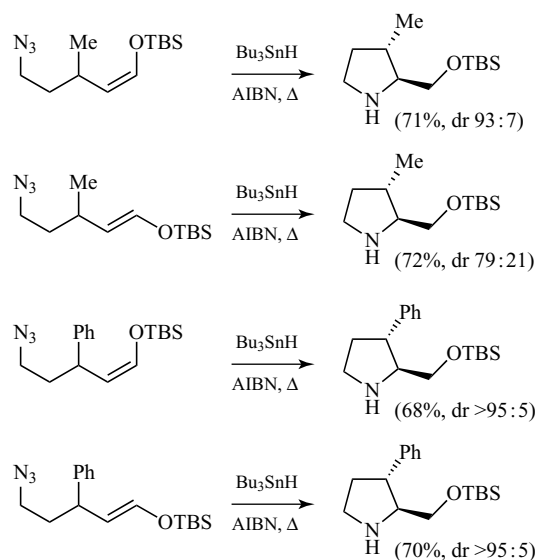


Scheme 10 Cyclizations of stannylaminyl radicals onto cyano groups.



Scheme 11 Cyclizations of stannylaminyl radicals onto silyl enol ethers.

of significant interest in the synthesis of polyhydroxylated alkaloids and also of D-ribitol sugars. The authors next reported a useful stereochemical study of their new cyclization reactions. Trans diastereoselectivities of substrates with alkyl or aryl substitution at C₃ have been found to be high to very high regardless of olefin geometry or substitution pattern (Scheme 12). With electronegative substituents adjacent to the silyl enol ether, only *Z*-silyl enol ethers provide high trans diastereoselectivities. Furthermore, temperature, steric size of the silyl group,

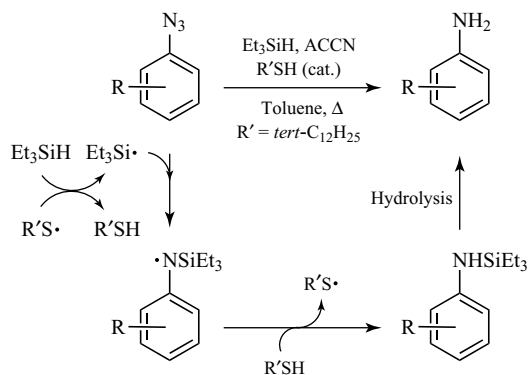


Scheme 12 Stannylaminyl radical cyclizations onto methyl- and phenyl-substituted silyl enol ethers.

and sterics and electronics of the tin hydride reagent affect the selectivity only to a modest extent.³⁷

The latest discovery of new effective stannylaminyl radical cyclizations onto electron-rich alkene acceptors provides further very attractive perspectives on the possible application of azides to the radical construction of nitrogen heterocycles.

The chemistry of azides as radical acceptors has long been dominated by the intermolecular reactions with tributyltin radicals; however, the popular adoption of these radicals is discouraged by the known toxicity of organotin compounds and, furthermore, the serious drawbacks connected with full removal of toxic organotin residues from the reaction mixtures. Fortunately, at the turn of the century several original studies of the radical reactivity of azides have disclosed that other benign heteroatom-centered radicals including silyl, germyl, and indyl could be promising substitutes for tributyltin radical. In refluxing toluene, many substituted phenyl azides and additional alkyl azides afford varying yields of reduced amines via isolable *N*-silyl derivatives upon reaction with triethylsilane in the presence of 1,1'-azobis-cyclohexane-1-carbonitrile (ACCN) initiator and additional *tert*-dodecanethiol as a “polarity reversal catalyst.”^{38,39} These reactions most likely occur through a radical chain mechanism entailing key H transfer from the (electrophilic) alkanethiol to a (presumably nucleophilic) *N*-triethylsilylaminyl radical derived from the addition of a primary triethylsilyl radical to the azide (Scheme 13).³⁸



Scheme 13 Radical reductions of aromatic azides with triethylsilane.

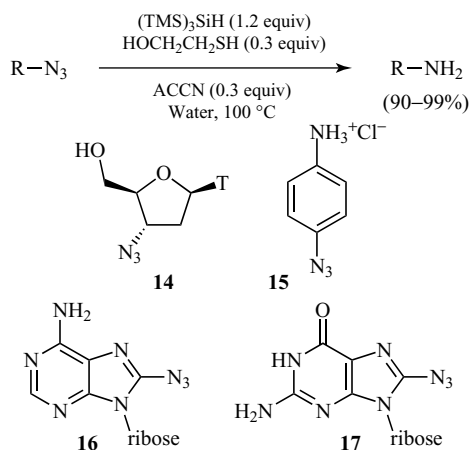
Under strictly comparable conditions, analogous aromatic/aliphatic azides are reduced to primary amines by tributylgermanium hydride via a similar radical chain mechanism involving the plausible intervention of *N*-(tributylgermyl)aminyl radicals.⁴⁰ The radical azide reactions with triethylsilane and tributylgermanium hydride usually afford aromatic amines in high to very high yields but give rise to the aliphatic ones only to a limited extent. This fact seems to indicate that aromatic azides might act as notably stronger acceptors of triethylsilyl and tributylgermyl radicals than the aliphatic counterparts. However, a subsequent work of Chatgililoglu *et al.* suggests that alkyl and aryl azides should be comparably able to intercept tris(trimethylsilyl)silyl radical (see **Silanes as Reducing Reagents in Radical Chemistry**). In fact, water-soluble alkyl and aryl/heteroaryl azides **14–17** were always found to furnish excellent yields of primary amines upon reaction with (TMS)₃SiH/ACCN in water at 100 °C in the presence of a catalytic amount of ambiphilic 2-mercaptoethanol (Scheme 14).⁴¹

Aliphatic and aromatic azides seem to have a strong propensity to trap dichloroindyl radicals even under very mild conditions to give the corresponding *N*-indylaminyl radicals after usual loss of dinitrogen. It has been observed that, in acetonitrile solution at 0 °C, a variety of phenyl and alkyl azides undergo fast reaction with only dichloroindium hydride affording good to excellent yields of primary amines after hydrolysis of the resulting reaction mixtures.⁴² These reactions do not

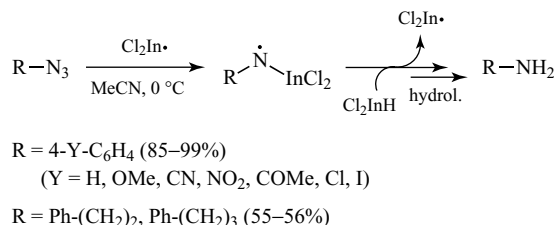
require the presence of any added radical initiator, but in certain cases the reaction rate is clearly enhanced by the presence of a suitable initiator like triethylborane; moreover, with certain azides, the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) has been found to cause evident inhibition of the usual reduction. It is therefore plausible that these very mild azide reductions should entail a radical chain mechanism based on fast H transfer from the indium hydride to smoothly formed indium-bound aminyl radicals (Scheme 15).⁴² It is noteworthy that dichloroindium hydride has been found to cleanly convert phenyl azide into aniline even in the presence of a readily reducible substituent such as iodine. This finding would substantiate a special aptitude of the azido group for trapping dichloroindyl radical. Indeed, silyl,^{12,18,38} germyl,⁴⁰ and stannyl^{12,18} radicals are generally found to achieve iodine abstraction from aromatic and aliphatic iodoazides in preference to addition to the azido moiety.

Under identical experimental conditions, dichloroindium hydride transforms a variety of aliphatic and aromatic azidonitriles into cyclized pyrrolidin-2-imines in virtually quantitative yields (Scheme 16).⁴² These amidine products are presumably due to highly efficient 5-exo cyclization of transient indium aminyl radicals onto the internal cyano group. Such data interestingly suggest that (dichloroindyl)aminyl radical should be capable of performing intramolecular addition to the electrophilic cyano group in an even more effective fashion than the tributyltin-substituted congener.

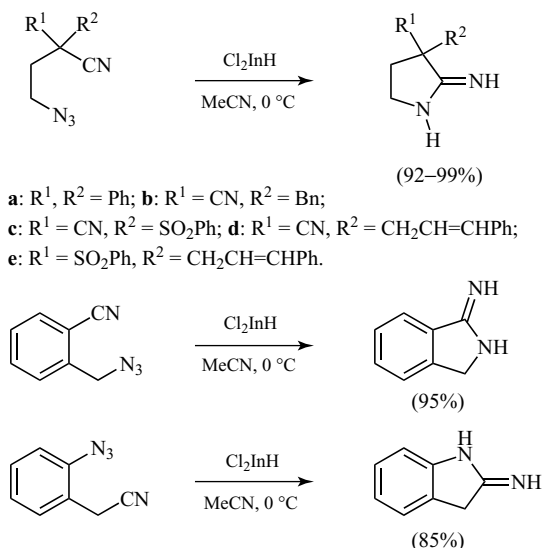
Indium aminyl radicals have also been found to act as distinctive intermediates in unprecedented transformations of aliphatic azides bearing suitable electron-withdrawing substituents in the side chain. In light of our new EPR spectral observation that photolysis at room temperature of accessible



Scheme 14 Radical reductions of aromatic and aliphatic azides in water with tris(trimethylsilyl)silane.



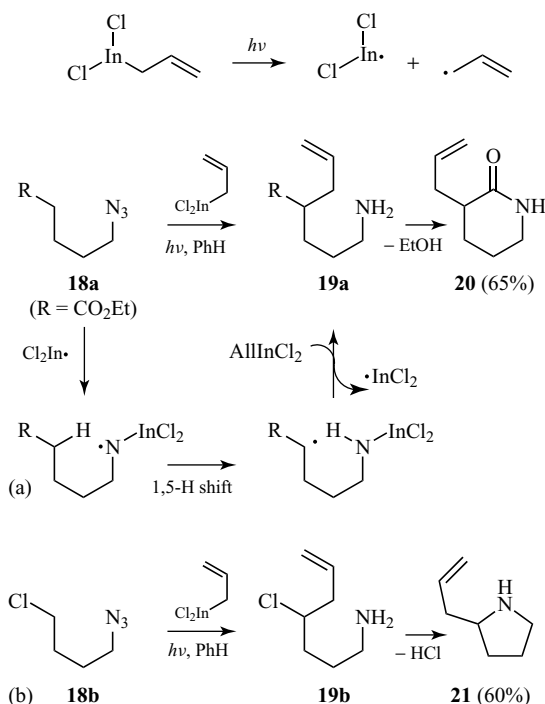
Scheme 15 Radical reductions of aromatic and aliphatic azides with dichloroindium hydride.



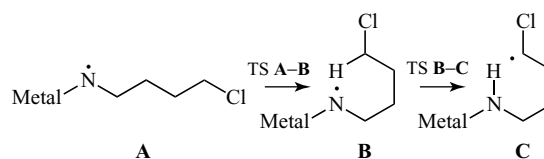
Scheme 16 Radical reactions of dichloroindium hydride with azidonitriles.

allylindium dichloride brings about homolytic fragmentation of the carbon–indium bond yielding allyl and dichloroindyl radicals, we have examined the photochemical reactions of that indium reagent with the azides **18a,b** shown in Scheme 17.⁴³ In benzene solution at room temperature, the reaction with azido ester **18a** gives rise to significant formation of the allylated amine **19a** which spontaneously affords the cyclized piperidinone **20** in good overall yield (Scheme 17a). Chloroazide **18b** is similarly transformed into the corresponding amine **19b**, from which the cyclized pyrrolidine **21** finally arises to a comparable extent (Scheme 17b). The allylated amines **19a,b** are reasonably formed through a tandem radical process involving fast 1,5-H transfer reaction of initial dichloroindium aminyl radical, followed by allylation of the (electrophilic) translocated carbon radical by the (nucleophilic) allylindium reagent (Scheme 17a).⁴³

It is worth noting that allyltributylstannane fails to react with azides **18a,b** under the same photochemical conditions, probably because the ensuing stannylaminyl radical fails to undergo analogous H-transfer reaction. Some comparative theoretical studies actually indicate that the 1,5-migration step should be somewhat more feasible with (dichloroindyl)aminyl radical than with the (trimethyltin)aminyl one (Scheme 18 and Figure 1).⁴³



Scheme 17 Light-induced radical reactions of aliphatic azides with allylindium dichloride.



Scheme 18 Intermediates and transition states (TS) entailed in calculations on 1,5-H transfer reaction of trimethyltin- and dichloroindium-aminy radicals (Metal = Me_3Sn , Cl_2In).

The overall results obtained with aliphatic and aromatic azides and “green” silyl, germyl, and, particularly, indyl radicals lead us to believe that the long domination of undesirable tributylstannyl radicals could be soon overcome.

2.2.3 Sulfonyl Azides as Acceptors of Carbon- and Heteroatom-Centered Radicals

Sulfonyl azides as possible radical acceptors remained virtually obscured up to 1996, when

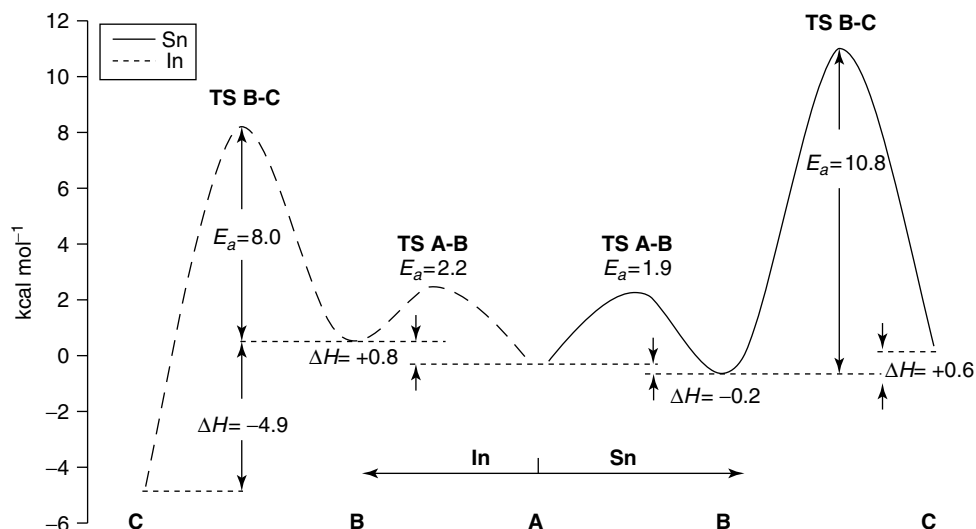
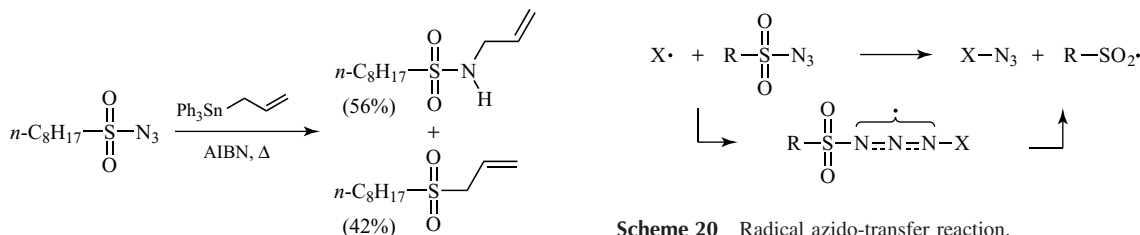


Figure 1 Reaction profiles for 1,5-H shift of trimethyltin- and dichloroindium-aminy radicals (UB3LYP, LanL2DZ ECP). [Ref. 43—Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/C001848A>.]

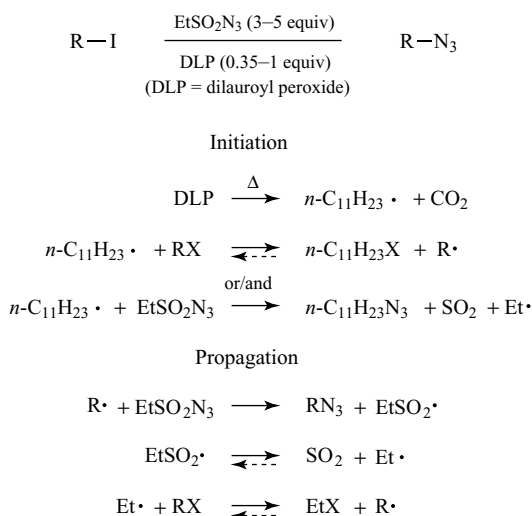


Scheme 19 Radical allylation of sulfonyl/sulfonamidyl radical.

Scheme 20 Radical azido-transfer reaction.

Roberts *et al.* published a study of their radical reactions with allylstannanes as a potential synthetic entry to *N*-allylsulfonamides.¹⁰ In refluxing benzene in the presence of azo-bis-*iso*-butyronitrile (AIBN), arene- as well as alkane-sulfonyl azides generally furnished satisfactory yields of allylsulfonamides, which were the desired allylation products of derived *N*-stannylsulfonamidyl radicals. However, the resultant allylsulfonamides were always accompanied to a notable extent by the corresponding allylsulfones and additional stannyl azides (Scheme 19). These latter unexpected products were believed to arise from tin radical addition to the terminal azide nitrogen, followed by peculiar elimination of an arene or alkane sulfonyl radical from the ensuing 1,3-triazenyl radical (Scheme 20).¹⁰

The peculiar behavior displayed by sulfonyl azides with tin radicals was strictly substantiated by later reactions with carbon radicals. A few years later, in fact, Renaud *et al.* happened to discover that fairly nucleophilic alkyl radicals reacted with both ethanesulfonyl and benzenesulfonyl azide leading to invariable formation of the corresponding alkyl azides.⁴⁴ The outcoming azides were basically ascribed to fragmentation of 1,3-triazenyl radicals analogous to those originally invoked for azidation of tin radicals (Scheme 20), but it was felt that alternate 3,3-triazenyl radicals, due to alkyl radical attack at the internal azide nitrogen, could possibly play some additional role. Conclusive chemical evidence for azido transfer reaction entailing exclusive radical attack at the terminal azide nitrogen came only in 2007 from a study of alkyl radical azidations with benzenesulfonyl azide bearing terminal nitrogen labeled with ¹⁵N.⁴⁵ The distinctive radical

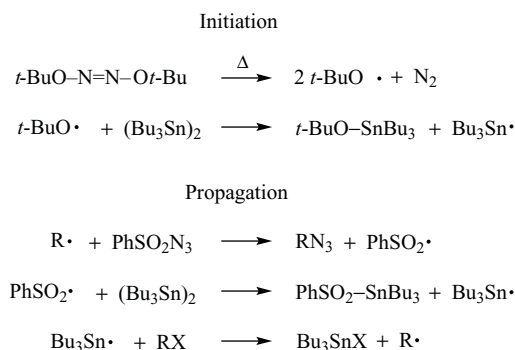


Scheme 21 Radical azidation with ethanesulfonyl azide.

chemistry of the electron-poor sulfonyl azides has been exploited by Renaud *et al.* in highly useful radical azidations of alkyl radical precursors, which are complementary to the well-established nucleophilic and electrophilic azidation methods. An initial protocol for the radical azidation of alkyl iodides and dithiocarbonates was based on reaction with a suitable excess of ethanesulfonyl azide in boiling chlorobenzene in the presence of dilauroyl peroxide initiator. The proposed radical chain mechanism involving key fragmentation of a released ethanesulfonyl radical is described in Scheme 21.⁴⁴

That protocol often provided good yields of the desired aliphatic azides but, owing to long reaction times and problematic purifications of the final azides, it was soon replaced by a faster and milder one using a threefold excess of benzenesulfonyl azide in boiling benzene, in conjunction with hexabutylditin chain transfer and di-*tert*-butyl hyponitrite (DTBHN) initiator (see **Overview of Radical Initiation**).⁴⁴ The protocol with benzenesulfonyl azide was suggested by the known reactions of alkoxyl and benzenesulfonyl radicals with distannanes affording tin radicals as well as by the disclosed preference of tin radicals for reaction with iodide and dithiocarbonate rather than with the azide reagent. The proposed chain reaction is described in Scheme 22.

Such a radical protocol affords aliphatic azides in a range of yields that become very good with secondary and tertiary alkyl iodides/

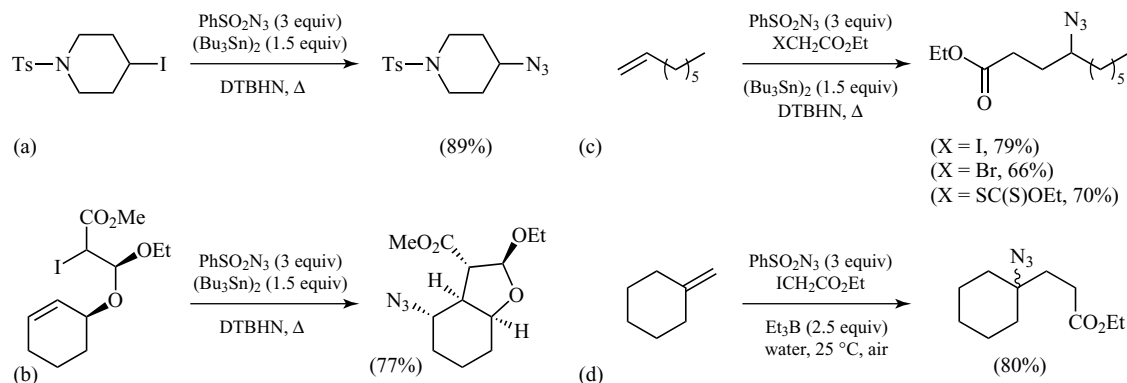


Scheme 22 Radical azidation with benzenesulfonyl azide.

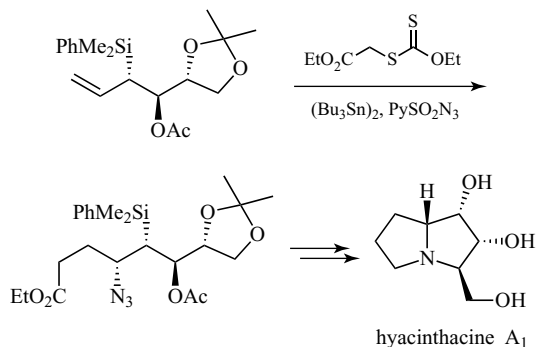
dithiocarbonates: that is, the precursors of more nucleophilic alkyl radicals (Scheme 23a).⁴⁴ The protocol has been interestingly applied to tandem cyclization/azidation reactions of alkyl iodides⁴⁴ (Scheme 23b) as well as to intermolecular carboazidations of alkenes where the radical azidation process is coupled with the formation of a carbon–carbon bond (Scheme 23c).^{46,47} In these latter tandem reactions, an electrophilic alkyl radical—often derived from α -iodo and α -xanthate ester—adds to an electron-rich terminal alkene giving rise to a secondary/tertiary alkyl radical which then reacts with benzenesulfonyl azide to deliver the final azide. Simple azidations of alkyl iodides as well as carboazidations of alkenes have been interestingly achieved also under tin-free conditions using a comparable excess of benzenesulfonyl azide and triethylborane initiator in aqueous medium at ambient temperature (Scheme 23d).^{48,49}

The synthetic value of these radical azidation processes has been further improved by the replacement of benzenesulfonyl with 3-pyridinesulfonyl azide (PySO_2N_3), a reagent that enables notably easier chromatographic separations of the azide products.⁵⁰ Radical carboazidations with PySO_2N_3 have been usefully applied to the total synthesis of certain alkaloids.^{51–53} For instance, a stereocontrolled carboazidation of a chiral allylsilane with PySO_2N_3 was adopted as a key step in the total synthesis of hyacinthacine A₁⁵² (Scheme 24).

Since methylenecyclohexanes are particularly appealing substrates for the application of the radical carboazidation to natural-product synthesis, a systematic study of the diastereoselectivity of the carboazidation of those unsaturated compounds bearing substituents at positions 2, 3, and 4 has



Scheme 23 Synthesis of various azido compounds via radical azido-transfer reactions.



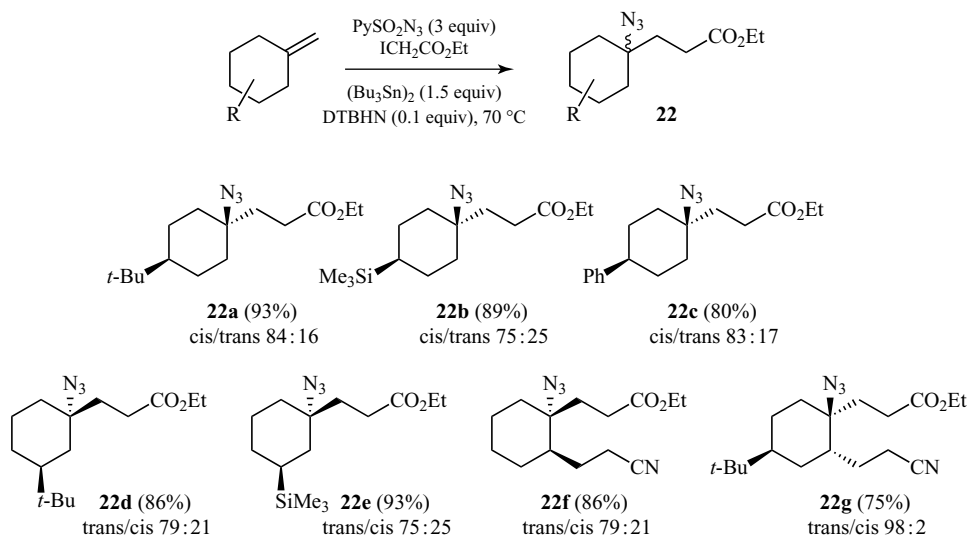
Scheme 24 Carboazidation of a chiral allylsilane with PySO_2N_3 : application to the total synthesis of hyacinthacine A_1 .

been also performed.⁵⁴ Under the standard conditions of the tin-mediated carboazidation, using PySO_2N_3 as the azidating agent and ethyl iodoacetate as the radical precursor, every investigated methylenecyclohexane afforded the corresponding carboazidated compound **22** in good yield (Scheme 25). 4-Substituted methylenecyclohexanes give *cis*-azides **22a–c** with fairly high stereoselectivity, whereas the 3-substituted ones give preferentially *trans*-azides **22d,e** with similar levels of stereocontrol. Methylenecyclohexane bearing only a primary cyanoethyl substituent at position 2 afforded azide **22f** with no significant stereochemical control, whereas very highly stereoselective production of azide **22g** occurred with methylenecyclohexane bearing an additional *tert*-butyl substituent at position 4. The observed stereochemical trends are explained in terms of preferential axial attack of PySO_2N_3 at the cyclohexyl radical arising from the addition of (ethoxycarbonyl)methyl radical

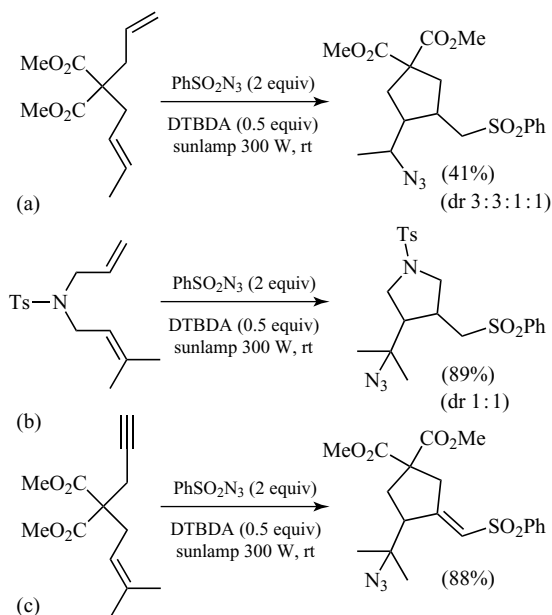
to the terminal alkene carbon of the original substrate.⁵⁴

Renaud *et al.* subsequently utilized benzenesulfonyl azide together with various 1,6-dienes and 1-en-6-yne in new radical chain reactions initiated by sunlamp irradiation of di-*tert*-butyldiazene (DTBDA).⁵⁵ Under these circumstances, addition of an initial benzenesulfonyl radical to the terminal alkene or alkyne moiety of the appropriate diene/enyne substrate affords a corresponding alkyl/vinyl radical which undergoes 5-exo cyclization onto the additional ethylene moiety. The ensuing alkyl radical undergoes final azidation by the sulfonyl azide leading to usual liberation of a benzenesulfonyl radical for the chain propagation. These azidosulfonylation processes allow the preparation of novel interesting secondary and tertiary azides in moderate to very good yields (Scheme 26a–c).⁵⁵

At the end of this section, it is useful to mention that some chemical information concerning the radical reactivity of sulfonyl azides with dichloroindyl radicals has become available by means of our radical reactions of benzenesulfonyl azide with dichloroindium hydride in acetonitrile at 0 °C (Scheme 15) and with allylindium dichloride in benzene under photochemical conditions (Scheme 17). With dichloroindium hydride, benzenesulfonyl azide only gave reduced benzenesulfonamide in high yield (80%), thus suggesting the exclusive occurrence of *N*-indylsulfonamidyl radical under the adopted very mild conditions.⁴² With allylindium dichloride, the sulfonyl azide afforded a mixture of benzenesulfonamide and *N*-allylbenzenesulfonamide along with comparable

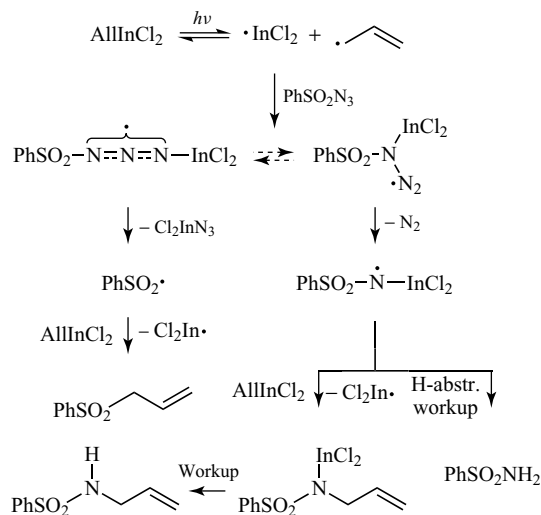


Scheme 25 Carboazidation of 2-, 3-, and 4-substituted methylenecyclohexanes.



Scheme 26 Azidosulfonylations of 1,6-dienes and 1-en-6-yne.

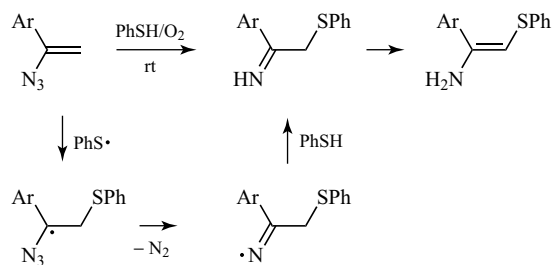
amounts of allylsulfonylbenzene.⁴³ Under more forcing conditions, dichloroindyl radical seemed to display a similar propensity to tin radicals to attack the terminal azide nitrogen, leading to expected release of benzenesulfonyl radical (Scheme 27).



Scheme 27 Light-induced radical reaction of benzenesulfonyl azide with allylindium dichloride.

2.2.4 Miscellaneous Radical Reactions of Aromatic and Aliphatic Azides

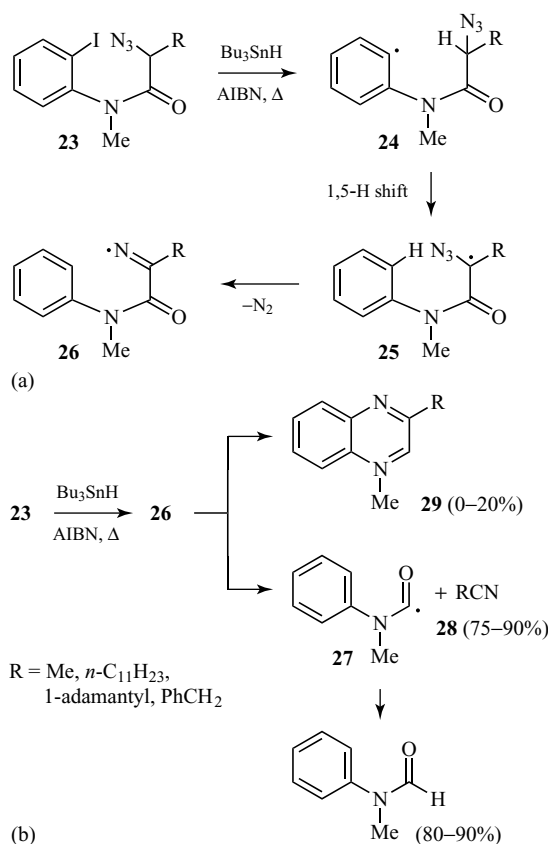
Until the end of the last century, the radical chemistry of organic azides has been invariably based on the peculiar propensity of the azido function to behave as a radical acceptor, but latest studies have disclosed that, under radical conditions, both aliphatic and aromatic azides can exhibit further



Scheme 28 Generation of iminyl radicals via α -azidoalkyl radicals.

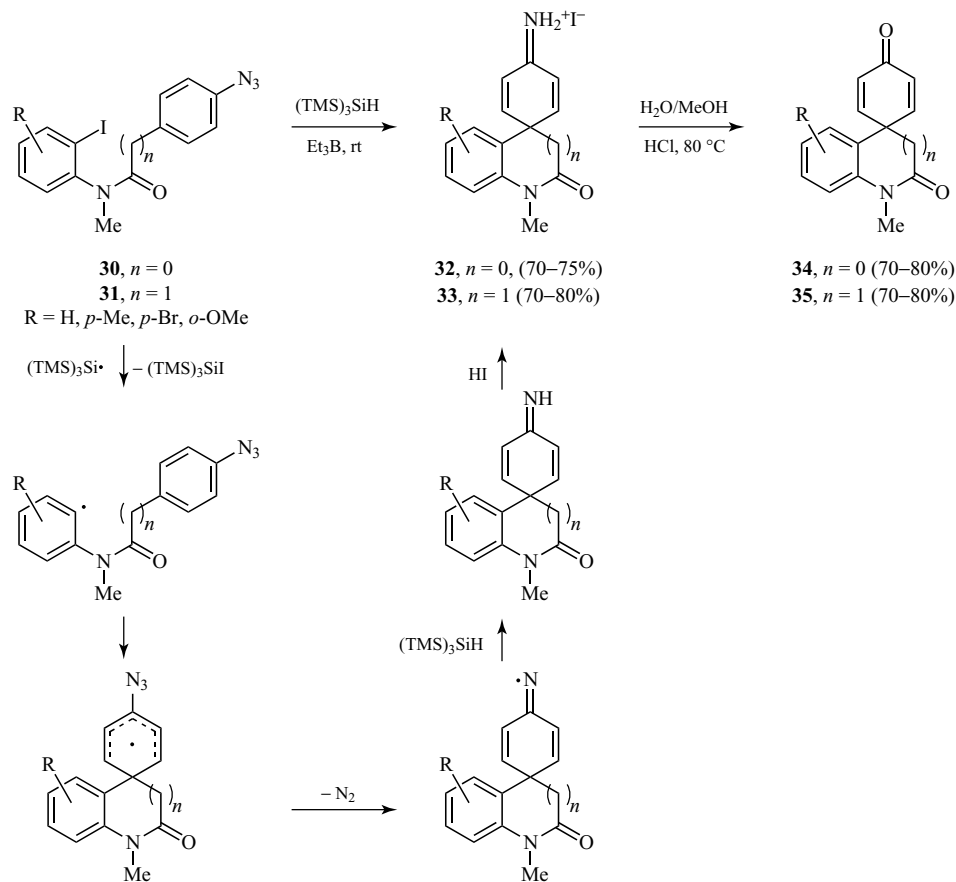
very interesting options which deserve adequate discussion for a more detailed comprehension of the impressive radical reactivity and connected utility of the whole azide family. In 1997, a paper dealing with new radical chain reactions of benzenethiol with α -azidostyrenes suggested that aliphatic azides might behave as progenitors of iminyl radicals, provided that transient radicals could be generated on the carbon atom attached to the azido function. At room temperature, those thiol reactions furnished virtually quantitative yields of sulfanylated imines and tautomeric enamines, reasonably ascribable to iminyl radicals derived from primary α -azidobenzyl radical adducts by elimination of molecular nitrogen (Scheme 28).⁵⁶

Following this long-neglected information, we have been led to prove that aliphatic azides could actually act as excellent sources of iminyl radicals through a study of the radical reaction of α -azido *o*-iodoanilides **23** with Bu_3SnH (Scheme 29a).⁵⁷ This study was based on earlier observations that aryl radicals derived from analogous iodoanilides rearrange to more stable alkyl radicals via internal 1,5-H transfer reaction. In refluxing benzene in the presence of Bu_3SnH and the usual AIBN initiator, the azido anilides **23** were found to generate in a virtually quantitative fashion α -(aminocarbonyl)iminyl radicals **26**. These intermediates were evidently formed by prompt elimination of dinitrogen from the corresponding α -azidoalkyl radicals **25**, in turn arising from fast 1,5-H transfer reaction of initial aryl radicals **24** (Scheme 29a). Under the reaction conditions, the resulting α -alkyl-substituted iminyls **26** gave high yields of alkanenitriles **28** by selective β -elimination of a carbamoyl radical **27**, along with limited amounts of oxoquinolines **29** due to parallel cyclization onto the internal aromatic ring (Scheme 29b).⁵⁷



Scheme 29 Generation and fate of iminyl radicals from aliphatic azides by 1,5-H radical shifts.

This work has clearly established that aliphatic azides can be regarded as highly efficient sources not only of aminyl radicals but also of the iminyl congeners, which are valuable intermediates in the radical synthesis of a broad variety of nitrogen compounds.^{21,58,59} Aliphatic azides could then lead to valuable applications to iminyl radical chemistry through the possible discovery of adequate synthetic entries to α -azidoalkyl radicals and thence the corresponding iminyls. In a following work, we demonstrated that also aromatic azides are possible precursors of iminyl radicals whenever homolytic ipso attack can occur at the para position of the azido-substituted benzene ring.⁶⁰ The radical reactions of the accessible *N*-methyl-substituted 2-iodo-*p*-azidobenzanilides **30** as well as the corresponding 2-(*p*-azidophenyl)acetanilides **31** with $(\text{TMS})_3\text{SiH}/\text{Et}_3\text{B}/\text{air}$ at room temperature afforded good yields of indolone/quinolinone imine



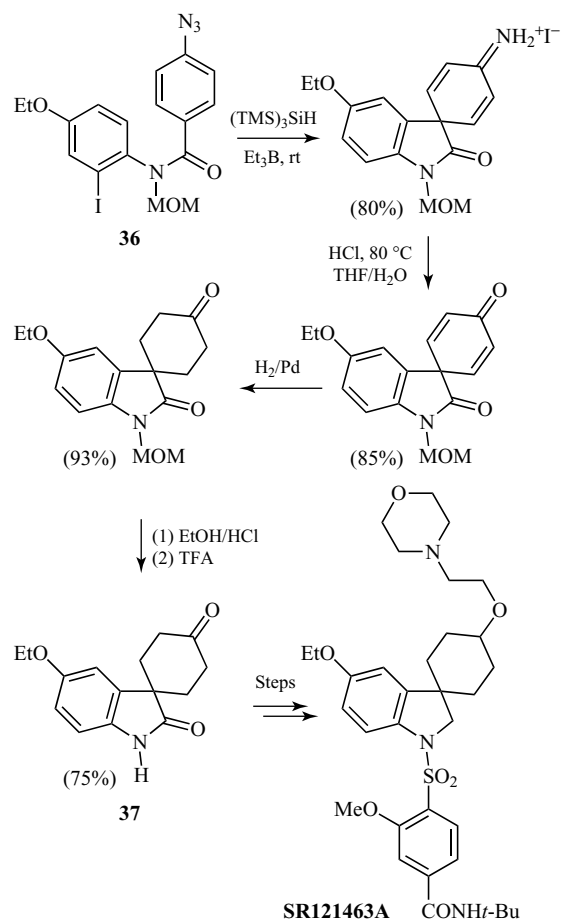
Scheme 30 Spirocyclic cyclohexadienimines and derived dienones obtained through iminyl radicals generated by ipso-cyclizations of aryl radicals onto aromatic azides.

hydroiodides **32/33**, isolable by direct filtration of the reaction mixtures (Scheme 30). Under these circumstances, the derived aryl radicals underwent smooth five- or six-membered ipso cyclization onto the internal aromatic azide, yielding spirocyclic azidocyclohexadienyl radicals, which in turn exhibited easy extrusion of molecular nitrogen to give cyclohexadienyliminyl radicals and then reduced imines. These last compounds eventually furnished their hydroiodides by further reaction with hydrogen iodide, probably formed by *in situ* hydrolysis of produced tris(trimethylsilyl)iodosilane. Upon conventional acid hydrolysis in methanol/water, all isolated imine hydroiodides **32/33** gave the respective spirocyclohexadienones **34/35** in satisfactory yields based on the original azides (Scheme 30).⁶⁰

Using the corresponding *N*-methoxymethyl (MOM) protected azidoacetanilides, an improved

synthesis of the *N*-unsubstituted quinolinone analogs has been next attained.^{61,62} Moreover, adoption of the MOM-protected azidobenzanilide **36** has enabled an advantageous preparation of the oxindole spirocyclohexanone **37**, an intermediate involved in the synthesis of the potent, selective vasopressin inhibitor **SR121463A** (Scheme 31).^{61,63}

A new intriguing propensity of aromatic azides to form cyclohexadieniminyl radicals has then allowed a straightforward access to both indolones and dihydro-2-quinolones bearing spirocyclohexadienone/-cyclohexanone rings, which are pivotal intermediates in the synthesis of biologically important indole compounds.^{62–64} It is therefore conceivable that aromatic azides could gain future interest in the radical production of a variety of other appealing spirocyclic compounds. The latest studies discussed in this section point out even



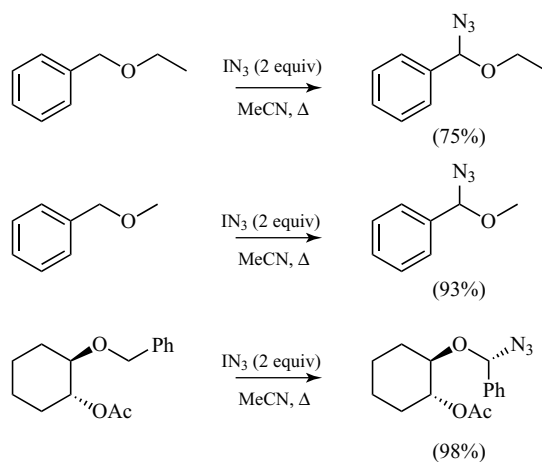
Scheme 31 Improved synthesis of *N*-unsubstituted spiroindolone **37** through key spirocyclization of *N*-MOM-protected azidobenzamide **36**.

more thoroughly the unique ability of the organic azides to form an extensive assortment of cyclic and acyclic nitrogen compounds under radical conditions.

2.3 Inorganic Azides

2.3.1 Iodine Azide in the Radical Azidation of Carbon Compounds

Iodine azide (IN_3), while being well known for its ability of ionic addition to olefins, is also known to undergo easy bond homolysis, providing azide and iodine radicals. In light of such promising

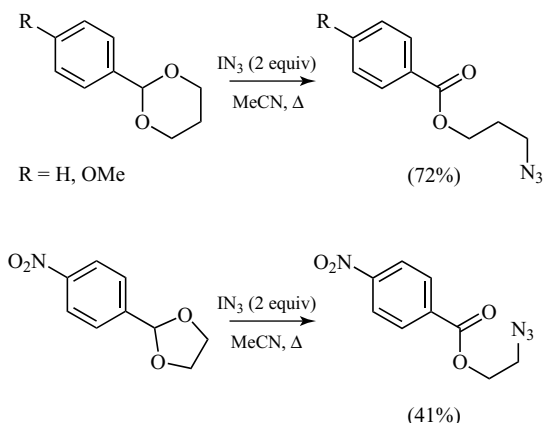


Scheme 32 Radical azidation of benzyl ethers with iodine azide.

information, Bols *et al.* have devised a useful protocol for the radical azidation of benzyl ethers using a twofold excess of iodine azide in refluxing acetonitrile. This protocol usually affords good to very good yields of the corresponding α -azidobenzyl ethers (Scheme 32).⁶⁵

Under these circumstances, homolysis of IN_3 results in an azide radical that abstracts a hydrogen atom from the substrate to form a benzylic radical. This radical is oxidized by IN_3 or I_2 to a benzylic cation that combines with the azide ion to give the final azide. Using an analogous radical protocol, various cyclic benzal acetals have been similarly converted by IN_3 to ring-opened 2-azidoethyl- or 3-azidopropyl benzoates via the final reaction of oxidized dioxolanium/dioxanum ion with the azide ion (Scheme 33).⁶⁶

In a subsequent work, Bols *et al.* demonstrated that IN_3 can also bring about highly efficient radical azidation of aldehyde compounds by acting as a powerful radical acceptor of acyl radicals.⁶⁷ Both aliphatic and aromatic aldehydes can be transformed into the respective acyl azides in good yields by simple treatment with 2 equiv of iodine azide in acetonitrile at 0 – 25°C . With certain aldehydes, the presence of a typical radical trap such as *N*-*tert*-butyl- α -phenylnitrone can prevent the usual production of acyl azide, which strictly supports the involvement of a radical reaction mechanism. Moreover, no production of any carboxylic acid ethyl ester can be observed when the usual IN_3

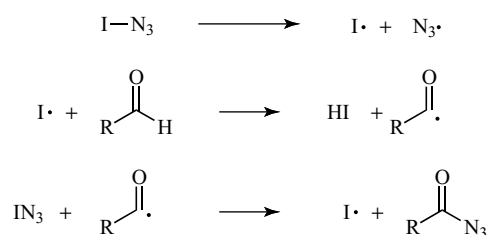


Scheme 33 Radical azidation of cyclic acetals with iodine azide.

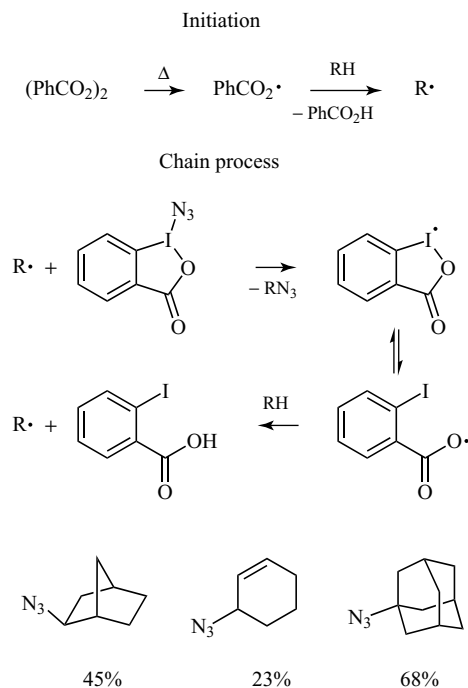
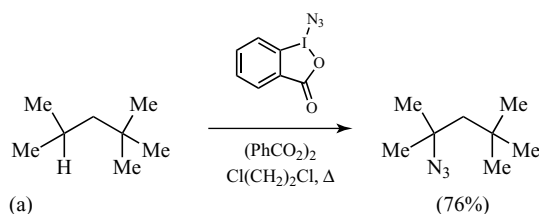
reaction is carried out in ethanol solvent, which clearly suggests that the acyl iodide or oxidized acylium ion cannot occur as possible intermediates. Accordingly, the radical chain mechanism shown in Scheme 34 has been proposed for the mild aldehyde azidation. An initially formed iodine (or azide) radical abstracts the aldehyde hydrogen atom, giving rise to an acyl radical. The resulting acyl radical is smoothly trapped by iodine azide, presumably yielding a 1,3-triazenyl radical whose prompt fragmentation would eventually afford an acyl azide as well as an iodine radical for the chain propagation.⁶⁷ Interestingly, if an aromatic or aliphatic aldehyde is allowed to react with IN_3 in refluxing acetonitrile in the presence of sodium azide, the ensuing acyl azide can afford a good yield of the corresponding carbamoyl azide through spontaneous Curtius rearrangement, followed by addition of azide to the isocyanate.⁶⁷ The radical azidation of an aldehyde with IN_3 has been adopted as a key step in a short synthesis of Cherylline dimethyl ether.⁶⁸ However, it is worth mentioning that another study has established that the notoriously hazardous iodine azide can be usefully substituted with $\text{PhI}(\text{OAc})_2/\text{Me}_3\text{SiN}_3$ in the above radical azidation reactions.⁶⁹

2.3.2 Azidoiodinanes in the Radical Azidation of Hydrocarbons

Azidoiodinanes, $\text{PhI}(\text{N}_3)\text{X}$ ($\text{X} = \text{OAc}$, Cl , OTMS , etc.) or $\text{PhI}(\text{N}_3)_2$, are proposed as reactive



Scheme 34 Mechanism of radical azidation of aldehydes with iodine azide.



Scheme 35 Radical azidation of hydrocarbons with 1-azido-1,2-benziodoxole-3-(1H)-one.

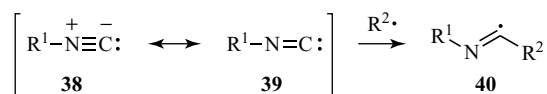
intermediates in the widely used azidation reactions involving the combination of PhIO or $\text{PhI}(\text{OAc})_2$ with trimethylsilyl azide or NaN_3 .^{69,70} Attempts to isolate these intermediates usually result in

fast decomposition at -25°C to 0°C with the formation of iodobenzene and dinitrogen. Importantly, in an excellent work that appeared in 1996, Zhdankin *et al.* reported the preparation of some thermally highly stable azidoiodinanes derived from 1,2-benziodoxole by reaction of the corresponding hydroxy compounds with trimethylsilyl azide.⁷⁰ The prepared azidoiodinanes proved to be good azidating agents toward various organic substrates and they could find especial use for direct radical azidation of hydrocarbons at high temperature and in the presence of suitable radical initiators. For example, 2,2,4-trimethylpentane reacted with 1-azido-1,2-benziodoxole-3-(1*H*)-one in refluxing 1,2-dichlorobenzene in the presence of dibenzoyl peroxide to give the corresponding aliphatic azide in 76% yield (Scheme 35a). The proposed radical chain mechanism involves hydrogen atom abstraction by the released 2-iodobenzoyl radical followed by key azidation of the resultant alkyl radical by the azidoiodinane. This chain process affords moderate to good yields of secondary and tertiary azides from several different alkanes (Scheme 35b).⁷⁰ However, in spite of the fact that Zhdankin's azidoiodinanes actually provided the first authenticated examples of reactions of azidating agents toward alkyl radicals, it appears that these azides have since found no practical application to other radical azidation processes.

3 ISONITRILES

3.1 Introduction

Isonitriles are a very unique class of organic compounds, as they are stable derivatives containing formally a divalent carbon, a property they share with very few molecules, such as carbon monoxide and *N*-heterocyclic carbenes (NHCs).⁷¹ They were discovered by Lieke, Gautier, and Hofmann as early as about a century and a half ago, but up to the 1960s only a relatively small number of studies concerning their chemistry were reported.^{72–77} This was probably due to the virtual absence of convenient, generally applicable synthetic methods, as well as to their very penetrating, unpleasant smell. The two classical isonitrile synthesis that had remained for long time the only access to this category of compounds, that is, the “carballyamine



Scheme 36 Resonance in isonitrile structure.

reaction”⁷² and the “alkylation method,”^{72,74} were indeed definitely not suitable for the preparation of appreciable quantities of pure isonitriles. They have been largely replaced now with the more widely applicable “dehydration method,”^{74,75,77} entailing transformation of primary amines into formamides, followed by dehydration either with phosgene (or its precursors) and triethylamine, or phosphorus oxychloride and di-*iso*-propylamine. The ready accessibility of isonitriles by this very general method has caused their chemistry to flourish, not only proving that these compounds are not merely a curiosity in the field of organic chemistry but also indicating that they possess outstanding versatility. Among the most renowned synthetic procedures, the Ritter-type processes⁷⁶ and the Passerini and Ugi reactions are worth mentioning.⁷⁷ The latter are remarkable multicomponent reactions that can easily afford a wide series of functionalized carboxamides, lactams, amino acids, and peptides, usually in high yields and often in a stereoselective way.

As anticipated, the structure of isonitriles can be described in terms of a divalent carbon atom, but in valence bond terms a full description of the isonitrile moiety requires the two resonance structures **38** and **39** (Scheme 36).

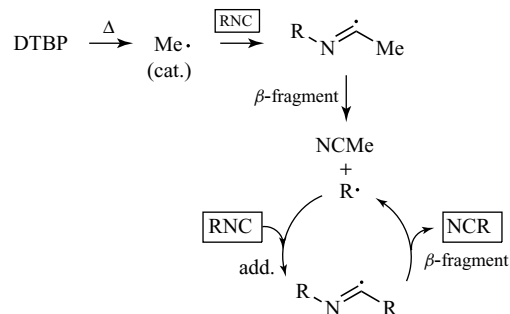
Although physical properties indicate that the dipolar contribution (**38**) is the major one, hence accounting for the nucleophilic behavior of the terminal carbon, in terms of radical chemistry the more interesting form is the divalent one (**39**). Indeed, this clearly shows that the isonitrile moiety does not behave, toward radical species, like a *vicinal* radical acceptor/radical donor synthon—that is like a usual unsaturated bond—but instead like a *geminal* acceptor/donor synthon,⁷⁸ where an incoming radical attacks the same carbon atom that will be the new radical center in the resulting imidoyl intermediate **40**. This terminology was first introduced by Curran *et al.* in 1991.⁷⁸ Actually, isonitriles can serve as very efficient radical traps and this section will review the mechanistic and synthetic studies carried out in this field, with outstanding results, in the last decades.

3.2 Radical Addition to Isonitriles and Fate of the Resulting Imidoyl Radicals

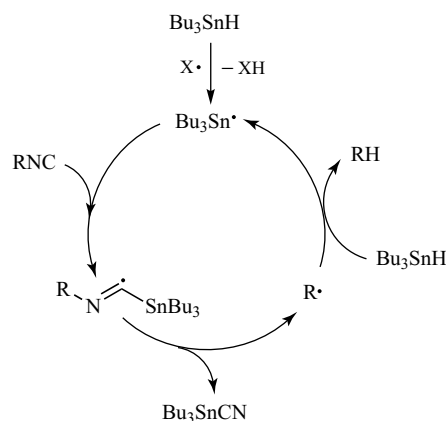
Imidoyl radicals are carbon-centered radical intermediates whose spin-bearing carbon atom belongs to a carbon-nitrogen double bond; the R^1 and R^2 groups (Scheme 36) can be alkyls, aryls, or, mainly in the case of R^2 , even heteroatom-containing moieties (e.g., alkoxy, sulfanyl, stannyl, silyl). To our knowledge, the existence of imidoyl radicals was first claimed in 1964 by Shono *et al.*⁷⁹ who proposed their intermediacy in the reactions of cyclohexyl isonitrile with radical sources such as dibenzoyl peroxide, *tert*-butyl perbenzoate, *N*-nitrosoacetanilide, and potassium phenylazoformate. However, apart from coupling or hydrogen transfer, none of the peculiar reactivities of imidoyl radicals was evidenced in that paper, probably as the result of very complicated reaction mixtures and approximate analysis methods. However, it is worth pointing out that this paper provided the first example of radical addition to isonitriles, a method that will be meant to be the main generation source of imidoyl radicals and by all means the most important resource for synthetic applications.^{80,81}

More interestingly, in 1967, Shaw and Pritchard⁸² studied the isonitrile–nitrile isomerization of methyl and ethyl isonitrile catalyzed by di-*tert*-butyl peroxide (DTBP). Although the concerted isonitrile–nitrile thermal (or photochemical) isomerization had been well known for many years,⁸³ they explained the process in terms of a radical chain mechanism involving the addition of (catalytic) methyl radicals to the isonitrile followed by β -scission of the resulting imidoyl radical adduct: the ensuing alkyl radical propagates the radical chain leading to the complete conversion of the starting isonitrile into its cyanoisomer (Scheme 37).^{84,a} A free-radical chain mechanism for the isonitrile–nitrile rearrangement in solution was definitely established by Rüchardt *et al.* in 1983.⁸⁵

As early as in 1968, Saegusa *et al.* reported the first example of addition to isonitriles of a kind of intermediate that had to become very popular in the field of radical chemistry: that is, tributyltin radical (see **Tin Hydrides and Functional Group Transformations**). The reaction of tributyltin hydride with some alkyl isonitriles in the presence of a radical initiator (AIBN) was found to afford the corresponding alkanes and tributyltin cyanide through an addition/fragmentation sequence



Scheme 37 Radical chain for conversion of isonitriles into the corresponding nitriles.



Scheme 38 Radical chain for addition of tin-centered radicals to isonitriles.

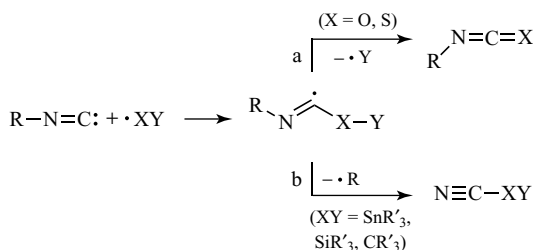
analogous to that reported in Scheme 37, in which tin radicals behave like additional chain-propagating species (Scheme 38).⁸⁶

A similar behavior was observed by the same author for phosphorus-centered radicals generated by hydrogen abstraction from diethyl or diphenylphosphine.⁸⁷ However, in this case, the reaction outcome was found to depend on the nature of the isonitrile: *tert*-butyl and benzyl isonitrile gave diethylcyanophosphine together with isobutane and toluene, respectively, whereas cyclohexyl and *n*-hexyl isonitrile yielded the corresponding diethylformimidoyl phosphines, arising from hydrogen transfer from the phosphine to the intermediate imidoyl radical. This result showed that hydrogen atom transfer to the intermediate imidoyl radical may well compete with β -fragmentation both/either in the absence of groups that can be released as

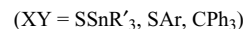
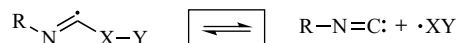
stable radicals and/or in the presence of very good H donors. Indeed, the reaction of tributyltin hydride with cyclohexyl isonitrile gave cyclohexane and tributyltin cyanide,⁸⁶ thus revealing that phosphines are better hydrogen donors than stannanes for imidoyl radicals.

During the 1970s, several papers have appeared^{88–92} dealing with addition of carbon-,^{90–92} oxygen-,^{89,90,92} and sulfur-centered⁸⁸ radicals to isonitriles. Interestingly, in the case of those heteroatom-centered radicals, the fate of the intermediate imidoyls depends upon the nature of both the attacking radical and the alkyl group of the isonitrile. Normally—even in the case of *tert*-butyl isonitrile—with oxygen- or sulfur-centered radicals, β -fragmentation on the O or S side prevails, resulting in scission of the O–Y or S–Y bond of the attacking radicals to give isocyanates or isothiocyanates, respectively (Scheme 39, path a). The only exception is addition of methylsulfanyl radical to *tert*-butyl isonitrile, which gives methyl thiocyanate and *tert*-butyl radical instead of *tert*-butyl isothiocyanate and methyl radical, due to the very strong S–Me bond of the intermediate imidoyl radical (see Ref. 93). Carbon radicals (as well as tin- and silicon-centered radicals)⁹⁴ produce, instead, nitriles through β -fragmentation of the original N–R bond of the isonitrile (Scheme 39, path b). Such reactions have a noteworthy synthetic potential and can be used either as an efficient, easy way to introduce a cyano group into a molecule or—by prior conversion of an amino group into the isonitrile moiety—as a useful deamination method (see below).

It should be noted that imidoyl radicals, when generated either from imines⁸¹ or isothiocyanates (see Section 4.2), can undergo an additional fragmentation reaction, that is, an α -scission



Scheme 39 Fragmentation products for addition of heteroatom-centered radicals to isonitriles.

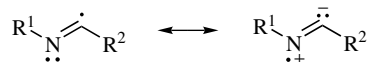


Scheme 40 α -Fragmentation of imidoyl radicals affording isonitriles.

with formation of an isonitrile. This process has been observed with α -(triphenylmethyl)-,^{95,96} α -(tributyltin)thio-, and α -(arylsulfanyl)-^{97–99} imidoyl radicals^{100,b} (Scheme 40). This would entail that the formation of imidoyls by radical addition to isonitriles can be a reversible process: this conjecture has been supported by some evidence in the case of particularly stable radicals.⁹⁵ This could definitely be an important detail that should be taken into account in designing a radical synthetic project involving isonitriles.

3.3 Structure, Spectroscopy, and Kinetics of Radical Adducts of Isonitriles

The first EPR study (see **Analysis of Radicals by EPR**) on the structure of imidoyl radicals dates back to 1973,¹⁰¹ although in that case imidoyls were generated by hydrogen abstraction from some aldimines. The low observed *g*-values (2.0016) and the β -hydrogen hyperfine splittings suggested that imidoyls are σ radicals with a nonlinear arrangement about the N=C–C bond. Their remarkable stabilization was explained in terms of the mesomeric forms shown in Scheme 41, in which the unpaired electron is stabilized by interaction with the lone pair on nitrogen, similar to what was suggested for the isoelectronic acyl radicals.¹⁰² The low *a*(N) values (1.20–1.85 G), which are in conflict with this kind of stabilization, were accounted for through a spin polarization mechanism that can induce a negative spin density at the nitrogen, thereby somewhat balancing the positive density resulting from resonance. The σ -electronic configuration of imidoyl radicals was confirmed some years later by Davies *et al.*,⁹⁴ who



Scheme 41 Resonance stabilization in imidoyl radicals.

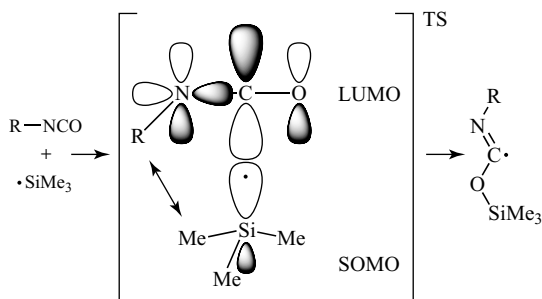
related their structure to that of the parent imines through a mathematical relationship between the EPR $a(\text{H}_\beta)$ constants of the former and the NMR 3J coupling constants of the latter.^{103,c}

A comprehensive EPR study on the spectroscopic properties of imidoyl radicals as well as the kinetics of their basic reactions was carried out by Roberts *et al.* in the subsequent two decades.^{93,104–111} In his seminal papers,^{93,104} he used isonitriles as the source of various α -heteroatom-substituted imidoyl radicals (for comparison purpose, Roberts generated some imidoyls also by hydrogen abstraction from imidates or imines by photolysis with bis(trimethylsilyl) or dicumyl peroxide (Refs 93 and 104)) and calculated some rate constants for both the radical addition and the β -fragmentation processes (Scheme 39, paths a and b). Addition of alkoxyls, for example, was found to be faster ($k \cong 6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ at 253 K) than that of alkyl radicals but slower than addition of phenyl radicals,⁹¹ whereas β -fragmentation of α -alkoxyimidoyls (Scheme 39, path a) was surprisingly slower ($k = 3.6 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ at 243 K) than that of the analogous α -(alkanesulfanyl)imidoyls. Interestingly, the $a(^{13}\text{C}_\alpha)$ and $a(\text{N})$ values were found to depend upon the nature of the α substituent R^2 (Scheme 41): the more electronegative R^2 is, the greater are $a(^{13}\text{C}_\alpha)$ and the $\text{N}=\text{C}^{\bullet}-\text{C}$ angle, as a result of an increase of the s-character of the semioccupied orbital. At the same time, the ability of R^2 to stabilize the negative charge on C_α enhances the positive spin density on nitrogen and hence the magnitude of $a(\text{N})$. These effects can account for the trend of the $a(\text{N})$ values observed with *tert*-butoxy, *tert*-butyl, *tert*-butylsulfanyl, and (trifluoromethyl)sulfanyl α -substituents (<0.3, 1.8, 5.0, and 5.8 G, respectively). When $\text{R}^2 = \text{SiEt}_3$, the electropositive silicon atom leads to quite a low $a(^{13}\text{C}_\alpha)$ value (29.8 G), whereas its ability to stabilize an adjacent negative charge gives rise to a rather large nitrogen hyperfine splitting (8.6 G). Since the pseudo- π overlap is maximum for a linear geometry, this specific imidoyl radical was hence suggested to be close to linear at C_α , similar to what was proposed for the isoelectronic β,β -bis(trimethylsilyl)- α -(trimethylsilyl)vinyl radical, which has a comparable $a(^{13}\text{C}_\alpha)$ value of 28.1 G.¹¹² This conclusion was nevertheless questioned by some theoretical calculations, which suggested that the radical structure is essentially independent of the electronic nature of the α -substituent, the $\text{N}=\text{C}^{\bullet}-\text{C}$ angle being virtually

constant at about 128° .¹¹³ It is worth noting that addition of silyl radicals to isonitriles was also kinetically studied by laser flash photolysis and was found to be a very fast process ($k = 1.6 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 300 K).¹¹⁴

α -(Trialkylsilyl)oxy-substituted imidoyls were generated by Roberts *et al.* through addition of silyl radicals to isocyanates (see also Section 4.1).¹⁰⁶ The addition was found to be considerably exothermic and probably involves early transition states with significant charge separation. The resulting imidoyls are strongly bent σ radicals with *E* and *s-trans* configurations about the $\text{N}=\text{C}$ and $\text{C}-\text{O}$ bonds, respectively, and they have the unpaired electron stabilized by both nitrogen and oxygen lone pairs. The rate of addition decreases along the series $\text{R} = \text{Me} > \text{Et} > i\text{-Pr} > \text{tert-Bu}$. The extremely low reaction rate observed with *tert*-butyl isocyanate ($k_{\text{tert-Bu}}/k_{\text{Me}} \leq 0.011!$) has been accounted for through a perturbational molecular orbital approach where the dominant frontier orbital interaction should occur between the SOMO of the nucleophilic trialkylsilyl radical (a hybrid of Si 3s and Si 3p orbitals) and the lowest unoccupied molecular orbital (LUMO) of the electrophilic isocyanate. Calculations predicted that the latter is a σ orbital primarily antibonding between the carbon atom and the two vicinal heteroatoms. The silyl radical should therefore approach the isocyanate in such a direction as to allow maximum overlap between the two orbitals (Scheme 42). The transition state can then evolve to the W-shaped imidoyl by shift of the silyl group onto the oxygen and concomitant localization of the spin onto the carbon atom. The lower reaction rates observed in the presence of bulky R groups are therefore the result of a steric compression between the *N*-alkyl and trimethylsilyl groups in the transition state.

Isonitriles can presumably be attacked by boron-centered radicals as well.^{107,108} Indeed, borane radical anions $\text{H}_3\text{B}^{\bullet-}$ and $\text{H}_2\text{B}^{\bullet}\text{CN}^-$, generated from the corresponding anions H_4B^- and H_3BCN^- by hydrogen abstraction with *tert*-butoxyls, have been found to displace alkyl radicals from alkyl isonitriles. While the expected C-borinated imidoyl radicals were not detected in any case, the reaction presumably entails their intermediacy, although an alternative mechanism involving an electron transfer from the borane radical anion to the isonitrile must not be excluded. Analogous alkyl radical displacements from alkyl

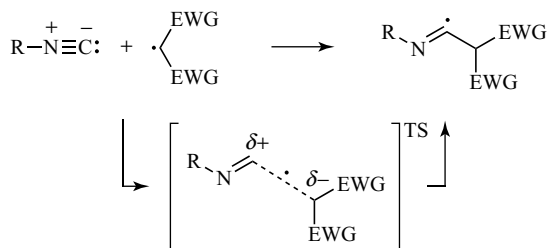


Scheme 42 Transition state for addition of silyl radicals to alkyl isocyanates.

isonitriles were also observed with boryl radicals ($\text{NH}_3 \rightarrow \text{BH}_2^\bullet$), generated by hydrogen abstraction from the ammonia–borane complex, but also in these cases no imidoys were detected.¹¹⁰

Imidoyl radicals were instead clearly observed in the reactions of alkyl isonitriles with phosphorus-centered radicals, obtained by hydrogen abstraction from dimethyl- or diethylphosphine–borane complexes. Some other phosphorus-substituted imidoys were also reported in Ref. 104.¹⁰⁹ Although it is not certain whether the attacking radical is a phosphinyl ($\text{R}_2\text{P}^\bullet \rightarrow \text{BH}_3$) or a phosphoranyl radical [$\text{R}_2\text{P}^\bullet(\text{BH}_2)\text{H}$] (with the former probably preferred), these imidoys, contrary to most congeners, are particularly stable toward β -fragmentation (see also Ref. 93), with the *N*-*tert*-Bu derivative still observable even at 293 K.

Other imidoyl radicals were later obtained by the addition of 1,1-bis(alkoxycarbonyl)alkyl- and tris(ethoxycarbonyl)methyl radicals to methyl and *tert*-butyl isonitrile.¹¹¹ These imidoys are strongly bent at C_α and the extent of bending increases with the number of electron-withdrawing groups attached to C_β , as expected from the previous studies.⁹³ More interestingly, addition of those electrophilic alkyl radicals to the nucleophilic carbon atom of isonitriles were found to be faster than that of unsubstituted (and hence nucleophilic as well) alkyl radicals, as a result of charge-transfer interactions in the transition state (Scheme 43). Therefore, as has been already emphasized for many radical processes, polar effects should be definitely taken into account in planning profitable synthetic procedures involving radical addition to isonitriles: substituents that increase both the nucleophilicity of the isonitrile and the electrophilicity of the attacking radical might provide a proper basis for a more likely success.



Scheme 43 Polar effects in addition of electrophilic radicals to isonitriles.

Analogous effects were suggested to explain the substituent effects observed by Kenttämäa *et al.* in the gas phase in the reaction of *tert*-butyl isonitrile with aryl radicals generated in a Fourier transform ion cyclotron resonance mass spectrometer.¹¹⁵ The efficiency of that reaction strictly follows the calculated electron affinity ordering of the aryl radicals and hence the authors concluded that the rate-determining step in the cyano-group abstraction from *tert*-butyl isonitrile by aryl radicals is the addition of the aryl radical to the isonitrile, with polar effects playing a crucial role in lowering the energies of the corresponding transition states. Addition of protonated 2-, 3-, and 4-dehydropyridine radicals to *tert*-butyl isonitrile in the gas phase was also studied¹¹⁶ and the different behavior of the 4-isomer, which gave predominantly HCN abstraction instead of the usual cyano-group transfer, was explained in terms of different charge and spin delocalization in the intermediate imidoyl radicals.^{117,d}

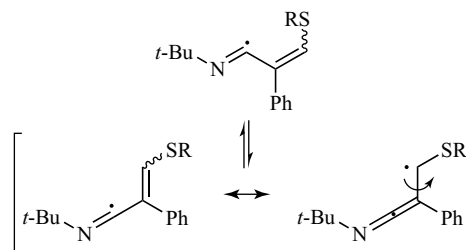
A thorough investigation on sulfanyl radical addition to isonitriles was carried out by us and Walton,^{118,119} who characterized the resulting thioimidoyl radicals by EPR spectroscopy and studied the β -scissions of their NC'S-C bonds by variable-temperature experiments. The obtained fragmentation rate constants and activation energies show that, at room temperature, the scission rates, although depend on the stability of the released alkyl radicals, are in any case very fast. Experiments carried out on unsymmetrical thioimidoys showed that competitive β -scission of the alkyl–N bond did not occur in any case, even in the simultaneous presence of a primary alkyl on the sulfur and a tertiary alkyl on the nitrogen. So fast is the fragmentation that practically every kind of C-centered alkyl (but, unfortunately, neither aryl nor vinyl) radical can be efficiently produced by this route at $T \geq 20^\circ\text{C}$.

($10^5 < k_f < 10^6 \text{ s}^{-1}$ at 298 K). Thermodynamic stabilization of the released radical plays, however, an important role: going, for example, from *S*-*n*-alkyl to *S*-*tert*-butyl causes an increase of the fragmentation rate of nearly two orders of magnitude at 200 K, and so fast is the release of resonance-stabilized radicals (e.g., benzyl) that the corresponding thioimidoyls could not be detected by EPR even at the lowest accessible temperatures.

Data collected on other heteroimidoyls revealed that oxyimidoyls, as expected,⁹³ exhibited slightly slower (≥ 16 times) fragmentations compared to those of analogous thioimidoyls, whereas theoretical calculations put forward for selenoimidoyls showed the lowest fragmentation rates. The competition between β -scission and 5-exo ring closure of *S*-but-3-enyl-substituted imidoyl radicals was also kinetically studied, showing that cyclization can prevail over fragmentation only at low temperatures (e.g., 200 K).

Density functional theory (DFT) computations on oxy-, thio-, and selenoimidoyls ($\text{RNC}^{\bullet}\text{-XR}'$, $\text{X} = \text{O}, \text{S}, \text{Se}$) gave further support to the postulated bent trans (W) σ structure of heteroimidoyl radicals and reproduced well the observed selectivity for *S*-alkyl with respect to *N*-alkyl fragmentation. Calculations also showed that, for all kinds of imidoyls, the scission preferentially occurs from the *s*-cis rotamer ($\text{NC}^{\bullet}\text{-X}$ bond) of the imidoyl radical. Since thio- and selenoimidoyls (but seemingly not oxyimidoyls) adopt a more stable *s*-trans conformation, but the rotation barriers around the $\text{NC}^{\bullet}\text{-X}$ bond ($E_a \cong 5\text{--}6 \text{ kcal mol}^{-1}$) are always lower than those for β -fragmentations ($E_a \cong 10\text{--}11 \text{ kcal mol}^{-1}$), those radicals can only fragment through prior rotation of the $\text{NC}^{\bullet}\text{-X}$ bond. Loss of the alkyl group at the X side seems therefore to resemble the anti-elimination process typical of many ionic reactions.¹²⁰

As far as the structure of imidoyl radicals is concerned, it is also worth noting that some experimental results coupled with theoretical calculations—although performed with semiempirical methods—suggest that the geometry of these intermediates could suitably change in the presence of resonance-stabilizing groups such as the carbon–carbon double bond of a vinyl moiety.¹²¹ Indeed, the geometry of the products obtained by vinyl radical addition to *tert*-butyl isonitrile was accounted for through an isomerization mechanism involving rotation around the vinyl carbon–carbon bond, transformed into a single bond by resonance



Scheme 44 Conjugation effects on the structure of imidoyl radicals.

effects that would convert the α -vinylimidoyl into an α -keteniminyl alkyl radical (see also Section 4.3). Calculations predicted for the imidoyl of Scheme 44 a practically linear assembly of the N-C-C moiety, with most of the spin density localized on the C_γ atom, a structure also suggested for isoelectronic β,γ -unsaturated acyl radicals.^{122,123}

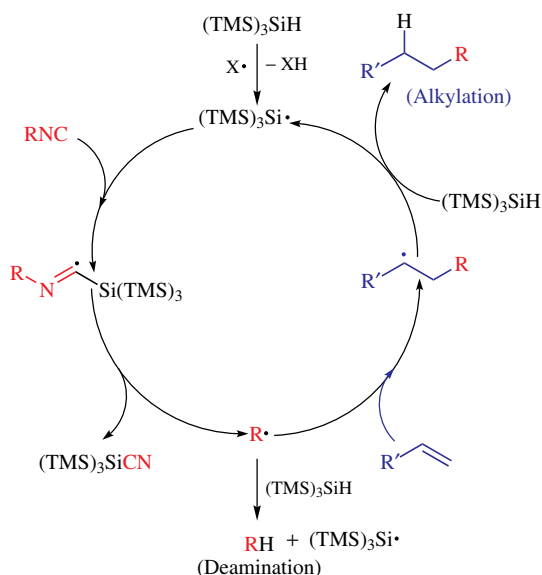
To conclude, it is worth noting that Yamago, Yoshida, *et al.* performed some comparative experimental and theoretical studies on radical additions to isonitriles and their analogous geminal acceptor/donor synthon carbon monoxide.¹²⁴ The results show that isonitriles are much better radical traps than carbon monoxide, specifically when stabilized radicals are involved. This stems from thermodynamic rather than kinetic effects, since activation energies are low for both kinds of reactants, whereas only isonitriles give rise to strongly exothermic additions, affording more stable radical intermediates (imidoyls vs acyls). As a result, not only do isonitriles behave like a valid substitute for CO (to circumvent decarbonylation of the intermediate isoelectronic acyl radicals), but they are also a suitable complement in radical-mediated C1 homologation reactions in the case of stabilized radicals that cannot react efficiently with CO.¹²⁵

3.4 Synthetic Applications

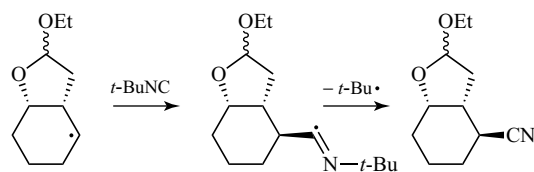
Examples of radical attack to isonitriles are copious, and isonitriles undoubtedly represent the lion's share among the existing methods of generation of imidoyl radicals. For synthetic applications of imidoyl radicals generated from imines or imine derivatives, see Ref. 81. Actually, we have shown that isonitriles have been the first source of imidoyls⁷⁹ and they have been used for all

the seminal studies about their general reactivity. As far as synthetic applications are concerned, the first reported example can be considered the work published in 1980 by Barton,⁹⁷ who was the first to recognize the potential of this reaction in organic synthesis and was therefore a pioneer in this field as well. Actually, he did not do anything else but realize that the already well-known β -fragmentation reaction of *N*-alkylimidoyl radicals could be a breakthrough as a deamination method. Indeed, he applied this idea in the defunctionalization of steroidal amines⁹⁷ and aminoglycosides such as the antibiotic neamine,¹²⁶ by prior conversion of those amines into the corresponding isonitriles, followed by reaction with tin-centered radicals. Some years later, Giese *et al.* showed that, by reacting alkyl isonitriles with tris(trimethylsilyl)silyl radicals, the ensuing alkyl radicals could add to alkenes. Hence, he demonstrated that, besides defunctionalization, that is, replacement of amino groups with hydrogen atoms, the alkyl radicals arising from C–N fragmentation of imidoyls could be exploited for other synthetically convenient reactions such as formation of new C–C bonds (Scheme 45).¹²⁷

If we change the point of view from the isonitrile to the attacking radical, we can exploit the same



Scheme 45 Radical addition to isonitriles as both a deamination and a functionalization method.

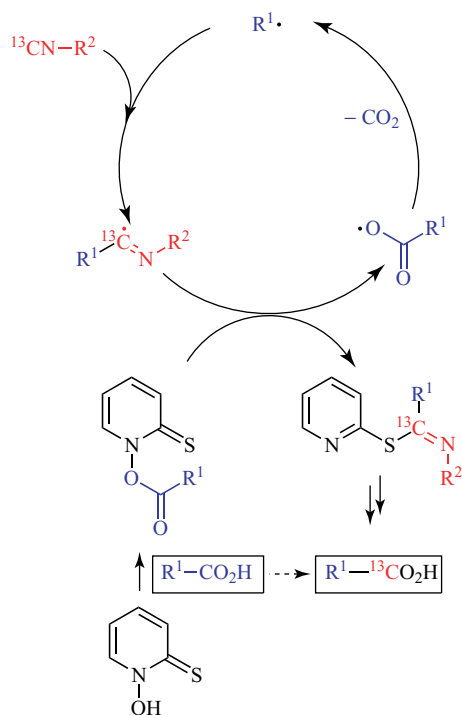


Scheme 46 Radical addition to isonitriles as a cyanation method.

β -scission reaction not as a deamination but rather as a radical cyanation method, as Stork *et al.* did in the same decade.¹²⁸ They showed indeed that alkyl and vinyl radicals arising from cyclization of bromoacetals can be efficiently trapped by *tert*-butyl isonitrile to give nitriles in good yields (Scheme 46). Aryl radicals can be used as well in this kind of radical cyanation reaction, as proved by Jones by reacting H-unprotected indol-2-yl radicals with *tert*-butyl isonitrile to obtain 2-cyanoindoles.^{129,130,e}

Later on, Barton again used his renowned method of radical generation from esters of *N*-hydroxypyridine-2-thione to invent a novel procedure for carboxyl group labeling involving isonitriles.¹³¹ His method entails thiohydroxamic ester-mediated generation of an alkyl radical, followed by addition to a suitable isonitrile to give a ¹³C-labeled imidoyl radical. Trapping of the imidoyl by the starting thiohydroxamate affords an adduct that can be easily hydrolyzed to the corresponding carboxylic acid. Since the starting thiohydroxamic ester is smoothly accessible from the same derivative, the overall process can serve as a method to incorporate ¹³C in the carboxylic acid simply by using an isotopically enriched isonitrile. This method can be useful for labeling the carboxyl group of prostaglandins and the side-chain carboxyls of peptides (Scheme 47).

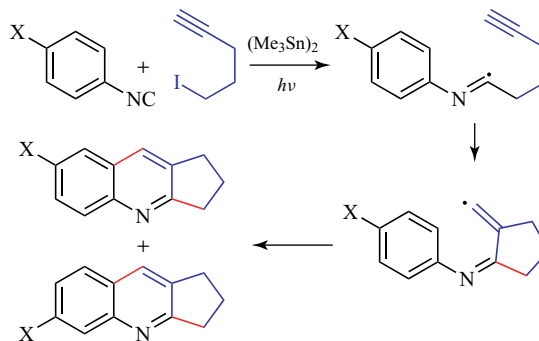
In principle, the presence of the N atom in the structure of radical adducts to isonitriles makes them very attractive intermediates for the synthesis of *N*-heterocycles. Nevertheless, the first examples of this application entailed generation of imidoyl radicals from imines or imidoyl derivatives,⁸¹ and it was not until 1991 that generation of imidoyl radicals from isonitriles was successfully employed in the synthesis of heterocycles thanks to the brilliant and pioneering work by Curran.⁷⁸ He accomplished indeed the first examples of [4 + 1] radical annulation by reacting aryl isonitriles with alkyn-5-yl radicals, in turn generated from



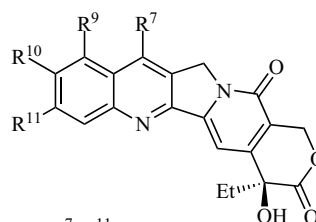
Scheme 47 Radical addition to isonitriles as a ^{13}C -labeling method for carboxylic acids.

the corresponding iodides. The reaction afforded cyclopenta-fused quinolines through a mechanism entailing addition of the alkynyl radical to the isonitrile, followed by 5-*exo*-dig-cyclization of the resulting imidoyl onto the carbon–carbon triple bond of the original alkynyl radical and eventual ring-closure of the produced vinyl radical onto the *N*-aryl ring (Scheme 48). The quinoline products were obtained as mixtures of isomers, as expected on the basis of the previously observed¹³² competitive six- and five-membered cyclizations of the intermediate vinyl radical.

With that result in his hands, the step toward more interesting applications was on his doorstep. The cyclopenta-fused quinoline moiety is in fact one of the main structural features of the camptothecin family, a group of molecules that has moved to the forefront of research in the treatment of solid tumors by chemotherapy and as antiviral drugs. Curran used his [4 + 1] radical annulation strategy as an outstanding breakthrough for the synthesis of (20*S*)-camptothecin and a wide series of approved drugs (mappicine,



Scheme 48 [4 + 1] Radical annulation with isonitriles involving vinyl radicals.



Camptothecin: $\text{R}^7\text{--R}^{11} = \text{H}$;

TopotecanTM: $\text{R}^7, \text{R}^{11} = \text{H}, \text{R}^9 = \text{CH}_2\text{NMe}_2, \text{R}^{10} = \text{OH}$;

IrinotecanTM: $\text{R}^{10}, \text{R}^{11} = \text{H}, \text{R}^7 = \text{Et}, \text{R}^{10} = \text{O}(\text{O})\text{CN}(\text{pyrrolidine})_2$

Silatecans: $\text{R}^7 = \text{Me}_3\text{Si}$

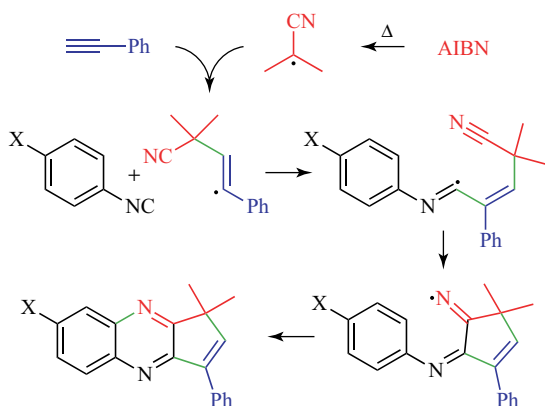
Figure 2 Camptothecin family compounds accessible by radical annulations with isonitriles.

topotecan, and irinotecan) and drug candidates (silatecans) (Figure 2), simply starting from suitable alkynyl-substituted radical precursors.^{133–140} The stereochemical requirements of the synthesis were fulfilled using enantiomerically pure alkynes, whereas the regiocontrol was achieved, when necessary, using *ortho*-(trimethylsilyl)-substituted aryl isonitriles. The overall procedure was therefore an asymmetric, regioselective, and widely applicable protocol that made accessible dozens different compounds.

During the 1990s, we carried out analogous reactions leading to heterocyclic compounds^{141–143} by reacting aromatic isonitriles with alkyl and sulfanyl radicals bearing a cyano-substituted side chain, thereby establishing the feasibility of attack of imidoyl radicals to the $\text{C}\equiv\text{N}$ triple bond. A few [4 + 1] annulation strategies involving a cyano group were also used by Curran: see Refs 136 and 139. The

overall reactivity of imidoyl radicals suggests that they are somewhat nucleophilic species, so that there was no surprise they could react well with the carbon atom of nitriles. This is also in agreement with the resonance form shown on the right side of Scheme 41, where the negative charge on the carbon atom plays a role in increasing the energy level of the radical SOMO, hence favoring SOMO–LUMO interactions with electron-deficient acceptors. An unprecedented trimolecular version of the radical addition tandem cyclization strategy was first carried out with a three-component system comprising an aromatic isonitrile, AIBN, and phenylacetylene.¹⁴¹ The 2-cyanoprop-2-yl radical arising from decomposition of AIBN adds to the terminal carbon of the alkyne to give a vinyl radical that attacks the isonitrile; the resulting imidoyl gives a tandem cyclization affording a quinoxaline derivative (Scheme 49). The formation of a unique quinoxaline isomer, rather than due to ring strain, seems a characteristic of the intermediate iminyl radical, since the analogous vinyl radical gives competitive cyclizations onto the aryl ring (Scheme 48).

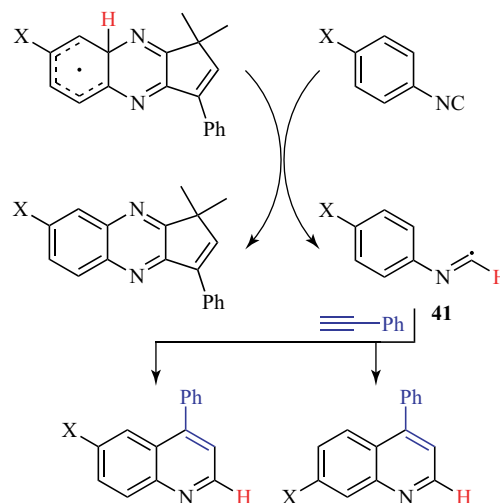
Similar results were also obtained by more usual two-component reactions carried out with cyano-substituted alkyl and sulfanyl radicals, the former obtained by photolysis of the corresponding iodides and the latter by hydrogen abstraction from thiols or photolysis of disulfides.¹⁴² In the case of *alkanesulfanyl* radicals, a significant competition between cyclization and C–S fragmentation of the imidoyl radicals was observed,⁸⁸ in line with the kinetic results obtained later on (Section 3.3). For



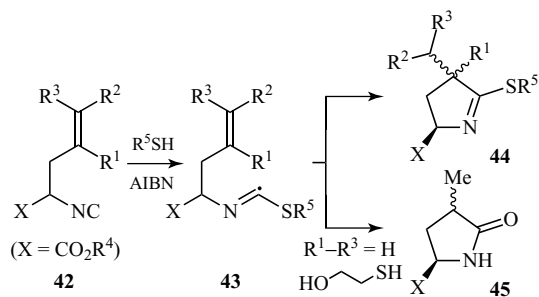
Scheme 49 [4 + 1] Radical annulation with isonitriles involving iminyl radicals.

another example of tandem cyclization triggered by attack of an alkylsulfanyl radical to an isonitrile, see Ref. 144.^{118,119} More profitable results could be obtained with cyano-substituted *arenesulfanyl* radicals, due to the stronger C–S bond. Cyclopenta-, thieno-, and benzothieno-quinoxalines have been synthesized with this methodology.

In those papers,^{141,142} the authors also showed that, in the absence of good oxidizing agents, isonitriles can be involved in the oxidation step of the cyclohexadienyl precursors of the final aromatic compounds: this might answer, at least to some extent, a *vexata quaestio* in the field of homolytic aromatic substitutions (see **Radical Arylations**).⁷⁸ The intermediacy of the C-unsubstituted imidoyl **41**, evidently associated with the intervention of the isonitrile in the aromatization process, was indeed clearly demonstrated by the occurrence, in the presence of phenylacetylene, of competing [4 + 2] and [3 + 2] annulations, affording two isomeric quinoxalines, a behavior that is typical of annulations involving imidoyl radicals (Scheme 50). It is not clear, though, whether isonitriles are implicated through a direct hydrogen abstraction—a mechanism that is the disproportionation analog of a radical–radical reaction—or a two-step reaction entailing a single electron transfer (SET) followed by proton transfer.^{145,f} This behavior was also observed in some cyclizations of biphenyl-2-yl isonitrile, and



Scheme 50 Involvement of isonitriles in aromatization of cyclohexadienyl radicals.



Scheme 51 Synthesis of five-membered heterocycles by sulfanyl radical addition to isonitriles.

its 2',3',4',5',6'-*d*₅-analog, to phenanthridine derivatives under various radical conditions.^{141,146,g}

The application of radical addition to isonitriles as a synthetic route to heterocycles has been further extended by Smith, who carried out [4 + 1] annulations using vinyl rather than aryl isonitriles as radical traps for alkynyl- or cyano-substituted alkyl radicals.¹⁴⁷ That paper also suggested the occurrence of a novel cyclic imidothiocarbonyl radical, generated by intramolecular aryl radical addition to an isonitrile moiety. Some mechanistic aspects of this reaction remain however unclear, since the postulated imidothiocarbonyl could be intermolecularly trapped only by an electron-rich alkene such as *tert*-butyl vinyl ether, in contrast with the general nucleophilic behavior exhibited by imidothiocarbonyl radicals.

A definite pioneer in the use of isonitriles in radical-mediated synthesis of heterocycles has been Bachi, who, during the 1990s, followed the way paved by Saegusa 20 years earlier⁸⁷ by exploiting sulfanyl radical addition to isonitriles for the synthesis of five-membered nitrogen heterocycles.^{148–152} As an example, treatment of the alkenyl-substituted isonitriles **42**, easily accessible from glycine imines, with an arene- or alkanethiol in the presence of AIBN afforded the *cis*- and *trans*-pyrroline derivatives **44** in high yields (Scheme 51). The use of mercaptoethanol gave instead a mixture of *cis*- and *trans*-pyroglutamates **45** probably through hydrolysis of a spirothioxolanepyrrolidine intermediate.¹⁴⁸

Of the two possible fragmentation side reactions that, in principle, imidothiocarbonyl radical **43** could undergo, that is, C–N bond breaking leading to deamination of the starting material, or C–S bond scission leading to an isothiocyanate, only the latter competed to some extent, especially when the scission yielded a fairly stable radical ($\text{R}^5 = \text{CH}_2\text{CO}_2\text{Me}$). However,

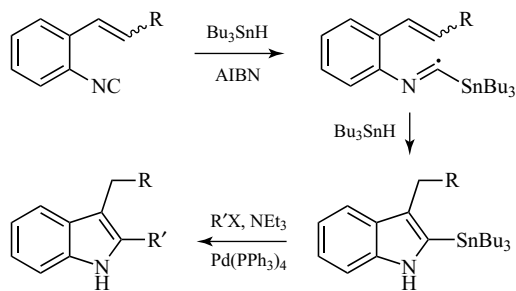
in those cases, adequate temperature adjustment allowed control over the two competing reactions.

As far as stereochemistry is concerned, whereas no or low diastereoselectivity was observed in the formation of the above pyrrolines and pyroglutamates (Scheme 51), an efficient stereocontrol was achieved with suitably designed starting materials bearing a bulky TBDMS–O (*tert*-butyldimethylsilyl, TBDMS) group vicinal to the site of radical addition.¹⁴⁹ This methodology was used as the key cyclization step in the stereo- and enantioselective synthesis of (±)- and (–)- α -kainic acid, the prototype of a group of neuroexcitatory amino acids that are important substrates in physiological and pharmacological studies of the central nervous system.^{150–153,h}

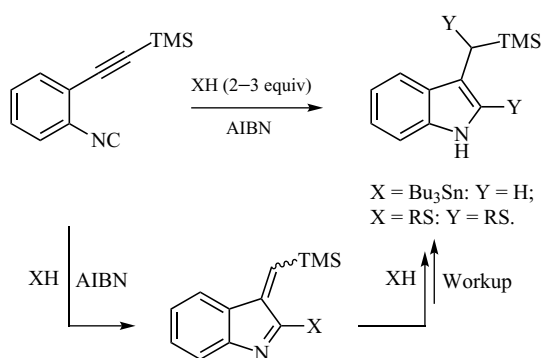
Analogous cyclizations of alkenyl- as well as alkynyl- isonitriles to pyrroline and pyroglutamate derivatives have been improved by the use of microwave flash-heating technology, which gave significantly superior results in terms of both reaction times and yields.¹⁵⁴ The same authors also developed an equivalent procedure based on polymer-supported alkenyl isonitriles.¹⁵⁵

Indoles are another important class of heterocycles that are accessible by radical isonitrile chemistry. *ortho*-Alkenyl-substituted aromatic isonitriles have indeed been successfully employed by Fukuyama *et al.* in a tin radical-mediated synthesis of indole derivatives bearing a stannylated moiety that is available for further manipulation through the Stille palladium-mediated coupling with aromatic or unsaturated halides or triflates (Scheme 52).^{156–158} This methodology has been also effectively used in the preparation of key intermediates for the total synthesis of some indole alkaloids.^{157,158} A variant of this procedure was developed by the same author through radical cyclization of *ortho*-alkenyl-substituted thioanilides.¹⁵⁹

Rainier *et al.* demonstrated that a very efficient synthesis of indoles can be carried out also with *ortho*-alkynyl-substituted aryl isonitriles (Scheme 53).¹⁶⁰ Five-membered ring-closure could be conveniently accomplished with either stannyl or sulfanyl radicals, and the presence of a TMS group linked to the alkyne moiety hampered concomitant formation of the six-membered cyclization quinoline product. The intermediate indolenines could be efficiently trapped by both nucleophilic radical precursors, that is, stannane and thiol, to give the final substituted indoles.



Scheme 52 Synthesis of indoles by tin-radical-mediated cyclization of alkenyl isonitriles.



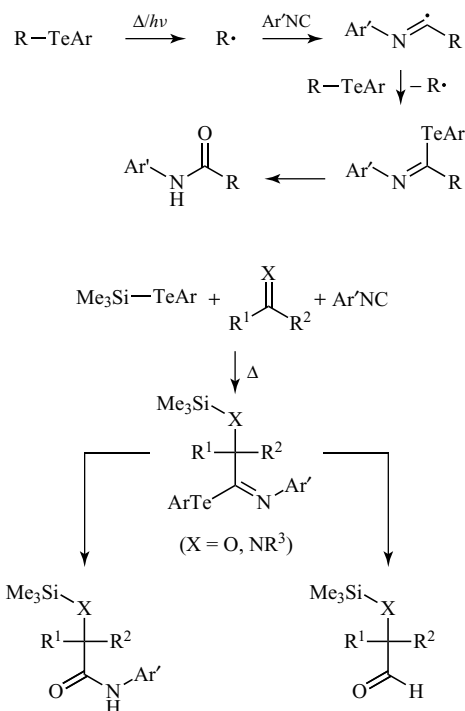
Scheme 53 Synthesis of indoles by tin/sulfanyl-radical-mediated cyclization of alkynyl isonitriles.

Yamago, Tokuyama, *et al.* have shown that indole derivatives can also be obtained by tin radical-mediated reaction of *N*-(2-alkenylphenyl) (phenyltelluro)imidates produced by thermal radical reaction of isonitriles with α -aminomethyltellurides.¹⁶¹ In this case, the intermediate imidoyl radicals cannot cyclize because of the very fast phenyltellanyl group transfer from the α -aminomethyltelluride. However, the same imidoyls can be regenerated by reaction of the resulting telluroimidates with tin radicals, and under these conditions they give ring-closure to indoles in high yields.

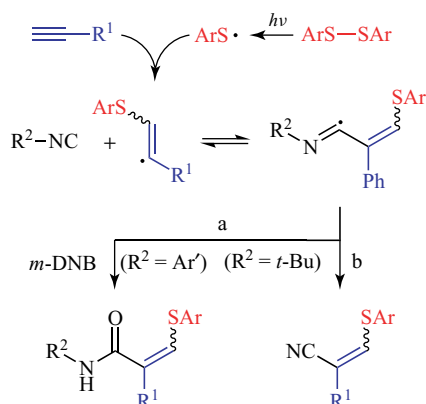
Yamago, Yoshida *et al.* have carried out a comprehensive study on the radical reactions involving telluro-derivatives and isonitriles.^{124, 161–166} Although only one example is related to the synthesis of heterocycles,¹⁶¹ the whole analysis is nonetheless of valuable synthetic interest, since it gave access to compounds susceptible to many further transformations. Their procedure involves

thermal or photolytic generation of alkyl or acyl radicals from the corresponding aryltellanides, followed by radical addition to an isonitrile and final aryltellanide group transfer from the starting telluro derivatives to the intermediate imidoyl radicals (Scheme 54).^{124, 162, 163, 166} The produced telluroimidates can be converted into amides or aldehydes and the reaction can be also captivatingly applied to three-component systems including silyltellurides, isonitriles, and either carbonyl compounds¹⁶⁴ or imines.¹⁶⁵ Appealing classes of compounds synthesized by this methodology include acyl glycosides,¹⁶² α -acylamides,¹⁶³ α -hydroxy carbonyl compounds,¹⁶⁴ and α -aminoacid derivatives.¹⁶⁵

We studied another efficient three-component radical cascade reaction with isonitriles, entailing the photolytic reaction between aromatic disulfides, alkynes, and isonitriles, affording β -arylthio-substituted acrylamides or acrylonitriles in fair yields (Scheme 55).¹²¹ The procedure involves the addition of photolytically generated sulfanyl radicals to the alkyne, followed by the attack of the resulting vinyl



Scheme 54 Radical reactions of isonitriles with telluro derivatives.

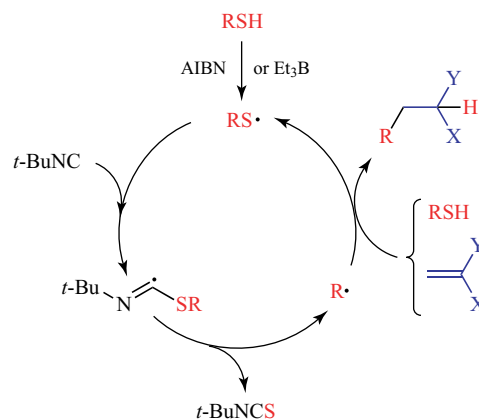


Scheme 55 Three-component radical reactions with isonitriles.

radicals to the isonitrile. The eventual imidoyl radical is trapped by a nitro-derivative (route a, *m*-DNB = *m*-dinitrobenzene) or undergoes β -fragmentation (route b). In the absence of either process, the imidoyl is unable to sustain the radical chain and only the starting material is recovered, possibly as the result of reversible addition of vinyl radicals to the isonitrile. The reaction provides very easy access to potentially useful polyfunctionalized alkenes through a very selective tandem addition sequence.

In those reactions, a lower or even inverted preference for either geometrical isomer was observed with respect to related hydrogen abstraction reactions by the same vinyl radicals. This was explained in terms of both/either transition-state interactions in the addition step to the isonitrile and/or isomerization of the final quasilinear imidoyl radical through a rotation around the C_β – C_γ bond: the latter process could efficiently compete with β -fragmentation, thereby affecting the final alkene *E/Z* ratio (see Section 3.3).

We also exploited radical addition to isonitriles—coupled with the results obtained from our contemporaneous spectroscopic/kinetic investigation on the β -fragmentation of thioimidoyl radicals^{118,119}—as the key step for a novel tin-free procedure for alkyl radical generation.¹⁶⁷ As shown in Section 3.3, so fast is that fragmentation that practically every kind of alkyl radical, from stabilized radicals to even primary unstabilized alkyls, can be easily generated from 110 °C down to room temperature, simply by reacting the

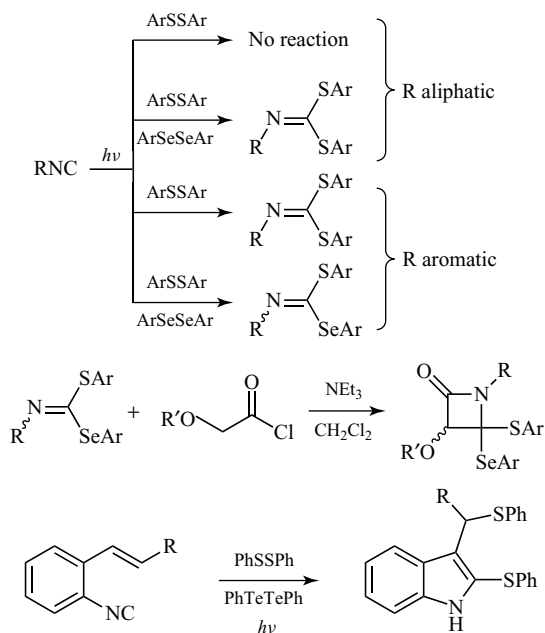


Scheme 56 Tin-free alkyl radical generation by isonitrile-mediated thiol desulfuration.

corresponding alkanethiols with *tert*-butyl isonitrile in the presence of a radical initiator such as AIBN (80 or 110 °C) or triethylborane (room temperature). The ease of workup is the foremost feature of this reaction: indeed, the volatile by-product *tert*-butyl isothiocyanate can be simply evaporated off with the solvent, yielding reaction mixtures in which, on average, the products are already so pure as not to need further chromatographic purification. The methodology has been applied to defunctionalizations (including Barton–McCombie-type reactions on thiol sugars) and intermolecular additions of electrophilic radicals to electron-rich olefins (Scheme 56). In a radical chemistry domain still considerably monopolized by toxic tin reagents, this procedure aims at being an appealing substitute for many stannane-mediated radical reactions.

To our knowledge, the most up-to-date example of synthetic application of radical addition to isonitriles is the double chalcogenation reported by Ogawa *et al.* in 2007.¹⁶⁸ The photoinitiated reaction (tungsten lamp through Pyrex) between *aryl* isonitriles, disulfides, and diselenides selectively afforded thioselenation products in high yields. *Alkyl* isonitriles, under the same conditions, gave instead bithiolation products, but only in the concurrent presence of diselenide: in the absence of the latter no reaction was observed (Scheme 57).

The key intermediate is assumed to be a thioimidoyl radical derived from the addition of an arylsulfanyl radical to the isonitrile; subsequent



Scheme 57 Double radical chalcogenation of isonitriles.

intermolecular S_H2 reaction of the imidoyl with the dichalcogenides reagents gives, depending on the characteristics of the isonitrile, the bis-chalcogenated reaction products, which can be employed for the construction of β -lactam derivatives by formal [2 + 2] cycloaddition with ketene equivalents. Analogous reactions can be carried out between electron-deficient aryl isonitriles and a disulfide/ditelluride mixed system. In the presence of suitable unsaturated side chains, the intermediate imidoyl radicals arising from the addition of sulfanyl radicals to the isonitrile give rise to five- and six-membered bis-sulfanylated cyclization products (indoles and quinolines, respectively, Scheme 57).¹⁶⁹

4 HETEROCUMULENES

4.1 Introduction

Heterocumulenes are a group of molecules containing cumulative double bonds in which one or more carbon atoms are replaced by heteroatoms (Figure 3). The most common members include isocyanates ($XR^1 = N, Y = C, ZR^2$

$= O$), isothiocyanates ($XR^1 = N, Y = C, ZR^2 = S$), carbodiimides ($XR^1 = N, Y = C, Z = N$), ketenes ($X, Y = C, ZR^2 = O$), and ketenimines ($X, Y = C, Z = N$); even diazo compounds, through one of their resonance forms ($X = C, Y = N^+, ZR^2 = N^-$), can be included in this class of organic compounds.

The free-radical chemistry of heterocumulenes is very diverse, depending on the nature of the heteroatoms and their positions in the cumulative system. In principle, they behave like *vicinal* radical acceptor/radical donor synthons, affording either vinyl- or allyl-like radicals by addition to either a side (X, Z) or the central (Y) atom of the cumulene moiety, respectively.

However, examples related to some categories of heterocumulenes are extremely scarce. For instance, only two examples have been reported concerning radical addition to diazo compounds:^{170,171} in those papers, addition to the carbon atom (X atom of Figure 3) was claimed, but neither of them identified the actual radical intermediate, although Roberts *et al.*¹⁷¹ suggested that a diazenyl radical is probably involved. The net result of this kind of addition was a *geminal* radical acceptor/radical donor synthon behavior, since, after loss of molecular nitrogen, the radical was actually centered on the carbon atom that was the addition target.^{172,i}

Addition to carbodiimides is even more uncommon: the only example was reported in 1976 by Ingold *et al.*¹⁷³ who identified by EPR a 1,3-diazaallyl radical arising from addition of a trifluoromethoxyl to the central carbon atom (Y atom of Figure 3) of *N,N'*-di-*tert*-butylcarbodiimide. Interestingly, azaimidoyl radicals arising from addition to the side nitrogen atom of the symmetric cumulene were never detected, whereas, in the same paper, *N,N'*-di-*tert*-butylsulfurdiimide was found to afford nitrogen-centered radicals by addition to the side nitrogen instead of the central sulfur.

Radical addition to isocyanates is surprisingly sporadic as well. A few imidoyls generated by the addition of silyl radicals to the oxygen atom of isocyanates (Z atom of Figure 3) have been studied

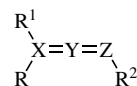


Figure 3 Heterocumulenes: general formula.

by EPR spectroscopy (see also Section 3.3),^{106,114} whereas addition of muonium was found to occur at the nitrogen atom (X atom of Figure 3) to give a β -muoniated carbamoyl radical,^{172,174} although hydrogen atoms had been previously found to prefer to add to the central C atom.¹⁷⁵ Intramolecular 1,5- and 1,6-ring closures of carbon radicals onto *N*-acyl isocyanates were kinetically studied: very rapid cyclizations always occur onto the central C atom with formation of imidyl radicals.^{176–179,j} Kinetic and theoretical studies have been also carried out on cyclization of 2-(2-isocyanatophenyl)ethyl radical, generated from the corresponding bromide via tin- or silicon-centered radicals.¹⁸⁰ The reaction afforded indole and quinolinone derivatives through competitive, very fast 1,5- and 1,6-ring closures, with the latter strongly prevailing, especially in the presence of tris(trimethylsilyl)silane. This was explained by a reversible five-membered (onto nitrogen) cyclization competing with a substantially irreversible six-membered (onto carbon) ring closure, due to formation of a cyclic amidyl radical stabilized by resonance with the *N*-aromatic ring.

As far as we know, the actual synthetic procedures involving radical addition to isocyanates are almost totally missing, with the exception of a radical carbamoylation, appeared in 2007, where the triethylborane-mediated addition of α -aminoalkyl radicals to aromatic isocyanates yielded *N,N*-dialkylated aminoacid derivatives.¹⁸¹ It is worth emphasizing that, in this case, radical addition occurs exclusively at the central carbon atom of the isocyanate moiety, thus showing that isocyanates can react at all viable atoms, depending on the nature of the approaching radical species.

Isothiocyanates and ketene derivatives raised a more extensive interest and the next two sections deal with the results reported by radical additions to those classes of heterocumulenes.

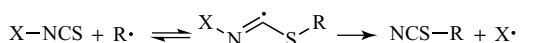
4.2 Isothiocyanates

Compared to isonitriles, examples of synthetic applications of radical addition to isothiocyanates are much less plentiful. Accessibility of starting materials is certainly not a drawback: indeed, like isonitriles, isothiocyanates are easily accessible from the corresponding amines,

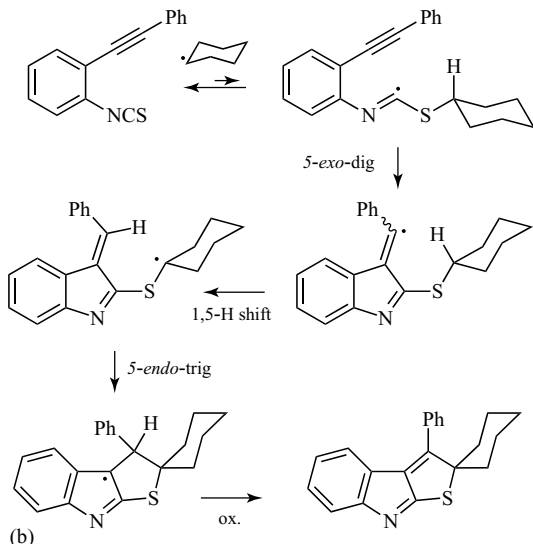
usually by reaction with either carbon disulfide/dicyclohexylcarbodiimide or (better) thiophosgene. Since all the reported examples, with the notable exception of muonium,¹⁷⁴ dealt with radical addition to the sulfur atom affording thioimidoyl radicals, it is likely that the number of achievable applications could be limited by the already mentioned fast C–S bond fragmentation of those thioimidoyls. In some cases, also α -scission of thioimidoyls affording isonitriles can become a competing, dangerous process, see: Refs 97–99.^{118,119,167} This process makes radical addition a reversible process in which the starting isothiocyanate is strongly favored, at least with usual alkyl radicals and at temperatures above 20 °C. Hence, useful synthetic procedures can only be designed either by means of suitable radicals that could bind to sulfur very tightly or in the presence of cyclizations (or other evolution routes) faster than back-fragmentation.

The pioneering work on synthetic applications of radical addition to isothiocyanates is once again one of Barton's papers,⁹⁷ where he used isothiocyanates (and isoselenocyanates as well) as intermediates for the stannane-mediated radical deamination of aminoglycosides.^{182,k} In this case, the strong tin–sulfur bond resulting by addition of tin radicals to the isothiocyanate prevents the retro-fragmentation, giving rise to a competitive α -scission of the thioimidoyl affording the corresponding isonitrile: attack of tin radicals to the latter gives a new imidoyl that eventually undergoes β -fragmentation of the C–N bond yielding the final deaminated product. Witczak observed that the intermediate isonitriles can also be obtained if the reaction of isothiocyanates with tributyltin hydride is carried out at low temperature and without a radical initiator,¹⁸³ whereas the occurrence of a radical mechanism is strictly required in order to reduce the isonitrile moiety.

On the other hand, Barton also discovered that alkyl radicals can trigger the transformation of sulfonyl isothiocyanates into alkyl thiocyanates: in this case, S–N β -fragmentation of the intermediate imidoyl with loss of sulfonyl radicals is so fast as to hinder S–C back-fragmentation, thus shifting the equilibrium of formation of the thioimidoyl radical (Scheme 58a).¹⁸⁴ We also observed a related behavior in the unusual multistep spirocyclization of an alkynylaryl isothiocyanate mediated by cyclohexyl radicals (Scheme 58b),¹⁴⁴ in which a very



(a) (X = Ts, MeSO₂, R = *c*-C₆H₁₁, PhCH₂CH₂)

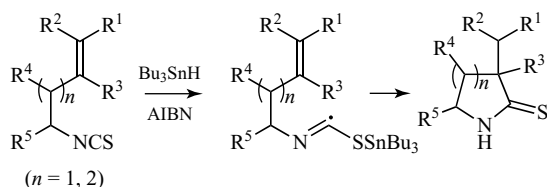


Scheme 58 Radical reactions of isothiocyanates mediated by alkyl radicals.

fast cyclization sequence overcomes the unfavorable fragmentation equilibrium of the intermediate thioimidoyl.

The alternative practice of circumventing the *S*-side fragmentation of thioimidoyls through formation of strong S–Sn bonds was exploited by John, Thomas, *et al.*¹⁸⁵ in the tin-radical-mediated isomerization of 6β-isothiocyanatopenicillanate and, above all, by Bachi *et al.*^{98,149,151} who used tin radical addition to isothiocyanates to perform cyclizations analogous to those previously reported for unsaturated isonitriles (Scheme 51). Accordingly, alk-3-enyl and alk-4-enyl isothiocyanates gave good yields of γ- and δ-thiolactams when treated with tributyltin hydride/AIBN at 75 °C (Scheme 59).⁹⁸ The reaction exhibited good stereocontrol with suitably substituted substrates (*n* = 1, R¹ = R² = Me, R³ = H, R⁴ = OTBDMS, R⁵ = CO₂Et), similar to that obtained with analogous isonitriles,¹⁴⁹ and was also applied as a route for the stereoselective synthesis of (±)-α-kainic acid.¹⁵¹

A further method for carrying out radical addition to isothiocyanates avoiding *S*-side back-fragmentation of the intermediate thioimidoyls entails the reaction with aryl radicals, which give

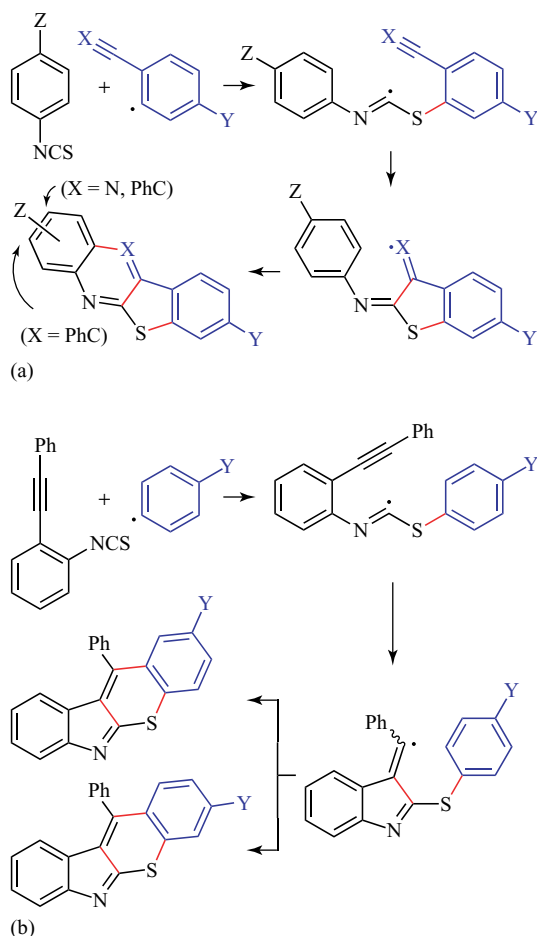


Scheme 59 Radical reactions of alkenyl isothiocyanates mediated by tin radicals.

rise to a substantially irreversible addition with formation of strong *S*-aryl bond. This methodology allowed the accomplishment of tandem cyclizations leading to heterocyclic systems, as shown in the reactions of aryl isothiocyanates with 2-cyano-⁹⁹ and 2-alkynyl-substituted aryl radicals¹⁸⁶ and in those of 2-alkynylaryl isothiocyanates with simple aryl radicals.¹⁸⁷

Aryl radicals were generated by decomposition of the corresponding diazonium tetrafluoroborates with either pyridine at –10 to –20 °C or ethyl acetate/potassium acetate/[18-crown-6] at room temperature, and were reacted with a series of aryl isothiocyanates to give benzothieno-quinoxalines (X = N) or -quinolines (X = PhC) (Scheme 60a). The mechanism entails the formation of thioimidoyl radicals, followed by 5-exo cyclization onto the cyano group (a rare example of [3 + 2] radical annulation) or the alkynyl moiety, and eventual cyclization of the resulting iminyl (X = N) or vinyl (X = PhC) radicals. In the latter case, mixtures of isomeric benzothienoquinolines were obtained, as the result of competitive five- and six-membered aromatic ring closure of the intermediate vinyl radicals. The isomer ratio was found to be dependent on the nature of the *Z*-substituent: the better the electron-withdrawing capability of *Z*, the higher the preference observed for the “rearranged” isomer, probably as a result of a SOMO/LUMO controlled cyclization of the slightly nucleophilic vinyl radical. The authors also found evidence that the attack of the aryl radical on the isothiocyanate is somewhat affected by polar factors: substituents that increase the electrophilicity of the aryl radical seem to favor addition to the substantially nucleophilic sulfur atom of the isothiocyanate, thereby increasing the overall efficiency of the cascade reaction.

The analogous reaction of aryl radicals with 2-alkynylaryl isothiocyanate gave mixtures of isomeric thiochromenoindoles through competitive [4 + 2] and [4 + 1] annulations. In this case, the



Scheme 60 Radical annulations of isothiocyanates with aryl radicals.

isomer ratio was found to be strictly correlated to the ability of the Y substituent to delocalize spin density and seems therefore the result of thermodynamic rather than kinetic control (Scheme 60b).

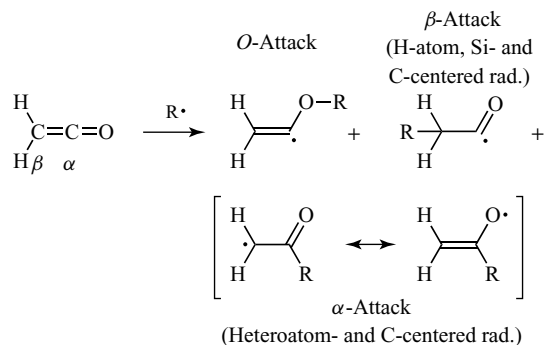
4.3 Ketenes and Ketenimines

References to free-radical reactions of ketenes are pretty scattered but more numerous than one would expect. Examples include reactions with peroxy radicals (as well as $^3\text{O}_2$), hydrogen atoms, fluorinated carbon radicals, alkoxy (and hydroxyls), halogen atoms, and carbon-centered radicals.¹⁸⁸ Most of the work has been carried out

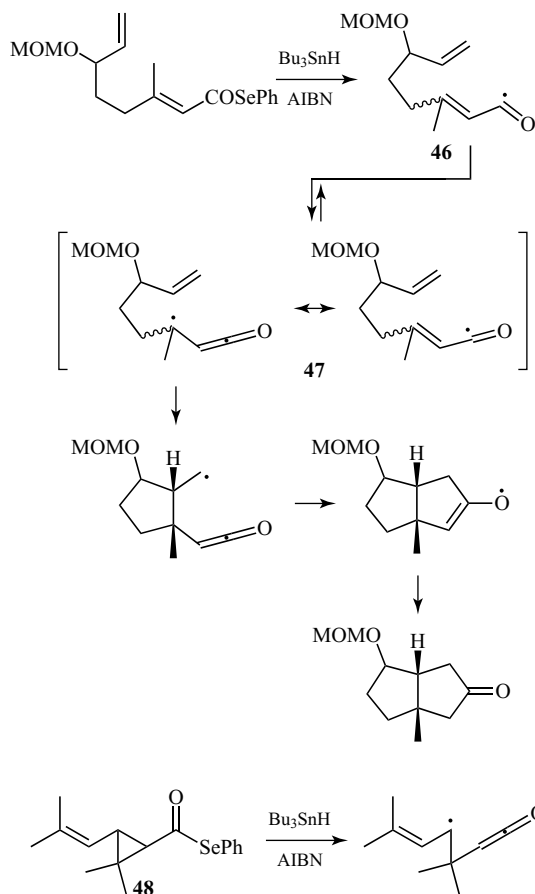
in the first decade of the new century by Tidwell *et al.*,^{188–197} who focused their attention on the regiochemistry of radical addition, which actually had been found to depend on the nature of both the ketene substituents and the attacking radical.^{198–200} In a theoretical study,¹⁸⁸ for example, they found that radicals containing lone pairs (e.g., $\cdot\text{OH}$, $\cdot\text{F}$, and $\cdot\text{Cl}$) preferentially attack C_α , owing to the stabilization arising from conjugation between the carbonyl group and the lone pairs; on the contrary, H atoms and silyl radicals ($\cdot\text{SiH}_3$) add to C_β (the latter as a result of hyperconjugative effects), whereas carbon radicals give rise to competitive C_α and C_β additions (Scheme 61).

Contrary to other lone-pair-containing radicals, which were predicted to give exothermic additions to both C_α and C_β , with the former however more favored, aminoxyls ($\cdot\text{ONH}_2$) were expected to show a more marked regioselectivity, because of an endothermic C_β -addition coupled with a competitive exothermic C_α -addition.¹⁸⁹ This opened the door to a thorough preparative, kinetic, and theoretical study on the addition of nitroxyls (namely TEMPO) to a wide range of ketenes:^{189–197} in all cases, regioselective addition to C_α afforded enolic radicals whose fate (trapping by a second TEMPO or dioxygen, rearrangements, cyclizations, etc.) depended on the type of ketene employed and the experimental conditions. In general, the reactivity is dominated by the nucleophilic character of the aminoxyl oxygen, which reacts more easily by increasing the electrophilicity of the ketene.

Amazingly, the only synthetic procedures reported so far concerning radical addition to ketenes do not really involve ketenes! Indeed, the nice work carried out by Pattenden *et al.*

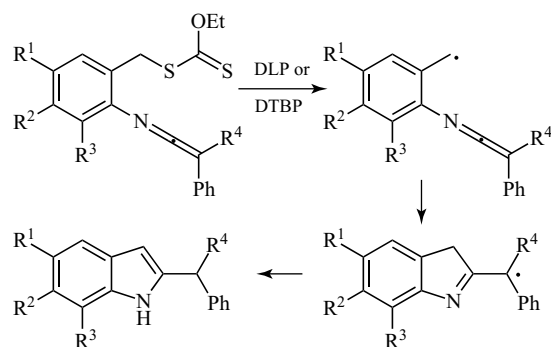


Scheme 61 Regiochemistry in radical addition to ketene.



Scheme 62 Generation and cyclization of α -ketenyl alkyl radicals.

in a decade around the end of the last century exploited cascade cyclizations of α,β -unsaturated acyl radicals, which reacted via their α -ketenyl alkyl radical equivalents by employing starting materials that actually did not contain at all ketene moieties.^{122,123,201–207} The results obtained were in fact explained in terms of the reactivity of the rearranged (and mesomeric) α -ketenyl alkyl radical form **47** of the initially generated β,γ -unsaturated acyl radical **46** (Scheme 62). The intermediacy of radicals **47** was initially suggested by the evidence of *E/Z* isomerization of the unsaturated acyl radicals²⁰¹ (a phenomenon analogous to that discussed above for imidoyls, see Scheme 44)¹²¹ and was exploited for tandem cyclizations leading to the synthesis of assorted cyclic and polycyclic compounds, including diquinanes^{201,203,205,206} and



Scheme 63 Cyclization of *o*-ketenimino-substituted benzylic radicals.

triquinanes.^{123,204,207} In all cases, only ring-closure onto the C_α atom was observed to give an enolic radical. The methodology was also applied to cyclopropane-substituted acyl radical precursors **48**, which can generate the same α -ketenyl radicals by ring-opening of intermediate cyclopropyl acyl radicals.^{122,201,202,205,206}

As far as ketenimines are concerned, this radical trap has remained totally unexplored since 2003, when Vidal *et al.* investigated cyclization of *o*-ketenimino-substituted benzylic radicals as a route to 2-alkylindoles.^{208–210} The protocol entailed a non-chain reaction between suitable xanthates and peroxides, with ring-closure of the intermediate benzylic radical onto the central carbon atom of the ketenimine moiety to afford an aza enolic radical analogous to that generated by C_α -attack on ketenes (Scheme 63). Interestingly, analogous cyclizations onto either *o*-carbodiimido or *o*-isothiocyanato moieties failed: see Ref. 209.

The protocol was extended to generation of benzylic and aryloxymethyl radicals from benzyl phenyl selenides²¹¹ and (phenylseleno)methyl aryl ethers,²¹² respectively, by treatment of the precursors with tris(trimethylsilyl)silane/AIBN: in the latter case, 2*H*-1,4-benzoxazines were obtained.²¹³

5 CONCLUSION

This review should have shown that the word “unusual” does not necessarily means “exotic” or “weird”! On the contrary, the “unusual” radical traps described in this article are very useful radical acceptors that, in most cases, are readily accessible

and allow the generation of very appealing intermediates and the consequent synthesis of an extensive assortment of compounds. Azides, in particular, should not be considered any more as hazardous chemicals, but instead as easy-to-make, attractive, and extraordinarily versatile compounds that can open the door to very convenient routes to both cyclic and acyclic nitrogen compounds through the intermediacy of a variety of nitrogen-centered radicals (triazenyl, aminyl, and even iminyl). Likewise, reactions involving isonitriles are not anymore a mere academic pastime but, on the contrary, via generation of imidoyl radicals, they represent a nice route to assorted nitrogen heterocycles and other remarkable derivatives, often through multicomponent procedures. Even the more unusual heterocumulenes are showing their potential in free-radical-mediated organic synthesis, especially as a route to cyclic and polycyclic compounds. The employment of the above moieties as radical acceptors in organic synthesis is certainly far from being close to an end, showing once more that radical reactions can be applied to a really huge range of substrates and are definitely one of the most widespread tools in organic chemists' hands.

END NOTES

^a. Although imidoyl radicals are *bona fide* intermediates in many examples of radical addition to isonitriles—as demonstrated by EPR spectroscopy—Kim has suggested that a concerted process, occurring through a polar transition state, could be involved in the isonitrile/nitrile isomerization when a particular stable radical, such as benzyl, can be released by β -fragmentation. This has been proposed for addition of phenyl and tributyltin radicals to benzyl isonitrile; see Ref. 84.

^b. An additional α -fragmentation of the imidoyl (Me_3Si) $\text{N}=\text{C}^*(\text{tert-Bu})$ to give Me_3SiNC and *tert*-Bu radical has been proposed by Ingold to explain the radicals detected in the addition of trimethylsilyl radicals to pivalonitrile; see Ref. 100.

^c. For an additional EPR study on radicals generated from imines; see Ref. 103, although in this paper detection of imidoyls was hindered by competing addition of *tert*-butoxy radicals to the parent imines, giving aminyls and nitroxides.

^d. Imidoyl radicals could also be formed by Group 11 metal atoms addition to isonitriles in a rotating

cryostat at 77 K. However, if ever formed, under those conditions they seem extremely prone to fragmentation and could not be observed even at so low temperatures; see Ref. 117.

^e. A cyanide transfer has been also observed between butyl isonitrile and the metalloradical rhodium(II) tetramesitylporphyrin. In that case, however, the reported kinetics suggest a more complicated mechanism compared to the usual radical addition/fragmentation pathway normally observed with organic radicals; see Ref. 130.

^f. The possibility of one-electron-transfer reduction of isonitriles to the corresponding radical anions has been suggested to occur in cyclizations of *o*-isocyano- β,β -difluorostyrenes mediated by *n*- Bu_3SnLi , which afforded, as major products, either 3-fluoroquinolines or 3,3'-difluoro-2,2'-biquinolines, depending on the order of addition of the reagents; see Ref. 145.

^g. For another example of attack on aromatic rings of imidoyl radicals generated from isonitriles, see Ref. 146. In that case, 2-(phenoxy)phenyl isonitrile, when treated with dibenzoyl peroxide, gave 2-phenyloxazole through presumable 1,5-phenyl radical migration followed by ring closure of the resulting phenoxyl with expulsion of benzoyloxy radicals.

^h. Another convenient enantioselective total synthesis of (–)- α -kainic acid was achieved by tin radical addition to an alkenyl thioformamide; see Ref. 153. Similar cyclizations to thiolactams were also carried out by tin radical additions to alkenyl isothiocyanates; see Ref. 98.

ⁱ. For addition of muonium to diazo-compounds giving α -muoniated alkyl radicals, see Ref. 172. In this paper also a stable carbene (1,3,4-triphenyl-4,5-dihydro-1,2,4-triazol-5-ylidene) was used as a trap for muonium.

^j. An intramolecular ring closure of biphenyl-2-yl isocyanate to carbazole and phenanthridone under photolytic conditions has been also reported; see Ref. 179. It is, however, unclear whether this reaction actually involves a free radical mechanism.

^k. There are actually a couple of previous papers, which date back to the beginning of the 1960s, that report some reactions of isocyanates and isothiocyanates with organostannanes; see Ref. 182a,b. Nevertheless, in those papers no evidence is reported about the intermediacy of radical species. See also Ref. 182c.

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Nitroxides in Synthetic Radical Chemistry

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1 INTRODUCTION

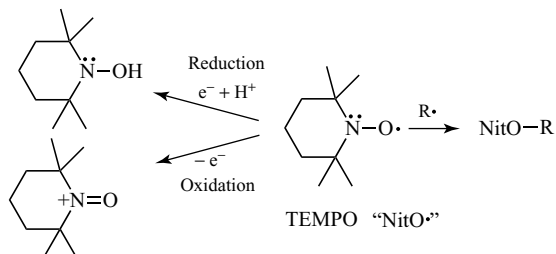
Nitroxides (NitO•) are kinetically persistent organic free radicals. Many are stable, commercially available compounds, and can be handled in the laboratory without any special requirements. The most commonly utilized nitroxide in synthesis is 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Nitroxides efficiently trap carbon radicals and are easily reduced to the corresponding hydroxylamines or oxidized to oxoammonium cations (Scheme 1). Synthetically, nitroxides have found utility as stoichiometric radical traps, often following radical cyclization processes. Nitroxides are also excellent mediators of redox processes, providing chemoselective methods for the oxidation of alcohols, often using very inexpensive ultimate oxidants such as oxygen from air, bleach, or peroxides. Nitroxides are used as mild, environmentally benign primary oxidants for transition metal catalyzed processes. Electron poor nitroxides abstract activated hydrogen atoms, and add to olefins, providing additional modes of reactivity. This article will outline the wide range of uses of nitroxides in synthesis, focusing on recent developments. A number of excellent reviews are available which highlight the state-of-the-art work at the time they were written.^{1–10}

2 NITROXIDES AS CARBON RADICAL TRAPS

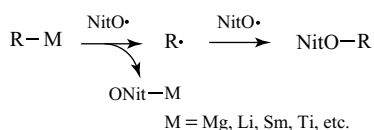
2.1 Direct Trapping of Carbon Radicals

Nitroxides trap carbon radicals at near-diffusion rate constants,^{11–13} converting organic radicals to alkoxyamines. As this is a radical-terminating event, this type of trapping cannot be utilized to perpetuate radical chain reactions. Nitroxide trapping has been used extensively as mechanistic probes¹⁴ for carbon radical intermediates and to calibrate the rate constants of radical rearrangements; however, these applications will not be covered here. In addition, the trapping of carbon radicals by addition to nitrene or nitroso species to form nitroxides, detected by EPR (“spin trapping”),¹⁵ is beyond the scope of this article (see **Spin Labels and Spin Probes**).

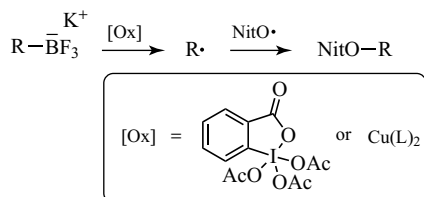
Nitroxides react with a variety of organometallic agents such as Grignard reagents; typically, 1 equiv of nitroxide affects oxidation of the organic moiety to the corresponding radical, which is then trapped by a second equivalent of nitroxide (Scheme 2).^{16,17} In an early example by Dalko,¹⁸ organolithiums bearing a chiral auxiliary trapped TEMPO with good diastereoselectivity. Fensterbank and coworkers have recently developed the generation of carbon radicals from alkyltrifluoroborates by addition of 1 equiv of a strong oxidant (either Cu(II) or



Scheme 1 Three main reactions of dialkyl nitroxides: reduction, oxidation, and trapping carbon radicals.



Scheme 2 Reaction of nitroxide with Grignard and other organometallic reagents.

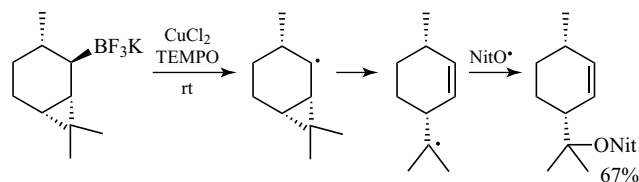


Scheme 3 Generation of a carbon radical from an alkyltrifluoroborate; trapping with nitroxide.

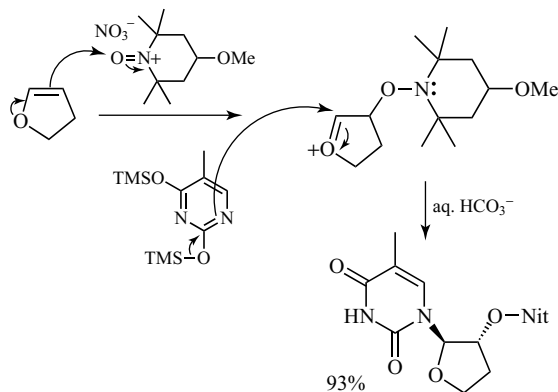
Dess–Martin periodinane); TEMPO trapping forms the alkoxyamines¹⁹ (Scheme 3).

Using these conditions, nitroxide trapping is faster than 5-*exo*-trig cyclization; however, cyclopropylcarbinyl ring opening is even faster, giving only the ring-opened cyclohexene product (Scheme 4).

Alkoxyamines have found extensive use as initiators for nitroxide-mediated radical polymerization (NMRP) (see **Nitroxide-Mediated Polymerization**



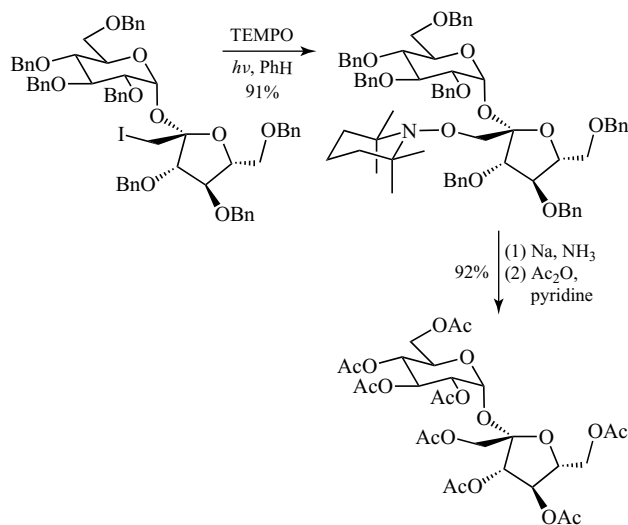
Scheme 4 Cyclopropylcarbinyl ring opening is faster than nitroxide trapping.



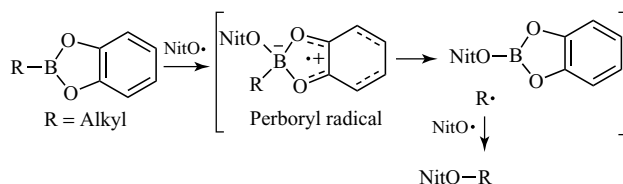
Scheme 5 Alkoxyamine synthesis via addition of an electron-rich olefin to an oxoammonium cation.

and its Applications). Numerous methodologies have been developed to prepare alkoxyamines for this purpose.^{20–26} The preparation of alkoxyamines to form NMRP initiators has been recently reviewed⁵ and has not been repeated here. However, one unusual mode of reactivity will be highlighted, in which nucleophilic addition of an electron-rich olefin to the oxygen of an oxoammonium cation forms the key carbon–oxygen bond.²⁷ For example, Church *et al.*²⁸ have created alkoxyamine nucleoside analogs by reaction of dihydrofuran with an oxoammonium salt in the presence of a silylated thymine (Scheme 5).

The trapping of carbon radicals by nitroxides for synthetic purposes has been utilized as a chemoselective method to introduce oxygen into complex molecules. For example, photolysis of a neopentyl alkyl iodide in the presence of TEMPO followed by reductive O–N bond cleavage with sodium-ammonia provided a hydroxyl group in the synthesis of sucrose (Scheme 6).²⁹ Attempts to use oxygen nucleophiles to introduce the hydroxyl group at this position failed due to steric hindrance.



Scheme 6 Trapping of a neopentyl carbon radical by TEMPO to install a hydroxy group at a very sterically hindered position.



Scheme 7 Generation of a carbon radical by nitroxide addition to an alkylcatecholborane.

2.2 Nitroxide Addition to Catecholboranes

Schaffner and Renaud³⁰ have developed a very mild methodology using catecholboranes as a convenient sources of alkyl radicals (see **Boron in Radical Chemistry**), which can undergo radical rearrangement or rapid olefin addition reactions before being trapped by nitroxides. This protocol is based on the facile addition of oxygen radicals, including nitroxides, to alkylcatecholboronates to form stabilized perboryl intermediates, which fragment by release of alkyl radicals (Scheme 7).

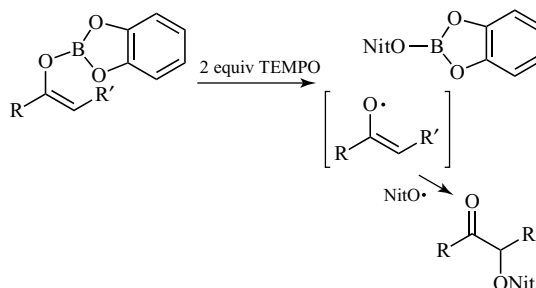
Since nitroxides couple with alkyl radicals very quickly, olefin addition is successful only with highly activated radical traps. As a collaboration between Renaud and Studer, catecholboron enolates were shown to react with TEMPO to give α -keto alkoxyamines (Scheme 8).³¹

Wagner and Studer³² have applied this direct radical trapping with functionalized nitroxides to “decorate” polymers and dendrimers bearing accessible terminal olefins (Scheme 9) with a variety groups,

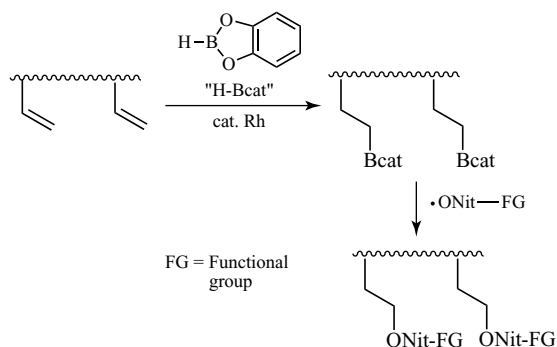
such as fluorescent tags, solubilizing poly(ethylene glycol) (PEG) groups, a protected sugar, and terminal alkynes for “click” functionalization.

2.3 α -Oxyamination of Enamines

Enamines are easily oxidized to radical cations, which can be trapped by TEMPO. Schamann and



Scheme 8 Reaction of a catecholboron enolate with TEMPO to form an α -keto alkoxyamine.

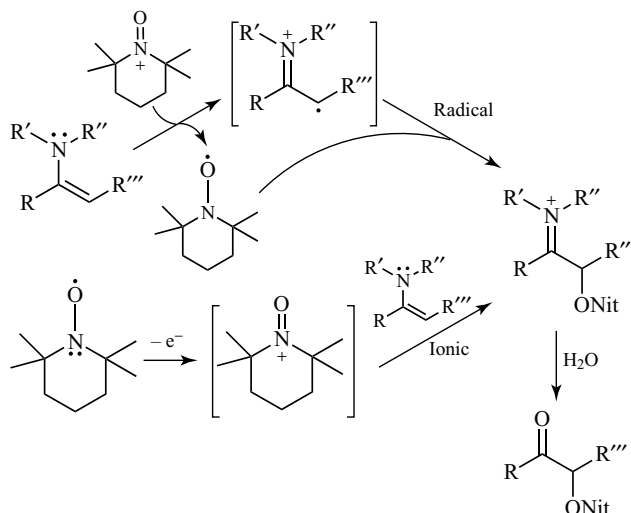


Scheme 9 Hydroboration, radical generation protocol to decorate macromolecules bearing terminal alkenes with nitroxides bearing useful functionality.

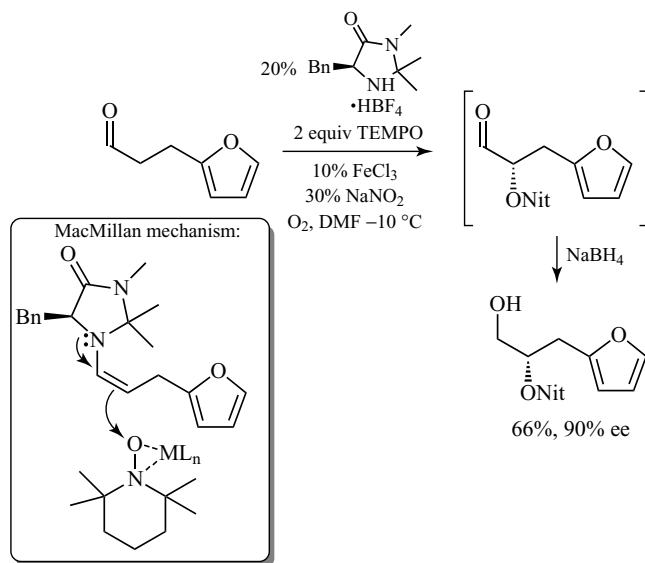
Schafer investigated anodic oxidation of TEMPO to form the oxoammonium salt in the presence of enamine to give the α -alkoxyamine.³³ The mechanism is either electron transfer to form the radical cation (“SOMO catalysis,” see **Synthetic Radical Photochemistry**) and the nitroxide, followed by heterocoupling, or electrophilic addition of the oxoammonium cation to the enamine (Scheme 10).

The mechanistic pathway is determined by the ease of oxidation of the nitroxide versus the enamine. Sibi and Hasegawa³⁴ extended this reaction using optically active amines as organocatalysts and Fe(III) (generated catalytically from NaNO₂ and O₂) as the oxidant to carry out enantioselective

α -alkoxyamination of aldehydes (Scheme 11) (see **Stereoselective Radical Reactions**). The resulting aldehyde can undergo epimerization, thus reduction to the alcohol was carried out to provide a stable product. A number of variations in this procedure include work using anodic oxidation³⁵ or benzoyl peroxide³⁶ as the oxidant. Use of a proline-terminated peptide on a solid support as the organocatalyst was reported by Kudo and coworkers.³⁷ A recent mechanistic investigation by MacMillan and coworkers,³⁸ based on kinetic studies, calculations, and use of a cyclopropyl carbinyl “radical clock” to probe for a free radical intermediate, suggests that many of these reactions occur through an electrophilic metal-activated TEMPO species reacting with an enamine nucleophile. Variation of the reaction conditions, including the choice of metal (Fe, Cu, etc.), ligands, and solvent shifts the reaction mechanism between electrophilic addition and radical character. An interesting use of a photoexcited Ru(II) catalyst³⁹ as the oxidant in a racemic α -oxyamination reaction may also be going through a metal-activated TEMPO electrophile rather than the reported enamine radical cation intermediate. The use of photocatalyzed Rose Bengal with 1,3-dicarbonyl compounds and TEMPO results in α -alkoxyamination,⁴⁰ presumably via single electron transfer (SET) of the enolate followed by nitroxide trapping.



Scheme 10 Two mechanistic pathways for the α -oxyamination of enamines with TEMPO.



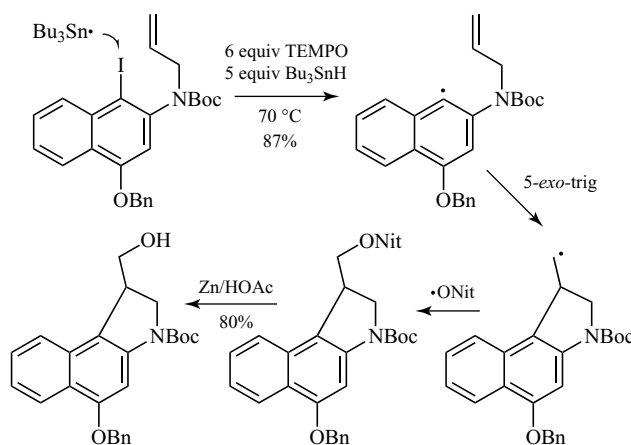
Scheme 11 Organocatalytic asymmetric α -oxyamination of enamines with TEMPO via an electrophilic metal-activated nitroxide complex.

2.4 Cyclization Followed by Nitroxide Trapping of Carbon Radical

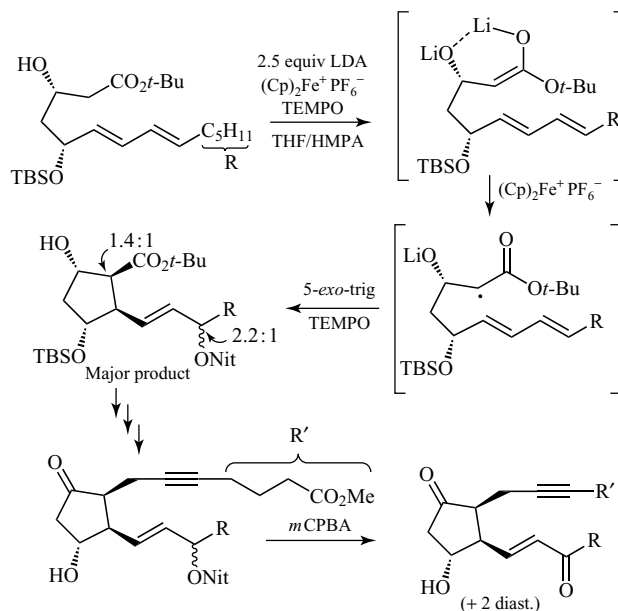
The development of synthetic radical sequences that incorporate formation of a covalent carbon–carbon bond before nitroxide trapping are not very numerous, as premature trapping of the initial radical by nitroxide must be avoided. Thus, very fast carbon–carbon bond forming reactions must be employed before nitroxide trapping to ensure success. Often fast unimolecular rates of

cyclizations can be used to successfully orchestrate conditions to allow useful covalent bond construction before termination by nitroxide trapping.

Tributyltin hydride-mediated radical formation followed by TEMPO trapping, with or without cyclization, was demonstrated by Bergman and coworkers in 1978.⁴¹ On the basis of this, an efficient synthesis of 3-(hydroxymethyl)indolines, using a radical cyclization, TEMPO trapping sequence was utilized by Boger and McKie⁴² in the synthesis of CC-1065 analogues (Scheme 12).



Scheme 12 Boger's radical 5-*exo*-trig cyclization followed by nitroxide trapping in the synthesis of CC-1065 analogues.

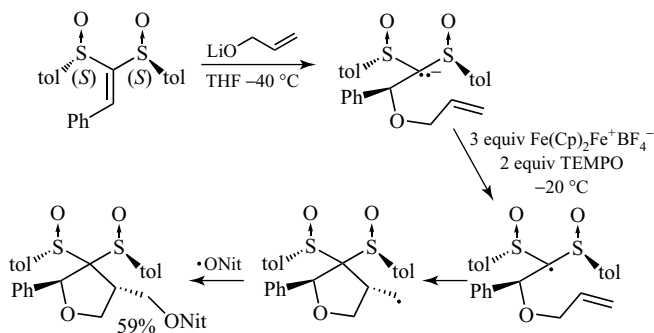


Scheme 13 Jahn's oxidation of an anion to radical, 5-*exo*-trig cyclization, and nitroxide trapping sequence in the synthesis of an isoprostane metabolite.

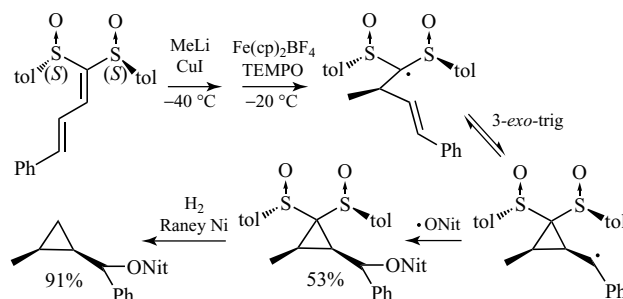
Extending the efficiency of radical tandem reactions to include a redox step, Jahn *et al.*⁴³ have developed an anionic Michael addition, radical cyclization, and nitroxide trapping sequence utilizing ferrocenium ion for enolate oxidation to a carbon radical. A recent variation of this chemistry toward the synthesis of isoprostane metabolites demonstrated diastereoreversibility by varying the enolate counterion between lithium (open TS) and magnesium (chelated TS).⁴⁴ For example, use of LDA gave predominately the diastereomer and regioisomer shown; the alkoxyamine–TEMPO

moiety was oxidatively converted to the ketone using *m*CPBA⁴⁵ (Scheme 13).

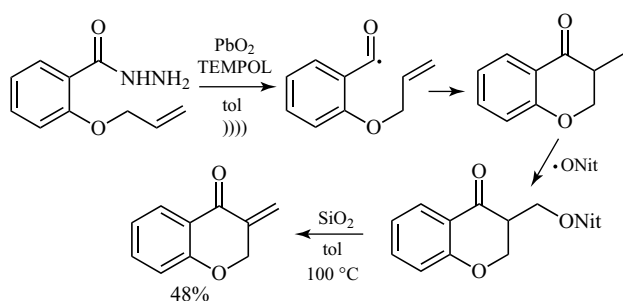
In a related ionic/radical domino reaction, Fensterbank and Malacria have utilized optically active alkylidene bis-sulfoxides in a Michael addition, radical cyclization protocol.⁴⁶ For example, Michael addition of the lithium anion of allyl alcohol gave the bis-sulfoxide-stabilized anion, which was oxidized to the radical, followed by 5-*exo*-trig radical cyclization and nitroxide trapping to give a single optically active diastereomer (Scheme 14).



Scheme 14 Fensterbank and Malacria's Michael addition, oxidation to radical, 5-*exo*-trig cyclization, and nitroxide trapping protocol with an optically active bis-sulfoxide.



Scheme 15 Fensterbank and Malacria's Michael addition, oxidation to radical, reversible 3-*exo*-trig cyclization, and nitroxide trapping protocol with an optically active bis-sulfoxide.



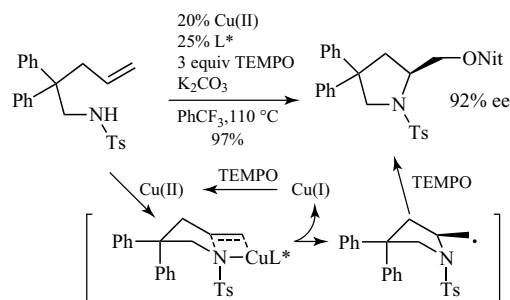
Scheme 16 Braslau's acyl radical 5-*exo*-trig cyclization and nitroxide trapping and elimination protocol.

This methodology was extended to the formation of a cyclopropyl ring using a reversible 3-*exo*-trig cyclization; as a demonstration of synthetic utility, the sulfoxides were reductively removed in excellent yield (Scheme 15).

In our own laboratory, oxidative formation of acyl radicals in the presence of nitroxides was utilized to effect a cyclization, nitroxide trapping sequence.⁴⁷ The alkoxyamine product was thermolyzed in the presence of acidic silica gel to afford the α,β -unsaturated ketone, the ionic elimination product (Scheme 16).

Chemler⁴⁸ has recently developed an intramolecular aminocupration, TEMPO trapping protocol in which the nitroxide acts as both a stoichiometric oxidant, converting the Cu(I) byproduct to the active Cu(II) catalyst, and as the final radical trap. Use of the optically active ligand (*R,R*)-Ph-Box (L*) provided highly enantioenriched alkoxyamines (Scheme 17).

Enediyne take part in Bergman cyclizations to form 1,4-benzene diradicals, which have been trapped by TEMPO by Grissom and Gunawardena.⁴⁹ The bis-alkoxyamine underwent homolysis

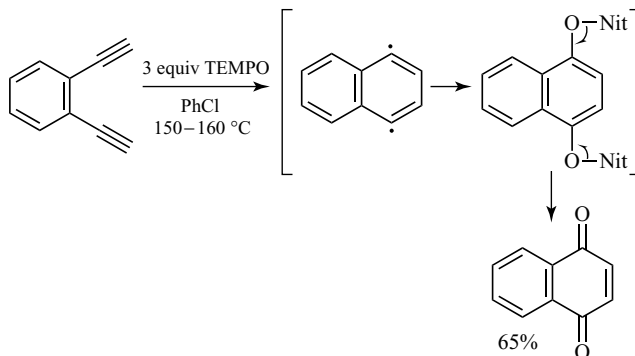


Scheme 17 Chemler's intramolecular aminocupration and TEMPO trapping protocol using TEMPO as both an oxidant of Cu(I) and the final radical trap.

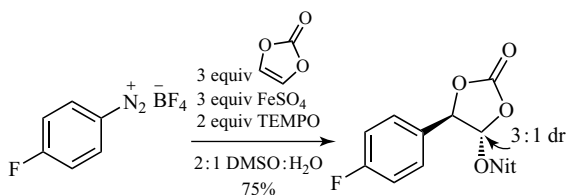
under the reaction conditions (heating to 160 °C) to yield the quinone (Scheme 18).

2.5 Carbon Radical Addition to Olefin Followed by Nitroxide Trapping

Aryl radicals have been generated by iron-mediated decomposition of diazonium salts in the presence of olefins and TEMPO. Heinrich *et al.*⁵⁰ found that by employing aqueous DMSO as a



Scheme 18 Grissom's Bergman cyclization of an enediyne; trapping of the 1,4-benzene diradical by TEMPO and fragmentation to the quinone.



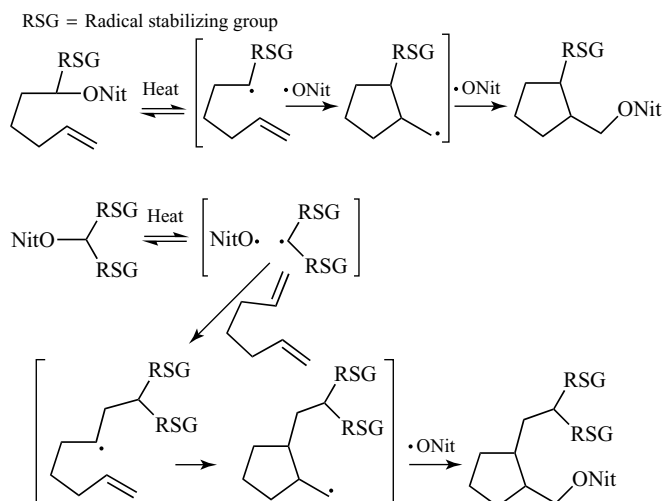
Scheme 19 Heinrich *et al.*'s oxidative aryl radical generation, addition to an electron-rich olefin, and nitroxide trapping sequence.

polar hydrogen-bonding solvent (which reduces the carbon-trapping rate of the nitroxide¹¹), aryl radical addition to olefins followed by nitroxide trapping could be achieved in moderate to very good yields (Scheme 19). The choice of solvent was critical:

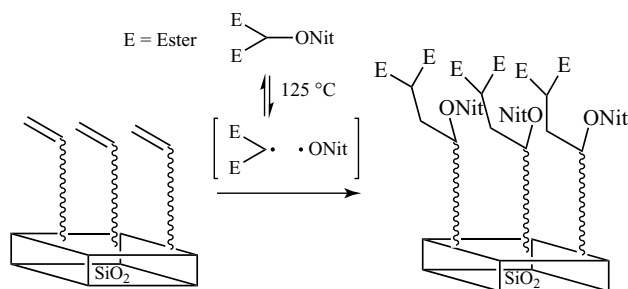
both activated and unactivated olefins could be utilized, without formation of the arylalkoxyamine direct trapping product.

3 HOMOLYSIS OF ALKOXYAMINES

On the basis of the persistent radical effect⁵¹ behind nitroxide-mediated polymerization (see **Nitroxide-Mediated Polymerization and its Applications**), a properly designed alkoxyamine can undergo reversible bond homolysis to give a stabilized carbon radical and nitroxide. As this is a degenerate reaction,⁵² addition of the stabilized carbon radical to olefin radical acceptors can be accomplished with even unactivated olefin traps, resulting in



Scheme 20 Both Studer and Ciufolini pioneered homolysis of an alkoxyamine followed by cyclization and nitroxide trapping.



Scheme 21 Studer has employed the reversible homolysis of malonylalkoxyamines to functionalize the outer surface of self-assembled monolayers.

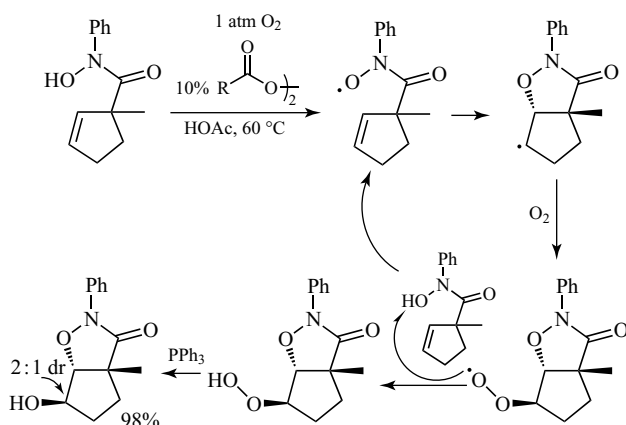
the formation of a carbon–carbon bond and a new alkoxyamine. Initial work by the groups of Studer⁵³ and Ciufolini⁵⁴ demonstrated both inter- and intramolecular radical additions (Scheme 20), and utilized a variety of nitroxides, focusing mainly on TEMPO and SG1, respectively.

Studer and coworkers developed malonyl⁵⁵ as the stabilized radical partner as well as 1,3-dithiane⁵⁶ as a 1-carbon radical synthon for this process. The use of microwave⁵⁷ and more recently microflow⁵⁸ reactors have been investigated to optimize the efficiency of this process. A number of synthetic applications include intramolecular cyclization of ester-stabilized radicals to form lactones,⁵⁹ addition of the carbon radical to carbon monoxide,⁶⁰ isonitriles,⁶¹ and a sequential radical addition with malonyl radical, followed by a Pd catalyzed π -allyl cyclization.⁶² The electron-poor malonyl radical adds well to electron-rich unactivated olefins; this method has been recently utilized to functionalize

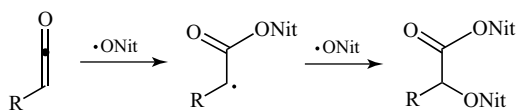
the outer surface of self-assembled monolayers bearing terminal alkenes⁶³ (Scheme 21). Alkoxyamines based on SG1 have been added by homolytic thermolysis to tri- and tetra-acrylates to form initiators for 3 and 4-armed star polymers.⁶⁴

4 ADDITION OF NITROXIDES TO UNSATURATION

Dialkyl nitroxides (such as TEMPO) do not add to olefins or alkynes, nor do they abstract hydrogen atoms under ambient conditions (although both reactions are observed at elevated temperatures⁶⁵). In contrast, electron-poor nitroxides, such as Fremy's salt ((KO₃S)NO[•]), acyl nitroxides, and diacyl nitroxides (such as phthalimide *N*-oxyl (PINO)), are far less stable than TEMPO and related nitroxides and undergo both hydrogen atom abstraction and addition to unsaturation (*vide infra*). Taking advantage



Scheme 22 Alexanian's acyl radical cyclization and oxygen trapping as a metal-free dioxygenation protocol.



Scheme 23 Tidwell's bisaddition of nitroxide to ketene.

of an acyl radical cyclization on a pendant olefin first described by Perkins and coworkers,⁶⁶ Schmidt and Alexanian⁶⁷ have recently utilized this reaction followed by trapping with molecular oxygen as a “metal-free dioxygenation” protocol for alkenes (Scheme 22). An analogous oxidative acyl radical cyclization on an allene has been reported.⁶⁸

TEMPO does add to ketenes: the scope⁶⁹ and kinetics⁷⁰ have been studied by Tidwell and coworkers (Scheme 23). Addition of the nitroxide to the carbonyl-like carbon generates an ester-stabilized radical, which is trapped by a second nitroxide. In the presence of a pendant olefin, thermolytic homolysis as a subsequent step leads to 5-*exo*-trig cyclization (Scheme 24).

5 NITROXIDES AS OXIDANTS

Oxidations using nitroxides are remarkably mild and chemoselective. Isomerizations of double bonds and stereogenic centers are rarely observed. Moreover, no heavy metals such as chromium or manganese are required. As a result, nitroxide-mediated oxidations are considered “green.” Nitroxide radicals, especially TEMPO and derivatives, are easily converted to the corresponding oxoammonium cations, which are highly reactive oxidants. In addition to alcohol oxidations, oxoammonium species are

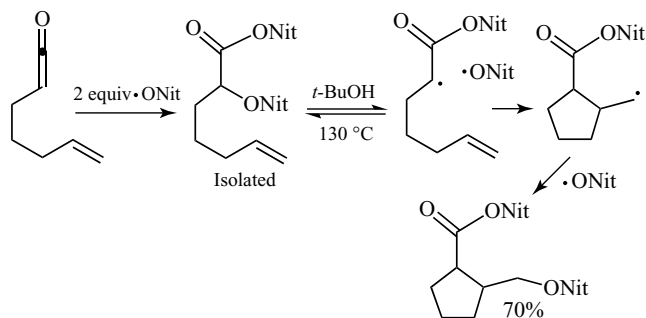
utilized as one-electron oxidants with a variety of substrates, including sulfides, thiols, phenols, and activated alkenes. Oxidations mediated by electron-poor nitroxides occur via hydrogen abstraction. Nitroxide-mediated oxidations have been covered in a number of reviews.^{71–80}

5.1 Nitroxide as a SET Oxidant

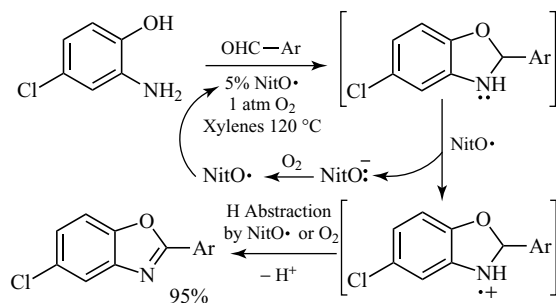
Nitroxides are easily oxidized to the corresponding oxoammonium ion, or reduced to the corresponding hydroxylamine anion, many in a reversible manner. The redox potentials for a range of nitroxides have been studied both experimentally and predicted by calculations.⁸¹ Thus, nitroxides, and TEMPO in particular, have been utilized as environmental-friendly one-electron oxidants in a variety of reactions. In some cases, the nitroxide can be utilized catalytically, with O₂ (ideally from air) being the ultimate oxidant.

5.1.1 Nitroxide as a SET Oxidant of Organic Species

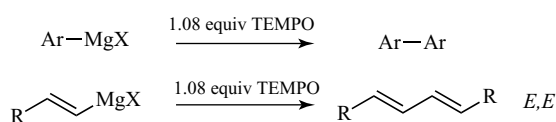
As chemists seek to avoid the use of metal catalysts for both environmental and economic reasons, alternative catalysts are being sought. Recently, chemists have found that TEMPO acts as an organic soluble single electron oxidant. For example, Han and coworkers have utilized 5% of 4-methoxy TEMPO and molecular oxygen to aromatize aminols to form benzoxazoles (Scheme 25).⁸² The mechanism most likely goes through a radical cation, which is further



Scheme 24 Alkoxyamine homolysis and cyclization of Tidwell's ketene plus nitroxides adduct.



Scheme 25 Han's aerobic nitroxide-catalyzed aromatization of a benzylic aminol to form a benzoxazole.



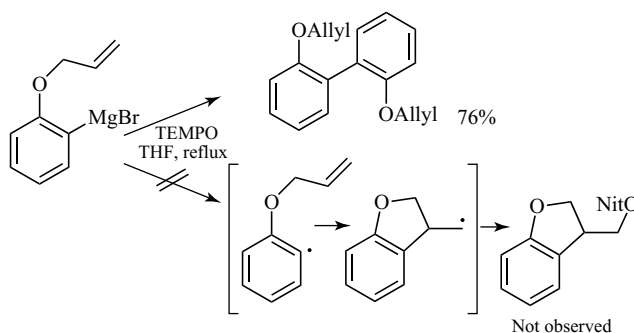
Scheme 26 Studer's stoichiometric use of TEMPO in the homocoupling of vinyl and aryl Grignards.

oxidized by TEMPO or oxygen to the aromatic system. An alternative mechanism involves 5-*endo*-trig cyclization of a phenoxy radical, followed by oxidative aromatization. Studer and coworkers have utilized TEMPO in the oxidative homocoupling of vinyl and aryl Grignards (Scheme 26).⁸³ The mechanism does not seem to go through a free radical intermediate, as no 5-*exo*-trig cyclization was seen with an *ortho*-allyloxy probe (Scheme 27). Alkynyl Grignards also work but do not require the nitroxide catalyst: air is sufficient. This methodology has been extended to the preparation of conjugated polymers such as polyfluorenes using symmetrical bis-bromofluorenes via the bis-Grignards.⁸⁴

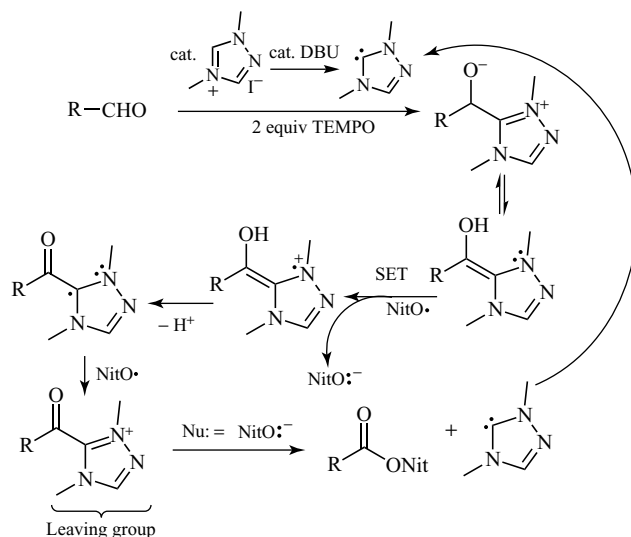
TEMPO has been employed as a double oxidant in a catalytic *N*-heterocyclic carbene oxidation of aldehydes to carboxylic acid derivatives (Scheme 28).⁸⁵ Condensation of the carbene with aryl or vinyl aldehyde forms a very electron-rich enol/enamine (Breslow intermediate); SET by the nitroxide gives a radical cation. Another SET reaction (or nitroxide trapping followed by ionic elimination) forms an activated cationic leaving group on the carbonyl. Displacement by the hydroxylamine anion (the reduced TEMPO) yields the ester in excellent yields. Use of alkyl aldehydes affects oxidation in moderate yields. This process is biomimetic, emulating the steps involved in pyruvate ferredoxin oxidoreductase in the oxidative decarboxylation of pyruvate, in which an [Fe₄S₄] cluster is the biological SET agent. More recently, TEMPO has been replaced by diphenoquinone as the oxidant (the reduction product is nonnucleophilic), allowing addition of exogenous nitrogen nucleophiles to trap the activated acyl intermediate.⁸⁶

TEMPO has been utilized to oxidize Hantzsch 1,4-dihydropyridines (an NADH analogue) in a photochemical process (Scheme 29)⁸⁷; the exact role of the UV light was not illuminated. Two equivalents of TEMPO per dihydropyridine were required for aromatization. A photoinduced electron transfer mechanism was proposed; however, hydride addition to an oxoammonium ion was not ruled out. Alternatively, hydrogen abstraction by a photoexcited nitroxide is a possible first step.

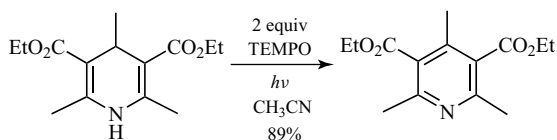
Preformed oxoammonium salts have been employed as well-behaved organic soluble oxidants to convert electron-rich tetrathiafulvalene to the radical cation.⁸⁸ A series of bis-1,3-dithiolium salts,



Scheme 27 Evidence against a radical intermediate in the TEMPO-mediated homocoupling of aryl Grignard.



Scheme 28 TEMPO as a two-step oxidant in the *N*-heterocyclic carbene-catalyzed oxidation of aldehydes to carboxylic esters.



Scheme 29 TEMPO as oxidant in the photochemical aromatization of a Hantzsch 1,4-dihydropyridine.

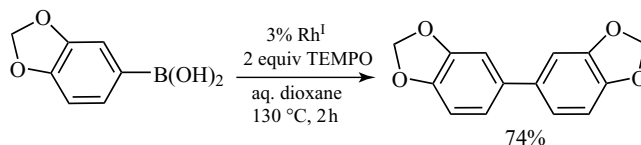
with potential applications as semiconductors, were isolated in high yields.

5.1.2 Nitroxide as an Oxidant of Metal Catalysts and Metal Complexes

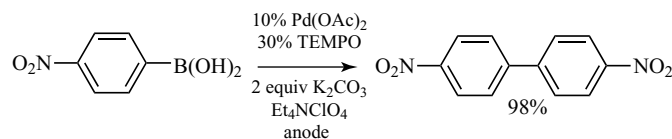
Nitroxides have been utilized as a reoxidant of the transition metal catalysts palladium and rhodium. Several homocouplings of aryl or vinyl boronic acids have been reported. Vogler and Studer⁸⁹ utilized TEMPO as a stoichiometric reoxidant to

convert Rh(I) to Rh(III) in the homocoupling of both aryl and vinylboronic acids, in moderate to very good yields (Scheme 30).

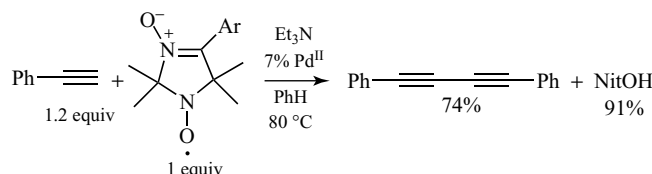
Mitsudo *et al.*⁹⁰ have successfully developed a similar palladium catalyzed reaction, in which both the metal and nitroxide are used catalytically using electrochemistry as the ultimate oxidant (Scheme 31). In this catalytic cycle, the active Pd(II) catalyst undergoes transmetalation twice with arylboronates to give Ar-Pd-Ar, which undergoes reductive elimination to form the biaryl product and Pd(0). An oxoammonium cation reoxidizes the Pd(0) to Pd(II), forming nitroxide, which is then oxidized at the anode back to oxoammonium ion. Another example of homocoupling, in this instance using an imidazoline nitroxide as the oxidant, is the formation of a symmetrical diyne in the presence of a palladium catalyst (Scheme 32).⁹¹ Presumably, Pd(0) inserts into the terminal acetylene C–H bond; however, the detailed mechanism is not clear. No reaction proceeded in the absence of the palladium catalyst.



Scheme 30 TEMPO as a stoichiometric reoxidant of Rh(I) to Rh(III) in the Rh-catalyzed homocoupling of an arylboronic acid.



Scheme 31 Anodic oxidation of TEMPO as a cooxidant in the Pd-catalyzed homocoupling of an arylboronic acid.

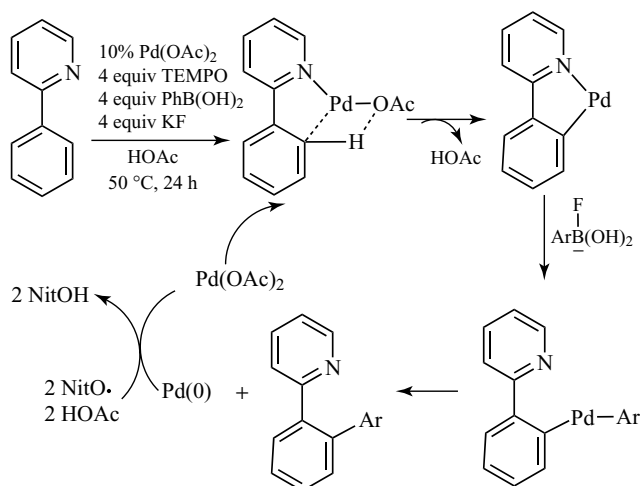


Scheme 32 An imidazoline nitroxide as the oxidant in the Pd-catalyzed homocoupling of a terminal alkyne.

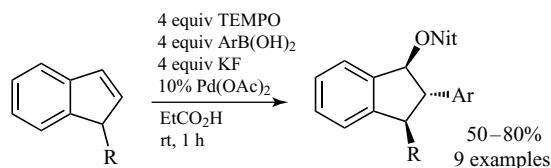
Using TEMPO as a stoichiometric oxidant, Studer and coworkers have demonstrated directed orthometallation using Pd⁹² or Rh⁹³ catalysts with 2-pyridyl aromatics (and heteroaromatics) and arylboronic acids (Scheme 33). Although the mechanism of C–H activation is not understood, despite several kinetic isotope experiments, one possible mechanism is illustrated here. Regardless of the mechanism of C–H insertion step, it is clear that the nitroxide acts as an oxidant to reoxidize Pd(0) to the active Pd(II) catalyst. The Rh catalyzed case is analogous. In another reaction using an indene substrate, a palladium catalyzed oxyarylation was observed with arylboronic acids and TEMPO (Scheme 34).⁹⁴

Only a single diastereomer was formed in this very acidic medium. The mechanism is not clear: a Heck-like addition was disfavored compared to electrophilic attack of the indene on an aryl palladium salt. Whatever the actual mechanism, the nitroxide is both a reagent in the reaction and is the stoichiometric oxidant, converting Pd(0) to the active Pd(II) catalyst. Several 4-substituted TEMPO derivatives were utilized in addition to the parent TEMPO nitroxide.

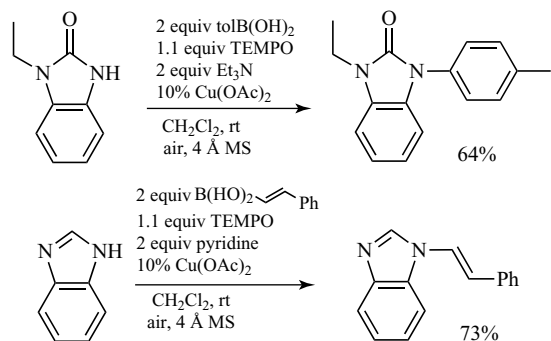
In an example of a copper-catalyzed process, Lam *et al.*⁹⁵ have used TEMPO as a stoichiometric oxidant in the *N*-arylation of anilines, carbamates, imides, sulfonamides, and amines as well as



Scheme 33 TEMPO as a superstoichiometric reoxidant of Pd(0) to Pd(II) in a Pd-catalyzed orthometallation, heterocoupling sequence with an arylboronic acid.



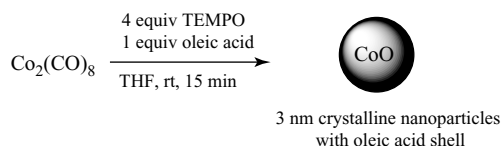
Scheme 34 TEMPO as both reoxidant of Pd(0) to Pd(II) and reagent in a Pd-catalyzed oxyarylation.



Scheme 35 TEMPO as a reoxidant in the Cu-catalyzed *N*-arylation of a carbamate with an arylboronic acid and in the *N*-vinylation of benzimidazole with a vinylboronic acid.

O-arylation of phenols in a cross-coupling reaction with the arylboronic acids (Scheme 35). Vinylation was also successful.

TEMPO has also been used as a mild oxidant for metals. In the Pauson–Khand reaction, the addition of superstoichiometric amounts of TEMPO was found to greatly accelerate the rates and enhance the yields of the Pauson–Khand reaction of dicobalt acetylenes with norbornadiene.⁹⁶ Calculations indicate that the nitroxide promoter facilitates the reaction by replacing or adding to one of the CO ligands on cobalt, resulting in decarbonylation of a radical complex. In another reaction involving cobalt, oxidation of dicobalt octacarbonyl with TEMPO in the presence of oleic acid has been utilized by Pericàs to form monodisperse CoO nanoparticles (Scheme 36).⁹⁷



Scheme 36 TEMPO as an oxidant of dicobalt octacarbonyl in the formation of monodisperse CoO nanoparticles.

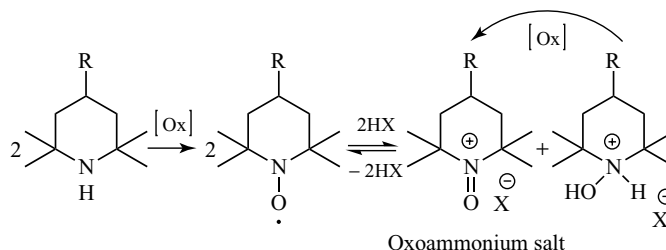
In general, the use of TEMPO as an oxidant in metal catalyzed or mediated reactions will be far more economical when the nitroxide can be used in small amounts. Efforts to utilize TEMPO as a catalyst, with air as the stoichiometric oxidant in metal catalyzed reactions, are being actively pursued by a number of laboratories: new advances in this arena are expected in the near future.

5.2 Oxidations via Oxoammonium Salts

5.2.1 Chemoselective Oxidation of Alcohols

Oxoammonium salts derived from nitroxides have been widely utilized in the oxidation of primary and secondary alcohols to the corresponding aldehydes, ketones, and carboxylic acids. The oxoammonium salt can be preformed and used stoichiometrically. Alternatively, it can be generated *in situ* from acid-catalyzed disproportionation of nitroxide radicals or from oxidation of a catalytic amount of nitroxide with a stoichiometric cooxidant. Since nitroxides are effective radical scavengers, potential autooxidation of the aldehyde products is inhibited.⁹⁸

There are reports of many structurally diverse oxoammonium salts⁷¹; however, most oxidations have been carried out using piperidinyl nitroxide-derived species. Oxoammonium salts can be prepared by acid-catalyzed disproportionation of nitroxides,⁹⁹ which in turn are prepared by oxidation of the corresponding hindered amines (Scheme 37). Disproportionation leads to a 1:1 mixture of the oxoammonium salt and the corresponding hydroxyammonium salt. The latter can be oxidized *in situ* by hypohalites to form the oxoammonium salt or the nitroxide radical on treatment with air. Alternatively, one-electron oxidation of nitroxide with halogen (Cl₂ or Br₂) or hypohalite gives oxoammonium cation with a halogen anion.¹⁰⁰ Use of bromine can result in bromide or tribromide as the counterion or a mixture.⁷¹ A side reaction is bromination of allylic alcohols.¹⁰⁰ Chloride as counterion can lead to unstable oxoammonium salts. Nitrogen dioxide (NO₂) has been used to make oxoammonium nitrate.⁷¹ The most common counterions are Br[−], Cl[−], Br₃[−], ClO₄[−], BF₄[−], SbF₆[−], NO₃[−],



Scheme 37 Preparation of oxoammonium salts via oxidation of the corresponding hindered amines to the nitroxides, followed by acid disproportionation.

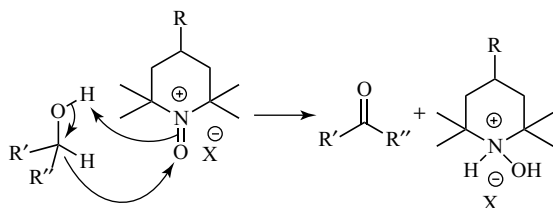
and ClO_2^- . The only commercially available oxoammonium salt is Bobbitt and coworkers¹⁰¹ stable, nonhygroscopic *N*-acetyl-4-amino oxoammonium tetrafluoroborate ($\text{X}^- = \text{BF}_4^-$ and $\text{R} = \text{NHAc}$). The perchlorate salt ($\text{X}^- = \text{ClO}_4^-$)¹⁰² is no longer used, due to its detonation potential.¹⁰³

Since oxoammonium salts are colored, many oxidations are monitored colorimetrically. The reaction mixture usually turns from a bright yellow slurry into a white slurry.¹⁰² Another advantage of using stoichiometric oxoammonium salts is that there is no cooxidant that might decrease selectivity. Reactions in acid and base differ in their mechanisms and chemoselectivities. The rate of the oxidation increases with increasing pH of the reaction medium; thus, most oxidations were carried out under basic conditions. Under strongly acidic conditions, oxidation is slow, and secondary alcohols are favored over primary. A mechanism involving hydride transfer to the electrophilic oxoammonium oxygen (Scheme 38) was first proposed by Golubev *et al.*^{99,104} A kinetic isotope effect of $k_{\text{H}}/k_{\text{D}} = 3.1$ supports deprotonation as the rate-limiting step. A similar hydride transfer to an oxoammonium salt in the oxidative cleavage of benzyl alkyl ethers (*vide infra*) was reported recently by Bobbitt and

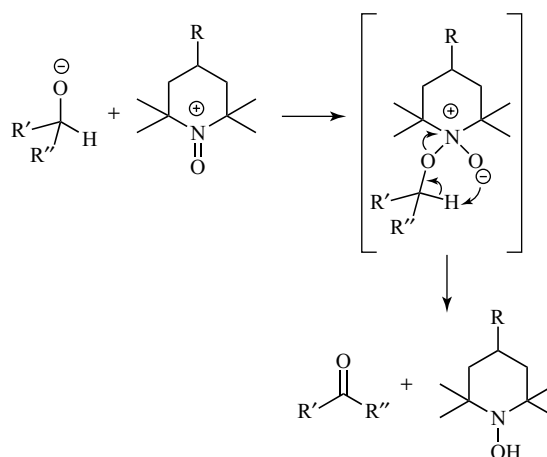
coworkers.¹⁰⁵ Secondary alcohols react in preference to primary alcohols because of the weaker carbon–hydrogen bond strength, making secondary alcohols better hydride donors.

Under mildly acidic or basic conditions, oxidation is rapid, and primary alcohols react preferentially over secondary alcohols. The mechanism, originally proposed by Semmelhack *et al.*,¹⁰⁶ involves the nucleophilic attack of the alcoholate on the nitrogen of the oxoammonium salt, followed by intramolecular deprotonation in an oxa-Cope fragmentation (Scheme 39).^{104,106} The slower addition of more hindered secondary alcohols to the oxoammonium species explains the preferential oxidation of primary alcohols. A kinetic isotope effect of $k_{\text{H}}/k_{\text{D}} = 1.8$ supports this mechanism.

The oxidation of alcohols with oxoammonium salts has been reviewed by Bobbitt *et al.*^{71,76}



Scheme 38 Oxidation of alcohols with oxoammonium salts under acidic conditions.

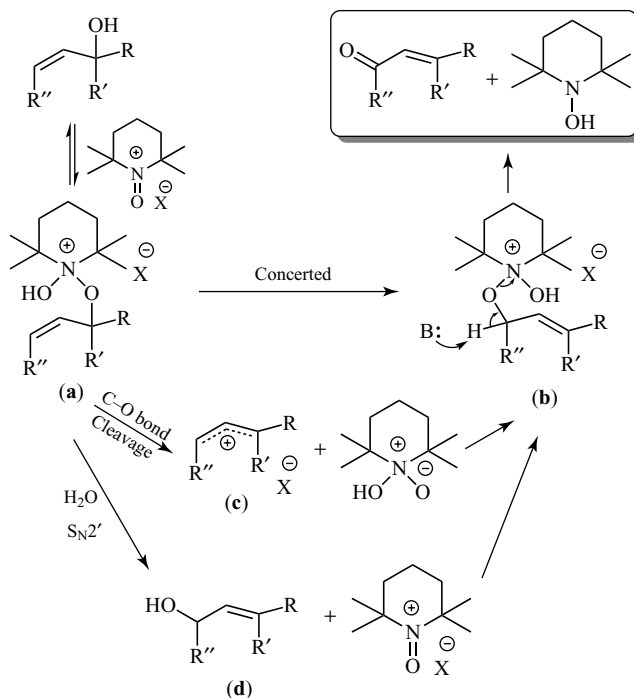


Scheme 39 Oxidation of alcohols with oxoammonium salts under basic conditions.

As an example, stoichiometric, *N*-acetyl-4-amino oxoammonium tetrafluoroborate has been used to oxidize unsaturated alcohols. In the synthesis of an insect pheromone, an ω -haloalkenol was oxidized in the presence of silica gel or pyridine in higher yield than with PCC.¹⁰⁷ However, alcohols bearing isolated dienes can suffer from acid catalyzed destruction of olefins in the presence of silica gel. The use of pyridine instead of silica gel circumvents this problem. Two equivalents of pyridine are required in the synproportionation reaction. The pyridine conditions allow oxidation of substrates bearing acid-sensitive protecting groups such as acetals and silyl ethers. Alcohols containing a β -oxygen substituent do not undergo oxidation under mildly acidic conditions due to intramolecular hydrogen bonding.¹⁰² However, they are oxidatively dimerized in the presence of pyridine to esters.¹⁰¹ Tetraethylene glycol was oxidized and cyclized to a 12-membered ring lactone with oxoammonium salts supported on a polymer surface.¹⁰⁸ Stoichiometric oxoammonium salt has been utilized in the selective oxidation of monosaccharides under basic conditions.^{109,110}

One pot oxidation of primary alcohols to the corresponding carboxylic acids using oxoammonium salts generated *in situ* from a unhindered class of nitroxides: 1-methyl-azaadamantane *N*-oxyl (1-Me-AZADO), in combination with NaClO₂ was recently reported by Iwabuchi and coworkers.¹¹¹ The oxoammonium ion reacts with the alcohol to give an aldehyde, which then reacts with NaClO₂ to give the carboxylic acid product. These reaction conditions are notable in that the reaction medium is virtually bleach-free, as the destructive NaOCl byproduct is immediately consumed by the hydroxylamine to regenerate the oxoammonium ion. As a result, carboxylic acids are obtained in good yields without competing oxidation of electron-rich alkenes and aromatic rings. In contrast, the use of the more traditional “Merck method” employing TEMPO/NaOCl/NaClO₂ failed.¹¹²

Tertiary allylic alcohols undergo an oxidative rearrangement on treatment with oxoammonium salts.¹¹³ Three possible mechanistic pathways have been purposed (Scheme 40). In the first, addition of alcohol to the oxoammonium salt forms adduct **a**, which undergoes a concerted intramolecular

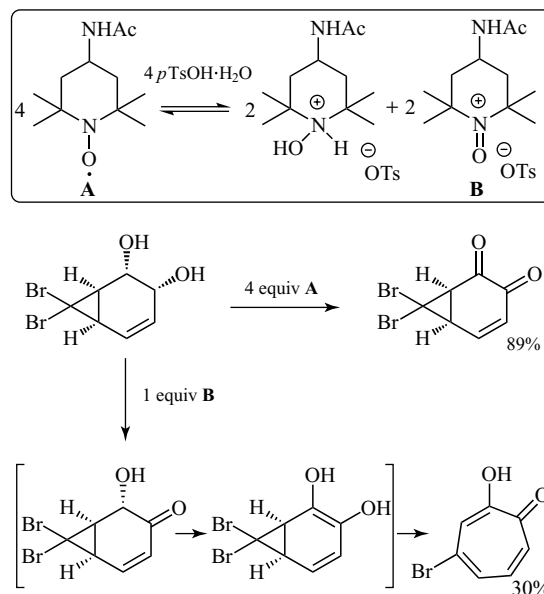


Scheme 40 Three plausible reaction mechanisms for the oxidative rearrangement of tertiary allylic alcohols with oxoammonium salts.

rearrangement to form adduct **b**. Alternatively, adduct **b** can form via ionization of the allylic cation **c**. A third possibility is intermolecular S_N2' displacement by water to form allylic alcohol **d**, which can add to another oxoammonium to form intermediate **b**. Adduct **b** then fragments, presumably by deprotonation, to form the α, β -unsaturated ketone. Addition of water improves the yield in some cases. This reaction only works with oxoammonium salts consisting of bulky, nonnucleophilic counter anions (BF_4^- and SbF_6^-).

Treatment of nitroxides with relatively strong acids such as peracids or *p*-toluenesulfonic acid facilitates disproportionation to form one oxoammonium salt *in situ* for every 2 equiv of nitroxide. Since the medium must be below $pH \approx 2$, this method is not suitable for acid-labile substrates. When using *m*-chloroperbenzoic acid, hindered amines could be used directly, as they are oxidized by peracids to the nitroxides.^{114,115} Bromide and chloride ions were found to be effective as cocatalysts. The disadvantages of using peracids are partial overoxidation of the aldehyde to the carboxylic acid and competing epoxidation of double bonds. Baeyer–Villiger oxidation usually does not interfere since it is significantly slower than the nitroxide-mediated oxidation.¹¹⁶ For example, 2 equiv of nitroxide and 2 equiv of *p*-toluenesulfonic acid were used to oxidize primary and secondary alcohols to aldehydes and ketones in high yield.¹¹⁷ The resulting hydroxylamine salt can be recovered by filtration using *N*-acetyl-4-amino-TEMPO instead of the parent TEMPO. This procedure was applied to the oxidation of open-chain and cyclic *vic*-diols to form α -dicarbonyls; C–C bond cleavage was not observed.¹¹⁸ In the example depicted in Scheme 41, the nitroxide-mediated oxidation gave the diketone in 89% yield, while use of the traditional Swern reagent produced only 68% yield. Interestingly, bromotopolone was the only product obtained when 1 equiv of the preformed oxoammonium salt was used. This product arose via mono-oxidation to form an acyloin intermediate, which underwent enolization, electrocyclization, and finally dehydrobromination.

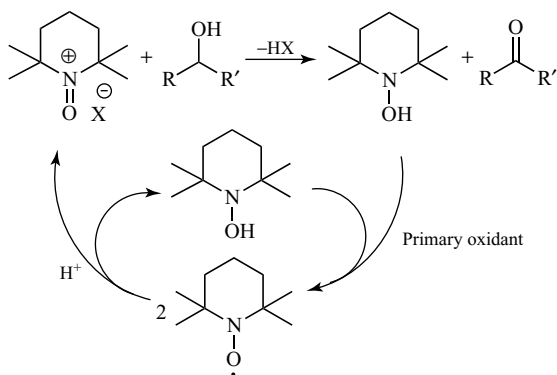
Although stoichiometric oxoammonium salts have been used successfully for the oxidation of alcohols, the ability to use the nitroxide in a catalytic manner is more attractive. A variety of organic and inorganic primary oxidants have been used to oxidize the nitroxide and to reoxidize the



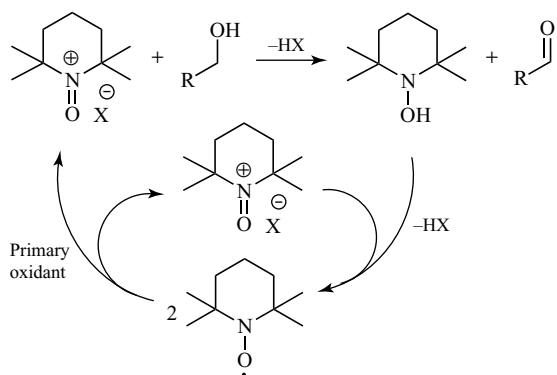
Scheme 41 Oxidation of 1,2-diol to α -diketone with oxoammonium salt generated *in situ* from acid-catalyzed disproportionation versus reaction with preformed oxoammonium salt.

resulting hydroxylamine to the oxoammonium salt *in situ*. In the best cases, the stoichiometric oxidant is cheap (such as bleach), or even cleaner, such as O_2 or electrochemical anodic oxidation. Conditions employing a stoichiometric cooxidant are generally milder than acid-catalyzed disproportionation. Since reactions are usually conducted under basic conditions, very high selectivity for primary alcohols in the presence of secondary alcohols is observed. Secondary alcohols can also be oxidized in good yields, but they need substantially longer reaction times. Despite the diversity of nitroxide radicals, TEMPO is frequently used, due to its cost and accessibility.

On the basis of the reversible acid-catalyzed disproportionation of nitroxides, the general mechanisms of catalytic oxidation are described by two different scenarios, dictated as a function of pH .^{73,119} Under highly acidic conditions ($pH < 2$) (Scheme 42), two nitroxides disproportionate to form one hydroxylamine and one oxoammonium salt. The latter oxidizes the alcohol; in doing so, it is reduced to the hydroxylamine. One-electron oxidation by the primary oxidant regenerates the nitroxide, which returns to the catalytic cycle.



Scheme 42 Catalytic cycle of nitroxide-mediated alcohol oxidation under strongly acidic conditions.



Scheme 43 Catalytic cycle of nitroxide-mediated alcohol oxidation under weakly acidic and basic conditions.

Alternatively, at higher pH (Scheme 43), the primary oxidant converts the nitroxide to the oxoammonium species, which is consumed by alcohol oxidation, reforming the hydroxylamine. The hydroxylamine can also react with an oxoammonium ion to regenerate two nitroxide radicals in a synproportionation reaction.

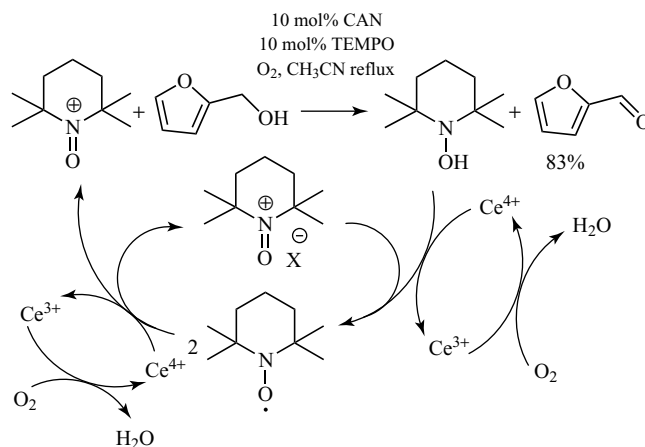
From both an economic and an environmental viewpoint, the use of “green” oxidants such as oxygen or hydrogen peroxide is ideal. The use of oxygen as a primary oxidant in conjunction with TEMPO and a transition metal catalyst (aerobic oxidation) has been investigated by a number of researchers (*vide supra*). Generally, the alcohol is oxidized by an oxoammonium cation, generating TEMPOH as a byproduct. The metal catalyst oxidizes the hydroxylamine to TEMPO, which is further oxidized by a second equivalent of metal

catalyst back to the key oxoammonium salt. The reduced form of metal catalyst is reoxidized by oxygen as the primary oxidant. These conditions work with a broad range of alcohols. For example, an oxoammonium cation is formed by aerobic oxidation of TEMPO with the heteropoly acid H₅PV₂Mo₁₀O₄₀¹²⁰ or with ceric ammonium nitrate (CAN)¹²¹ (Scheme 44).

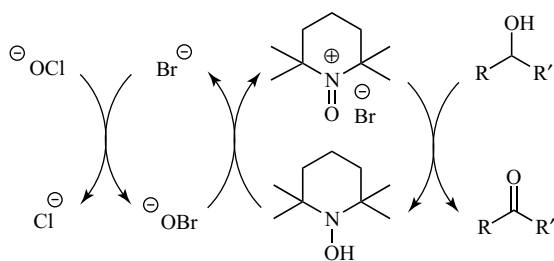
Alternatively, the oxoammonium salt can be generated via disproportionation of TEMPO in acetic acid under Minisci conditions,^{98,122} in which Mn(II)–Co(II) or Mn(II)–Cu(II) nitrates are used to regenerate TEMPO from TEMPOH in the presence of oxygen. An easily recyclable reagent is the tetranitroxide derived from the commercially available hindered amine “CHIMASSORB® 966,” which can be recovered by precipitation from organic solvents.¹²³

The use of multicopper laccase enzymes has attracted much attention as a catalytic metal oxidant. These oxidase enzymes contain four copper centers per protein molecule. Laccase enzymes are secreted by white rot fungi to delignificate the lignocelluloses found in wood.¹²⁴ Galli and coworkers have reported a laccase/TEMPO system that catalyzes the oxidation of benzylic, allylic, and aliphatic alcohols as well as benzylic amines.¹²⁵ However, 20–30 mol% of TEMPO is required, and this system is most effective with benzylic and allylic substrates. TEMPO outperforms other nitroxides examined in this oxidation.^{126,127} The mechanistic details of this oxidation process are not completely clear, but it is assumed that electron transfer occurs from TEMPO to a Cu(II) in the laccase, forming an oxoammonium cation.^{128–130} A kinetic isotope effect of $k_H/k_D = 2.05$ is consistent with an oxoammonium pathway.¹²⁷ Air is necessary to regenerate the Cu(II) species. The mechanistic pathway of the laccase/TEMPO system is different from other Cu/TEMPO systems (*vide infra*) due to the much higher redox potential of Cu(II) in laccase. It has been shown that laccase/TEMPO can catalyze the aerobic oxidation of primary alcohols in carbohydrates to form polycarboxylic acids.¹¹⁹ The biodegradable carboxystarch product is an excellent water absorbent, with potential applications for use in diapers. However, obstacles toward large-scale manufacture include the high cost and the instability of the enzyme.

Anelli *et al.*^{131,132} have developed a popular protocol that utilizes household bleach (sodium



Scheme 44 Catalytic cycle of CAN-mediated aerobic oxidation of alcohols.

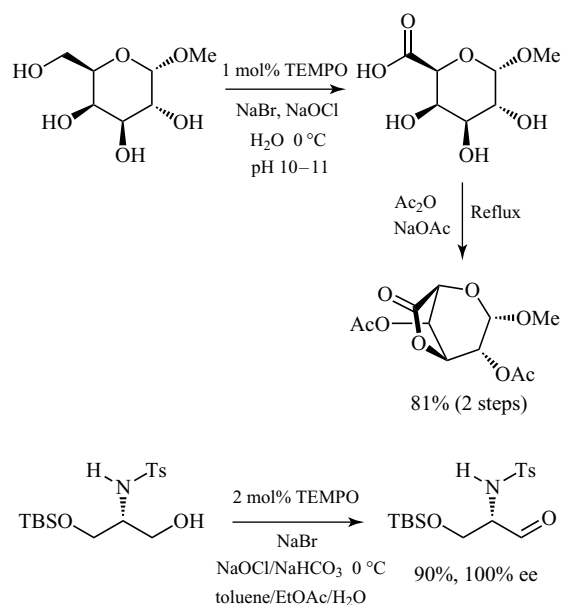


Scheme 45 Anelli oxidation of alcohols with TEMPO/NaOCl/KBr.

hypochlorite) as the stoichiometric oxidant and requires only 1 mol% of the nitroxide. This oxidation uses mild biphasic conditions ($\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, pH 8.6–9.5); addition of bromide ion as a cocatalyst provides aldehydes in high yields with reaction times of only minutes. Bromide is oxidized by bleach to form hypobromite (a more reactive oxidant than hypochlorite) for regeneration of the oxoammonium salt (Scheme 45). Oxidation of secondary alcohols requires slightly longer reaction times. Overoxidation of aldehydes to carboxylic acids resulted on addition of a phase transfer reagent. Carboxylic acids were obtained cleanly using sodium chlorite (NaClO_2) as the terminal oxidant with catalytic amounts of TEMPO and bleach in aqueous acetonitrile (Merck's method).^{112,133,134} The oxoammonium salt, resulting from the combination of TEMPO and bleach, oxidizes the alcohol to the corresponding aldehyde. The hydrated hemiacetal then reacts with sodium chlorite to form the carboxylic

acid. Anelli conditions have been utilized for the selective oxidation of monosaccharides^{135–137} (Scheme 46), disaccharides,¹³⁸ oligosaccharides,¹³⁹ and polysaccharides^{119,140–144} to their corresponding carboxylic acids. These reaction conditions are mild enough that epimerization does not occur with optically pure α -amino and α -hydroxy aldehydes (Scheme 46).^{145,146} Recently, TEMPO-catalyzed oxidation with bleach has been performed in a spinning tube-in-tube reactor,¹⁴⁷ eliminating the need for slow addition of bleach to control the exothermic reaction. The rapid mixing and efficient heat transfer resulted in increased yields and enhanced reaction rates.

Although the Anelli protocol is widely utilized, it is not waste-free: the use of bleach produces 1 equiv of sodium chloride for every molecule of alcohol oxidized. Chlorinated byproducts are sometimes formed. Alternative cooxidants include iodine-based oxidants, such as [bis(acetoxy)iodo]benzene ($\text{PhI}(\text{OAc})_2$, BAIB),¹⁴⁸ iodine (I_2),¹⁴⁹ periodic acid (H_5IO_6),¹⁵⁰ iodine pentoxide (I_2O_5),¹⁵¹ sodium periodate (NaIO_4),¹⁵² iodobenzene dichloride (PhICl_2),¹⁵³ and 1-chloro-1,2-benziodoxol-3(1*H*)-one.¹⁵⁴ Other oxidants examined include *N*-chlorosuccinimide,¹⁵⁵ Oxone®,¹⁵⁶ hydrogen peroxide,¹⁵⁷ sodium bromite (NaBrO_2),¹⁵⁸ and pyridine/ HBr_3 .^{159,160} Trichloroisocyanuric acid (TCCA) can also be used as a hypochlorite equivalent.^{161,162} Margarita's TEMPO-mediated alcohol oxidation protocol using BAIB as the terminal oxidant¹⁴⁸ is particularly good at avoiding epimerization with sensitive substrates. Thus, it



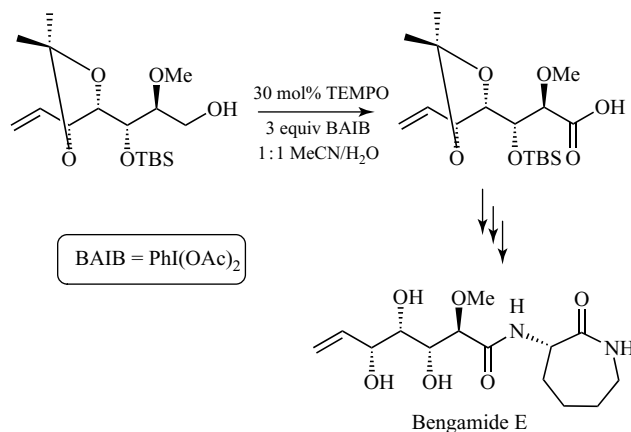
Scheme 46 Anelli oxidation of methyl α -D-galactopyranoside¹³⁷ and *N*-tosyl- α -amino alcohol.¹⁴⁶

has become very popular, as exemplified by its use in the total syntheses of natural products such as pteridic acid A,¹⁶³ guanacastepene A,¹⁶⁴ and bengamide E.¹⁶⁵ In the case of bengamide E, an antitumor natural product of marine origin, oxidation of an alcohol to the carboxylic acid was successful in the presence of water (Scheme 47).

Both the Anelli¹³² and Margarita¹⁶⁶ conditions oxidize 1,4- and 1,5-diols to the corresponding γ - and δ -lactones, respectively, via a cyclic hemiacetal

intermediate. Both conditions also exhibit high chemoselectivity for oxidation of primary alcohols. Aerobic oxidation of benzylic alcohols has been demonstrated with catalytic amounts of TEMPO/BAIB/ KNO_2 under solvent-free conditions.¹⁶⁷ Immobilization of BAIB on polystyrene (PS) allows for the recycling of this catalyst. An oxidative rearrangement of tertiary allylic alcohols with catalytic TEMPO failed using bleach, BAIB, or Oxone[®] as the stoichiometric oxidant. However, it worked well when NaIO_4 on silica gel¹⁶⁸ or PhIO in conjunction with a Lewis acid^{169,170} were employed as terminal oxidants. TEMPO and related derivatives are more effective catalysts than other nitroxides.¹⁷¹ Recently, unhindered 1-methyl-azaadamantane *N*-oxyl (1-Me AZADO)^{77,172} and several azabicyclo *N*-oxyls,^{173,174} such as 9-azabicyclo[3.3.1]nonane-*N*-oxyl (ABNO)¹⁷⁴ (Figure 1), have been shown to exhibit even greater activity than TEMPO under Anelli, Margarita, and electrochemical oxidation conditions.

Hu and coworkers reported the first transition metal-free aerobic alcohol oxidations with catalytic TEMPO using $\text{Br}_2/\text{NaNO}_2/\text{O}_2$.¹⁷⁵ They demonstrated that HCl ¹⁷⁶ or 1,3-dibromo-5,5-dimethylhydantoin¹⁷⁷ could serve the same function as Br_2 . The nitric oxide precursor NaNO_2 can also be replaced by *tert*-butyl nitrite.^{178,179} Recently, Yang and coworkers have shown that both NO and Br^- can be generated *in situ* by reaction of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and KBrO_3 .¹⁸⁰ The proposed mechanism for alcohol oxidations using catalytic amounts of TEMPO/ NaNO_2/HCl



Scheme 47 TEMPO/BAIB oxidation of a primary alcohol to the carboxylic acid in the total synthesis of bengamide E.

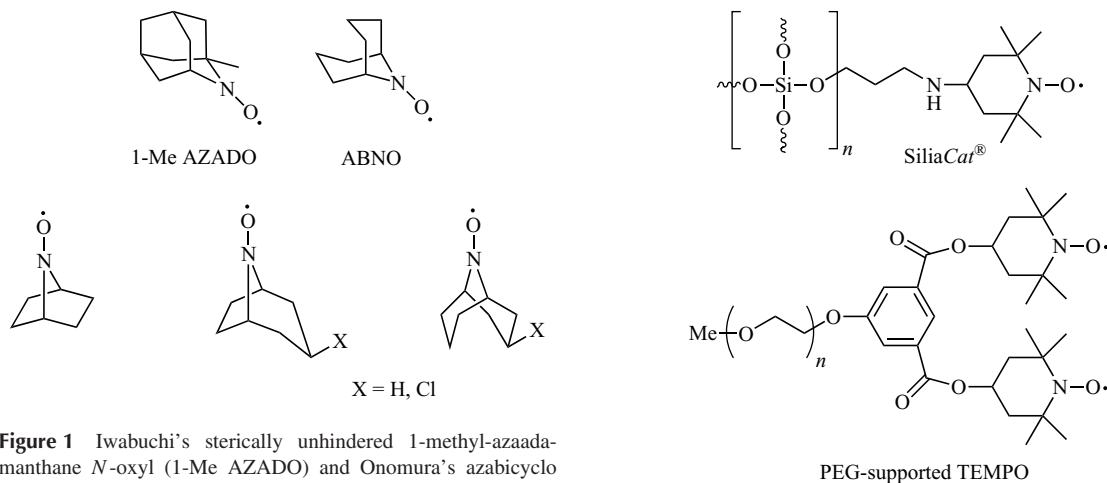
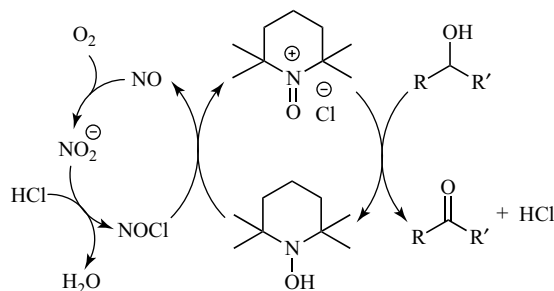


Figure 1 Iwabuchi's sterically unhindered 1-methyl-azaadamantane *N*-oxyl (1-Me AZADO) and Onomura's azabicyclo *N*-oxyl nitroxides effective in catalytic oxidations.



Scheme 48 Mechanism of aerobic transition metal-free oxidation with TEMPO/HCl/NaNO₂.

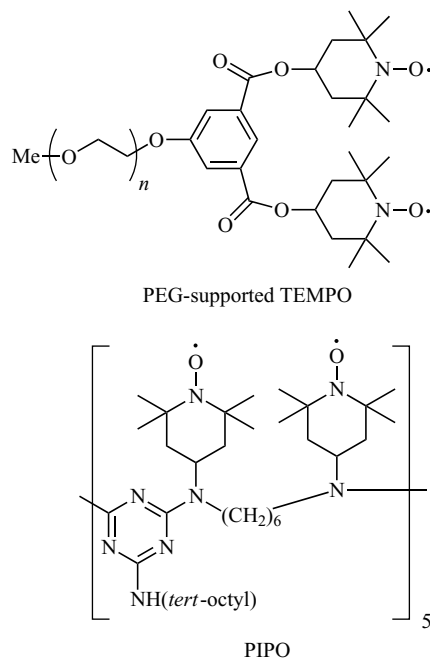
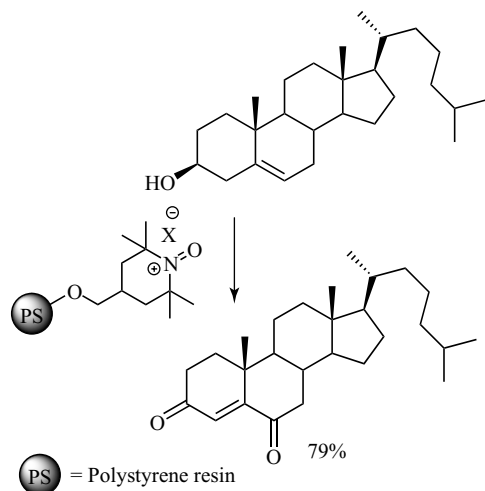


Figure 2 Examples of silica- and polymer-supported TEMPO reagents.

and air as the ultimate oxidant is described in Scheme 48. The alcohol is oxidized by the oxoammonium salt, which is regenerated by oxidation of TEMPOH with NOCl. NOCl is formed by reaction of HCl and NO₂⁻, which is generated by air oxidation of NO. Water is a byproduct of this reaction cycle.

Although only catalytic amounts (often 1 mol%) of nitroxide are commonly used in alcohol oxidations, the ability to efficiently isolate and recycle the catalyst is also important. Hence, many groups have designed variants on immobilized nitroxides anchored to solid supports, such as silica^{181–183} or mesoporous silica MCM-41.¹⁸⁴ Other strategies include entrapment in a silica sol–gel^{185–187} or coupling the nitroxide to functionalized polymers.^{188,189} Silica-supported TEMPO catalysts have several advantages: they are easily

isolated by filtration, a high catalyst activity can be realized due to the high surface area, the nitroxides can be cleanly regenerated electrochemically, and some are commercially available (e.g., SiliaCat^{®190} (Figure 2) and FibreCat^{®191}). The heterogeneous catalysts are often less active than the homogeneous catalysts.¹⁹² Most of the TEMPO–polymer conjugates are soluble in selected organic solvents; the catalyst is recovered by precipitation induced by changing the solvent system¹⁹³ or by dialysis.¹⁹⁴ PEG-supported TEMPO (Figure 2)¹⁹⁵ is the most popular homogeneous catalyst for use under Anelli,^{189,196–198} Minisci,¹⁹⁹ and aerobic copper-mediated conditions.^{195,200} The recyclable polyamine-immobilized piperidinyl oxyl (PIPO)^{192,201} (Figure 2) prepared from the commercially available antioxidant and light stabilizer CHIMASSORB[®] 944, in combination with bleach



Scheme 49 Oxidation of cholesterol by a polystyrene oxoammonium resin.

exhibited higher activity (per nitroxyl group) than TEMPO, silica-, and MCM-41-supported TEMPO.

There are several TEMPO–polymer conjugates that behave as insoluble heterogeneous catalysts, such as polystyrene PS-based TEMPO^{188,194,202,203} and TEMPO-functionalized PS encapsulated in polyurea microcapsules.²⁰⁴ Recently, Studer and coworkers reported TEMPO–poly(amidoamine) dendrimer conjugates coated inside polyparaxylylene nanotubes²⁰⁵ for benzylic alcohol oxidations under Anelli conditions. As shown in Scheme 49, cholesterol was oxidized by a preformed oxoammonium PS resin to form an enolizable ketone intermediate, which was further converted to the dione.¹⁰⁸ Tanaka and coworkers have regenerated polymeric oxoammonium salts by electrochemistry.²⁰⁶ Immobilized cooxidants such as poly[4-(diacetoxyiodo)styrene],^{207–209} polymer-supported bis-acetoxylbromate(I) anion,^{210,211} and polymer-supported hypochlorite resins^{212,213} have been developed.

Instead of attaching the nitroxide to a solid support, monomeric TEMPO tethered to a charged imidazolium species (Figure 3)²¹⁴ can be isolated by extraction into an ionic liquid, leaving the oxidized product in the organic layer.^{215,216} Imidazolium salts have also been tethered to 2,2'-bipyridine (bipy) ligands for use in TEMPO/Cu oxidations.²¹⁷ The nitroxide *N*-acetyl-4-amino-TEMPO was found to be soluble in an ionic liquid, but

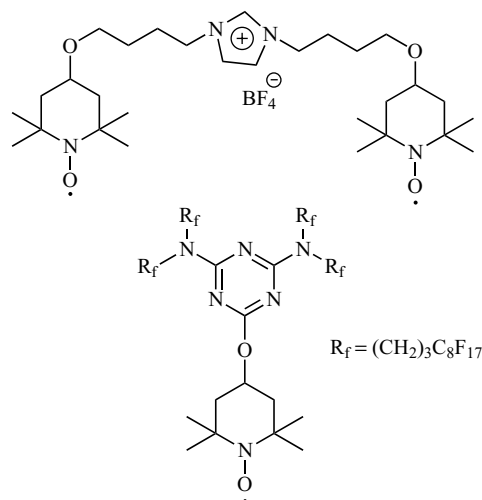
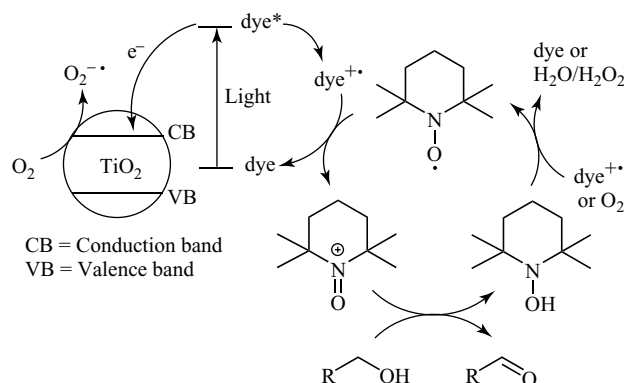


Figure 3 Examples of TEMPO derivatives bearing imidazolium salt and fluororous tags.

not in ether, allowing it to be recycled thrice without loss of activity.²¹⁸ Perfluoroalkyl chains impart solubility in fluororous solvents (Figure 3).²¹⁹ Several fluororous-tagged TEMPO derivatives have been applied successfully under Anelli,^{219–222} Margarita,²¹⁹ and Minisci^{221,223} oxidation conditions. This strategy has also been used to append perfluoroalkyl chains on 2,2'-bipy ligands for TEMPO/Cu-mediated alcohol oxidations, allowing the Cu–ligand complexes to be reused several times.^{223–226} Recently, TEMPO was immobilized on saponite, allowing isolation of the nitroxide by filtration,²²⁷ and on graphene-coated cobalt nanoparticles,²²⁸ which can be separated from solution by magnetic decantation.

As an alternative to chemical oxidants, electrochemistry has also been utilized to reoxidize nitroxides in alcohol oxidations. Cyclic voltammetry has been used to measure the formation of oxoammonium salts from nitroxides: the lower the oxidation potential of the nitroxide, the more effective the nitroxide is at mediating alcohol oxidation.¹⁷¹ Oxidation potentials are also a function of solvent polarity; polar solvents enhance the oxidation efficiency.²²⁹ Electrooxidations have been conducted in dichloromethane, acetonitrile, biphasic medium, or water in a divided cell^{230,231} as well as in undivided cells.²³² Ionic, water soluble,^{233,234} or polymer immobilized^{206,235,236} nitroxides have been used in electrooxidation of alcohols (see



Scheme 50 Mechanism for the visible light-induced aerobic oxidation of primary alcohols in a coupled photocatalytic dye-sensitized TiO_2 /TEMPO system.

Electrochemically Initiated Radical Reactions).

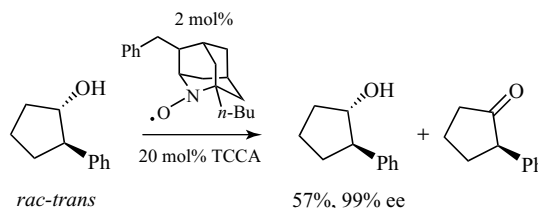
Nitroxides have been immobilized on the electrodes to simplify the work-up.^{237–239} The popular nitroxide SG1, commercially available from Arkema, was successfully used in electrooxidation of 4-methylbenzyl alcohol, which showed smoother electron transfer on the electrode compared to TEMPO.²⁴⁰ TEMPO electrooxidation has been performed in an ionic liquid.²⁴¹ Schafer and Bashiardes have demonstrated the nitroxide-catalyzed oxidation of mono-, di-, oligo-, and polysaccharides electrochemically.^{33,110,232,242}

Recently, an interesting method to regenerate an oxoammonium cation from the nitroxide using visible light has been reported (Scheme 50).²⁴³ This system consists of the dye Alizarin as a sensitizer, TiO_2 as an electron acceptor, and TEMPO as a cocatalyst in benzotrifluoride as solvent. Under irradiation with visible light ($\lambda > 450 \text{ nm}$), an electron from the excited state of the dye is transferred to the conduction band of TiO_2 ; the dye radical oxidizes TEMPO to the oxoammonium cation. After alcohol oxidations, the resulting TEMPO is then regenerated by either oxygen or the dye radical cation. In a similar system, porphyrin was utilized as the photosensitizer and quinone as the electron acceptor.²⁴⁴

5.2.2 Kinetic Resolution and Desymmetrization

Optically pure nitroxides¹⁰ have been used as oxidants to carry out kinetic resolution of racemic

substrates and desymmetrization of *meso* substrates. The selectivity value S is often used to combine both %ee (enantiomeric excess) and conversion into a measure of overall effectiveness in kinetic resolution. Bobbitt and coworkers reported the first examples of kinetic resolution of alcohols with a chiral nitroxide using 4-NHAc SPIROXYL,^{245,246} including the asymmetric lactonization of diols.^{245,247} Using an axially chiral nitroxide²⁴⁸ or nitroxyl peptide (TOAC)²⁴⁹ under Anelli conditions, moderate selectivities in the kinetic resolution of secondary alcohols was achieved ($S = 3.9\text{--}7.1$ and 2.3 , respectively). Electrochemical oxidation with the axially chiral nitroxide provided S values as high as 20 .²⁵⁰ Several chiral bridgehead nitroxides were examined; however, most of them were unstable under oxidation, resulting in poor S -values.²⁵¹ Recently, excellent enantioselectivities (S values up to 82) using the chiral azaadamantane nitroxide AZADO in combination with TCCA has been reported (Scheme 51).^{252,253} (–)-Sparteine has been used as a chiral base with TEMPO-modified electrodes^{247,254,255} and as



Scheme 51 Enantioselective organocatalytic oxidative kinetic resolution of secondary alcohols using optical AZADO.

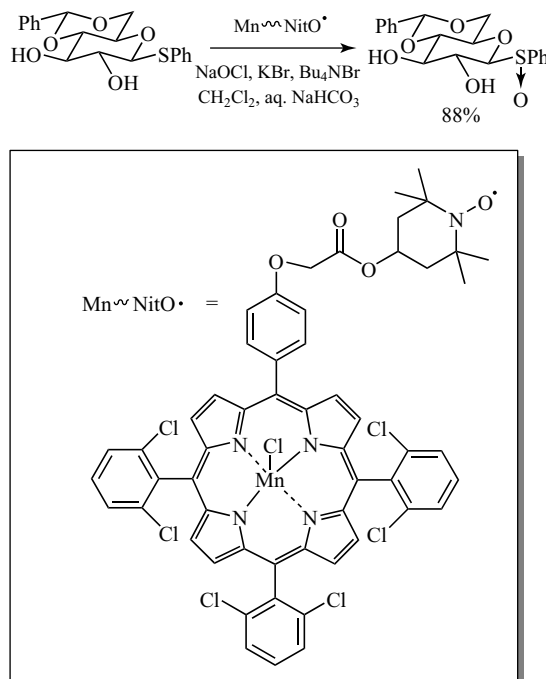
a ligand with copper²⁴² in enantioselective oxidations. A chiral copper complex, prepared from $\text{Cu}(\text{OTf})_2$ and (*R*)-BINAM was used with TEMPO in the oxidative kinetic resolution of racemic amino alcohols,²⁵⁶ benzylic alcohols, and benzoin.²⁵⁷ Kinetic resolution of secondary amines²⁵⁸ and oxazolidines²⁵⁹ have also been reported. Optically active acyl and diacyl (phthalimido) nitroxides have been used in both oxidative kinetic resolution and desymmetrization^{260,261}; however, the mechanism does not involve an oxoammonium salt, but rather hydrogen abstraction (*vide infra*).

5.2.3 Other Oxidations Mediated by Oxoammonium Salts

A variety of sulfides can be oxidized selectively to sulfoxides in nitroxide-mediated reactions under Anelli^{262–265} or copper-mediated²⁶⁶ conditions. For example, TEMPO-linked Fe- and Mn-metalloporphyrins were used as a catalyst to oxidize sulfides to the corresponding sulfoxides without overoxidation to the sulfone.²⁶⁵ The glycosyl sulfide in Scheme 52 was chemoselectively oxidized in the presence of two hydroxyl groups under Anelli conditions. The electrochemical oxidation of thiols to disulfides has been accomplished with a TEMPO-modified electrode.²⁶⁷

Trisubstituted alkenes can undergo allylic oxidation with oxoammonium salts to form alkoxyamines: Bobbitt and coworkers have suggested an ene-type mechanism.²⁶⁸ Similar examples include the allylic oxidation of dienes, activated alkenes,²⁶⁹ and tetrahydrocarbazole²⁷⁰ to form the corresponding conjugated ketones in excellent yields. For example, 1,2,3,4-tetrahydrocarbazole (Scheme 53) was oxidized to the ketone in 71% yield. The proposed mechanism involves nucleophilic attack by the indole on the oxoammonium salt, followed by intramolecular elimination to give the unsaturated iminium cation. Conjugate addition of water forms the 4-hydroxytetrahydrocarbazole, which is subsequently oxidized to the ketone product.

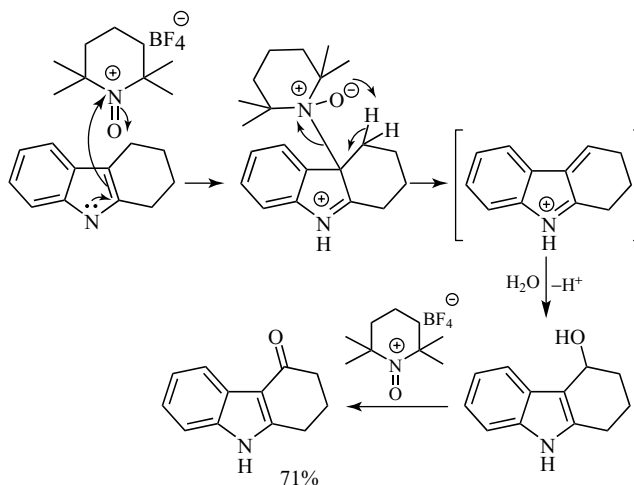
Oxidative cleavage of benzyl alkyl ethers occurs on treatment with oxoammonium salts bearing nonnucleophilic counterions such as BF_4^- (Scheme 54). The mechanism occurs via benzylic hydride transfer to the electrophilic oxygen of the oxoammonium salt; hydrolysis of



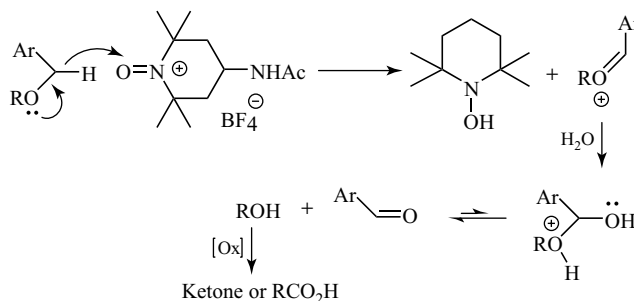
Scheme 52 Oxidation of a glycosyl sulfide to the corresponding sulfoxide with a TEMPO-linked Mn-metalloporphyrin under Anelli conditions.

the oxygen-stabilized benzylic cation forms an aromatic aldehyde and an aliphatic alcohol.¹⁰⁵ The aliphatic alcohol is further oxidized to the corresponding ketone or carboxylic acid. In contrast, using a nucleophilic bromide counterion to the oxoammonium cation, anhydrous conditions result in the formation of an aromatic aldehyde and an alkyl bromide.^{271,272}

Baeyer–Villiger reactions of α -hydroxy ketones can be carried out by nitroxides plus an oxidant, such as bleach.^{273–275} In the first step, the α -hydroxy ketone is oxidized by the oxoammonium salt to the corresponding α -diketone, which undergoes further oxidation to form the anhydride. The mechanism for the oxidative ring enlargement is not clear, but may occur by nucleophilic addition of the hydroxyamine anion to one of the carbonyls, followed by ring expansion with loss of the hindered aminyl anion. For example, peptides can be prepared from β -lactams via nitroxide-mediated Baeyer–Villiger reaction under Anelli conditions, followed by nucleophilic amidolysis with an amino acid (Scheme 55).²⁷⁵



Scheme 53 Allylic oxidation of 1,2,3,4-tetrahydrocarbazole to 4-keto-1,2,3,4-tetrahydrocarbazole by 2 equiv of an oxoammonium salt.



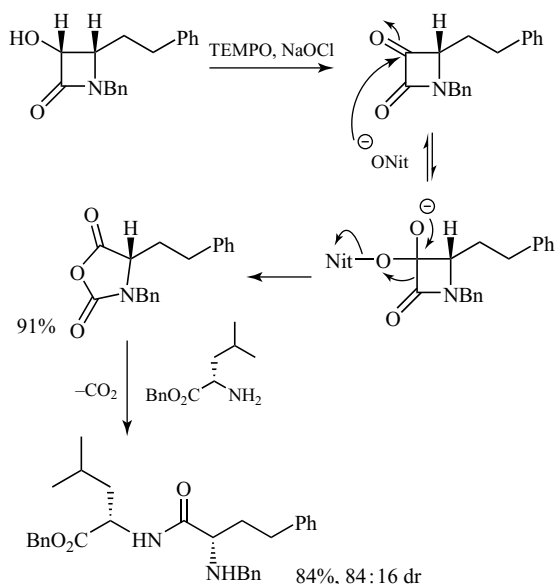
Scheme 54 Oxidative cleavage of a benzylic ether using a typical oxoammonium salt.

5.3 Oxidations via Hydrogen Abstraction

5.3.1 Copper-, Ruthenium-, and Iron-Catalyzed Aerobic Oxidations

A number of reports utilize copper, ruthenium, or iron with a nitroxide and oxygen to oxidize alcohols to carbonyl compounds. This literature has been reviewed by Sheldon and Arends^{7,8} and Sheldon *et al.*⁷⁵ Copper cocatalysts are the most extensively investigated among the transition metals in these aerobic nitroxide oxidations. Semmelhack *et al.* proposed that benzylic and allylic alcohols were oxidized by CuCl/TEMPO via the oxoammonium salt.^{106,276} Evidence against this pathway includes the lower reaction rates of aliphatic and alicyclic alcohols compared to benzylic and allylic substrates. This chemoselectivity is inconsistent with a mechanism involving an oxoammonium cation,

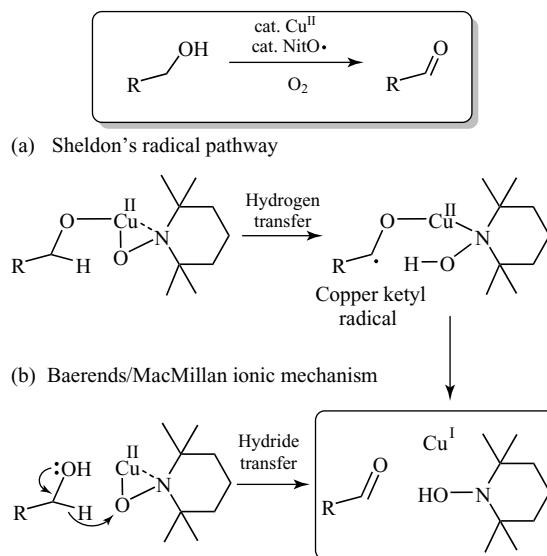
whose reactivity is broad in scope. Stoichiometric experiments under anaerobic conditions support the formation of an electrophilic Cu/TEMPO complex rather than an oxoammonium species.²⁷⁷ Additional evidence for an alternative reaction pathway includes kinetic isotope effects and Hammett correlation studies. The primary kinetic isotope effect for the CuCl/TEMPO catalyzed aerobic oxidation ($k_H/k_D = 5.42$) compares well with those observed with other metal-centered dehydrogenations of alcohols, such as a Ru/TEMPO system,²⁷⁸ galactose oxidase,²⁷⁹ and a biomimetic copper complex.²⁸⁰ In contrast, the kinetic isotope effects observed in stoichiometric oxoammonium cation oxidations are much smaller ($k_H/k_D = 1.7\text{--}2.3$).¹⁰⁶ The Hammett ρ value for the CuCl/TEMPO system also compares well with that of a galactose oxidase mimic. Sheldon and coworkers have proposed an intramolecular hydrogen atom abstraction as the key step in



Scheme 55 Synthesis of a peptide via Baeyer–Villiger reaction of a β -lactam with TEMPO and bleach.

the Cu/TEMPO catalytic aerobic cycle^{281,282}; however, calculations support a possible ionic hydride transfer mechanism^{38,283} (Scheme 56). After alcohol oxidation, the resulting Cu(I) and TEMPOH are reoxidized by O_2 to Cu(II) and TEMPO, respectively.

Several ligands, such as 2,2'-bipy,^{281,282,284} 1,10-phenanthroline (phen),²⁸⁵ pyrazole derivatives,²⁸⁶ and DABCO,²⁸⁷ as well as bases such as *t*-BuOK,^{281,282} NaOH,^{281,285} KOH,^{281,284} and DBU²⁸⁴ have been utilized in copper complex-mediated aerobic oxidation of alcohols. Under one set of conditions, no base was required, and the Cu(II) complex could be reused thrice without loss of reactivity.²⁸⁸ The use of a dinuclear Cu(II) complex was reported, but only works with primary benzylic alcohols.²⁸⁹ Recently, a Cu(II) complex immobilized on a silica support was utilized in supercritical carbon dioxide (scCO₂).²⁹⁰ These copper-mediated oxidations are selective, giving very good yields with primary benzylic and allylic alcohols, and in a few cases with secondary benzylic alcohols.²⁸⁵ There are a few reports in which primary aliphatic alcohols can be used.^{281,288} Recently, TEMPO/Cu has been employed in the aerobic oxidative rearrangement of a tertiary allylic alcohol.²⁹¹

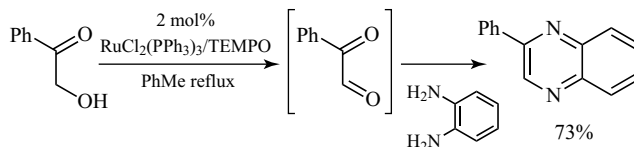


Scheme 56 Two proposed mechanisms for Cu/TEMPO cocatalyzed aerobic oxidation of alcohols: (a) via an intramolecular hydrogen atom transfer and (b) via hydride transfer to an electrophilic Cu/TEMPO complex.

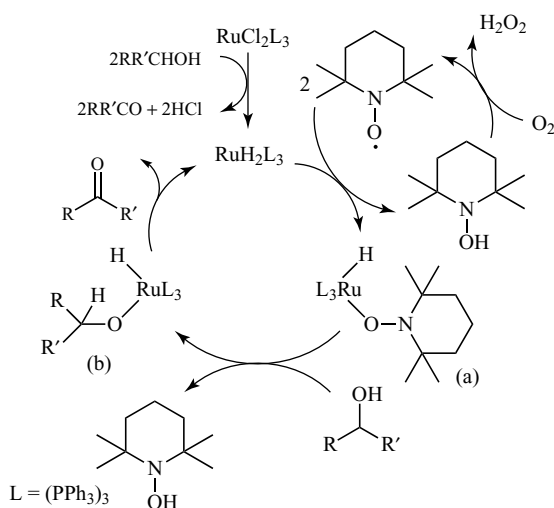
In contrast with copper, catalytic TEMPO/RuCl₂PPh₃ at 100 °C is effective for the aerobic oxidation of a broad range of alcohols, including aliphatic alcohols.^{278,292} The autooxidation of aldehydes to carboxylic acids under these conditions is completely suppressed by TEMPO, which acts as a carbon free radical scavenger. However, alcohols containing heteroatoms such as nitrogen cannot be oxidized by this system, as they deactivate the ruthenium catalyst by coordination as ligands.⁷⁵ This aerobic Ru/TEMPO system was shown to convert α -hydroxy ketones into 1,2-diketones, which were trapped *in situ* with aromatic 1,2-diamines to form quinoxalines (Scheme 57).²⁹³

From mechanistic studies on the Ru/TEMPO system, RuCl₂(PPh₃)₃ gets reduced to RuH₂(PPh₃)₃, possibly by oxidation of a small amount of alcohol (Scheme 58).⁷⁵ Reaction with 2 equiv of TEMPO forms TEMPOH and the ruthenium alkoxyamine complex **a**. The piperidinyloxy ligand in complex **a** is displaced by alcohol to form another equivalent of TEMPOH and complex **b**, which undergoes the key β -hydride elimination, to afford the carbonyl product and regenerating the RuH₂PPh₃ catalyst.

Interestingly, Liang *et al.* have investigated the use of an inexpensive and environmentally friendly TEMPO/FeCl₃/NaNO₂ system^{294,295} to oxidize



Scheme 57 Oxidation of α -hydroxy ketones with Ru/TEMPO, followed by trapping with 1,2-diamines to form quinoxalines.



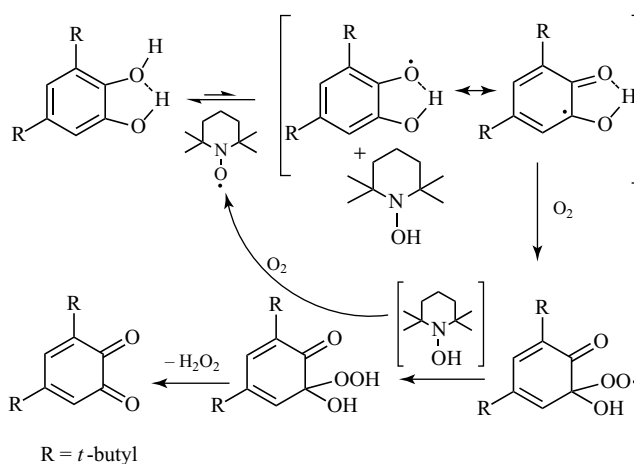
Scheme 58 Proposed mechanism for the Ru/TEMPO catalyzed aerobic oxidation of alcohols.

a broad range of alcohols including aliphatic alcohols under ambient conditions, in contrast to the TEMPO/ $\text{RuCl}_2\text{PPh}_3$ system which requires heating to 100°C .²⁷⁸ Further optimization of these

reaction conditions has been explored by several groups.^{295,296} An iron-activated electrophilic TEMPO complex involving a hydrogen abstraction pathway reminiscent of the Cu(II)/TEMPO system is likely. The catalytic cycle involves the oxidation of Fe(II) to Fe(III) by NO_2 and the oxidation of TEMPOH to TEMPO by Fe(III). The stoichiometric oxidant, molecular oxygen, regenerates the NO_2 .

5.3.2 TEMPO Reactions with Phenols and Catechols

TEMPO and derivatives oxidize phenols and catechols, such as 3,5-di-*tert*-butylcatechol,²⁹⁷ 2-aminophenol,²⁹⁸ L-tyrosine,²⁹⁹ and *o*-phenylenediamine³⁰⁰ via hydrogen atom abstraction under aerobic conditions. A proposed mechanism for the oxidation of 3,5-di-*tert*-butylcatechol is shown in Scheme 59. Semiquinone radical, produced by hydrogen abstraction by TEMPO of the very activated catechol OH, is readily trapped by molecular oxygen to give a peroxy radical. This peroxy radical in turn abstracts hydrogen atom



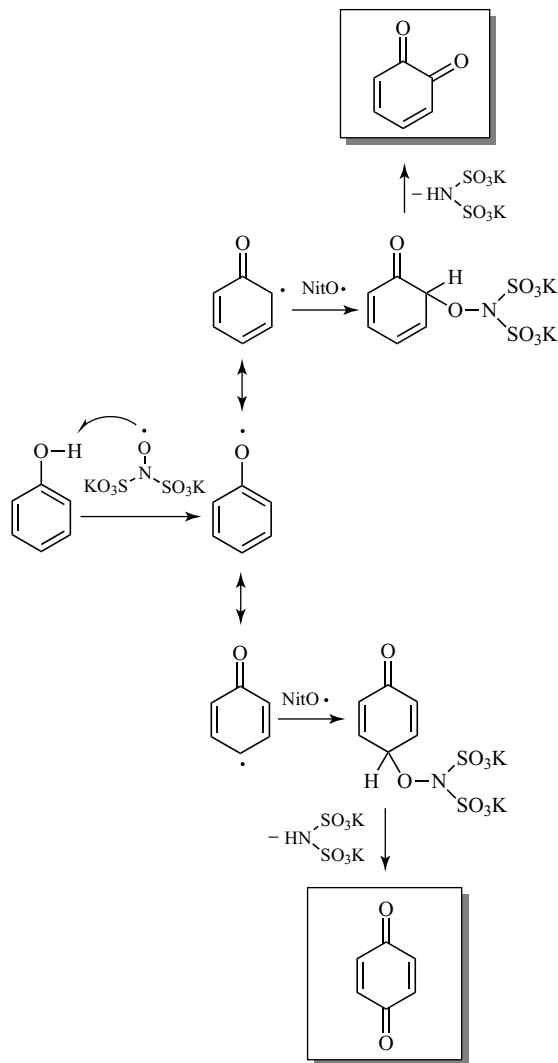
Scheme 59 Proposed mechanism for aerobic TEMPO-catalyzed 3,5-di-*tert*-butylcatechol oxidation.

back from TEMPOH to regenerate TEMPO. The hydroperoxide intermediate breaks down to form quinone and hydrogen peroxide.

5.3.3 Electron-Poor Nitroxides

Fremy's salt, potassium nitrosodisulfonate, was the first reported nitroxide. The applications of Fremy's salt in synthesis have been reviewed by both Zimmer³⁰¹ and Parker³⁰² and include the oxidation of heteroatom-substituted aromatic compounds, such as phenols,^{303,304} naphthols, indoles,³⁰⁵ carbazoles, quinolines,³⁰⁶ benzylic alcohols,³⁰⁷ and α -amino and α -hydroxy acids.^{308,309} In the oxidation of phenols to benzoquinones,³¹⁰ very electron poor Fremy's nitroxide abstracts the phenolic hydrogen to give a resonance-stabilized phenoxy radical intermediate (Scheme 60). This delocalized radical is trapped at carbon with another Fremy's nitroxide, followed by elimination of the aminosulfonate group to provide the *ortho*- or *para*-benzoquinones. Amino acids can be oxidized by Fremy's salt, followed by hydrolysis to the corresponding α -keto acids (Scheme 61).³⁰⁹ Oxidation of phenols or anilines to quinines by Fremy's salt has been used in the total synthesis of several biologically active compounds.^{311–314}

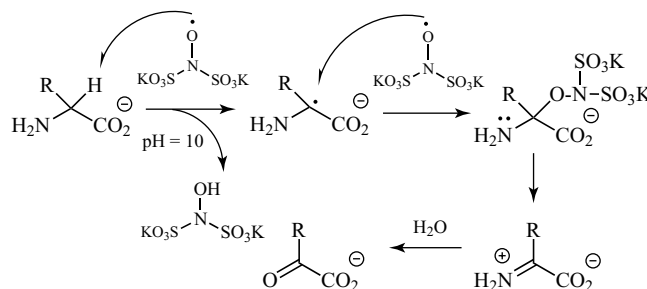
In contrast to stable dialkyl nitroxides, the diacyl nitroxide PINO, generated from *N*-hydroxyphthalimide (NHPI) (Scheme 62), is far more reactive at hydrogen atom abstraction than TEMPO due to the higher bond dissociation energy of NO–H bond in PINO–H.³¹⁵ The electron withdrawing carbonyl groups destabilize the diacyl nitroxide, but increase the stability of the hydroxylamine via intramolecular hydrogen bonding.⁷ The reactivity of PINO can be tuned by adding substituents to the aromatic moiety.³¹⁶ PINO in combination with *m*-chloroperbenzoic acid, $(\text{NH}_4)_5\text{H}_6\text{PV}_8\text{Mo}_4\text{O}_{40}$, or $\text{Co}(\text{OAc})_2$ and O_2 (the Ishii system) as an initiator has been used to oxidize alcohols to aldehydes or ketones^{75, 317–321} to oxidatively cleave benzylidene acetals³²² and to effect the autooxidation of unactivated alkanes and alkyl aromatics.^{318, 323–325} For example, aerobic oxidations to prepare commercially important fine chemicals, such as benzoic acid³²⁶ and nicotinic acid (vitamin B_3),³²⁷ can be performed in acetic acid under relatively mild conditions. A suggested



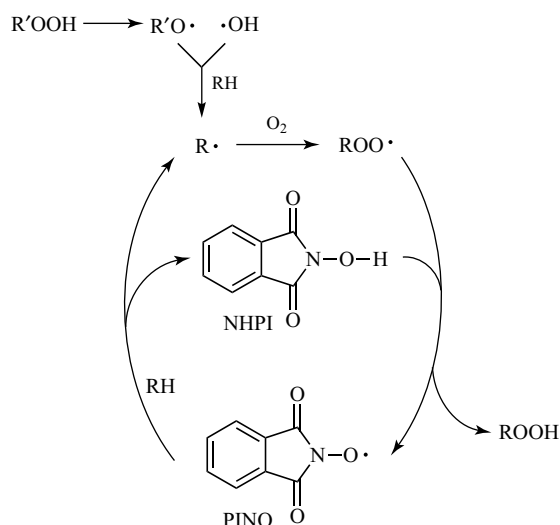
Scheme 60 Mechanism for the oxidation of phenol to benzoquinone with Fremy's salt.

mechanism in the presence of peroxide as an initiator is shown in Scheme 62.³²⁸ Initiation involves formation of a radical species, followed by abstraction of hydrogen atom from NHPI to form PINO, which then propagates the radical chain.

The nitroxide generated from *N,N',N''*-trihydroxyisocyanuric acid (THICA) (Figure 4) can be more effective than PINO in hydrogen abstraction, probably due to the greater stability of the corresponding nitroxide against decomposition.³²⁹ *N*-Hydroxysaccharin (NHS)



Scheme 61 Mechanism for the oxidation of amino acids to α -keto acids with Fremy's salt.



Scheme 62 Mechanism of autooxidation catalyzed by NHPI/peroxide.

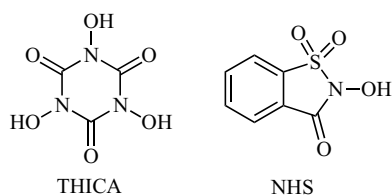


Figure 4 Precursors to highly reactive (nonpersistent) nitroxides utilized in autooxidation.

(Figure 4), in which one carbonyl group of NHPI has been replaced by the more strongly electron withdrawing sulfonyl group, was shown to be a highly effective catalyst in the autooxidation of large-ring cycloalkanes,^{330,331} under conditions

where PINO did not work. NHS also catalyzes oxidation at benzylic positions, in addition to primary and secondary alcohols³³¹; however, the rates are lower than that with NHPI.³¹⁷

In contrast to electron-poor nitroxides, hydrogen atom abstraction by TEMPO under normal reaction conditions is not efficient due to the weak O–H bond in TEMPOH. However, on photoexcitation, TEMPO is much more reactive and is able to abstract hydrogen atoms from solvents such as toluene, xylene^{332,333} and acetonitrile³³⁴ as well as cyclohexene,^{335–337} phenols,^{338,339} and even unactivated hydrocarbons.³⁴⁰ However, the use of photoexcited nitroxides in hydrogen abstraction reactions has not yet been developed into synthetically viable procedures.

6 CONCLUSIONS

The use of nitroxides in synthetic organic chemistry has blossomed over the past 15 years. While nitroxides were largely used as spin labels in the past, nitroxides are now common reagents in synthesis, operating as oxidizing agents, and carbon radical traps. The oxoammonium salts act as both electrophiles and single electron oxidants, whereas the hydroxylamine anions act as both nucleophiles and single electron reductants. In redox processes, the nitroxide can often be used in catalytic amounts, allowing the use of inexpensive primary oxidants. Applications to the oxidation of organic molecules, metal catalysts, and metal complexes are growing at an accelerating rate. Electron-poor nitroxides take part in a different manifold of reactions, abstracting hydrogen atoms in a variety of processes (including autooxidation), and adding to unsaturation. A

number of highly designed nitroxides are emerging with specific properties, ranging from bridged, sterically unhindered nitroxides, nitroxides bearing an α -hydrogen (providing a slow but important decomposition pathway), electron-poor nitroxides, and nitroxides with appended functionality, including fluorophores, solubility tags, and reactive groups to allow for further synthetic elaboration. The commercial availability of TEMPO makes it the most popular of the nitroxide reagents; however, as the chemistry becomes highly developed, it is inevitable that a variety of nitroxides will become regular reagents in the synthetic organic laboratory.

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Biological Chemistry of Reactive Oxygen Species

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1 INTRODUCTION

Free radicals and other reactive oxygen species (ROS) are produced in a wide range of physiological processes. They are capable of inflicting biological damage and are implicated in aging and the pathology of many conditions including cancer, cardiovascular, inflammatory, and degenerative diseases. Whereas the traditional way of thinking is that they are a necessary evil of living with oxygen in our environment, it is now apparent that they are also produced intentionally by living organisms and used to regulate processes such as cell growth and differentiation. Within this context, the objective of this article is to discuss the free radicals and other reactive oxidants that are most relevant in biology, how they are formed, their reactivity, and how we can assess which reactions are likely to be of biological significance. There is an extensive literature on this topic and some aspects have been covered only briefly and reference to recent reviews is made. For more extensive coverage, Halliwell and Gutteridge's book, *Free Radical Biology and Medicine*¹ is highly recommended. Interactions of free radicals with DNA, proteins, lipids, and other classes of biomolecules are also the focus of subsequent articles of this encyclopedia (see **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA, Oxidatively Formed Sugar Radicals in Nucleic Acids, Reactions of Small Reactive Species with**

DNA, Oxidative Damage to Proteins, and Lipid Peroxidation).

Biologically relevant ROS include radicals and non-radical species. The term *ROS* is widely used to encompass oxygen radicals and non-radical derivatives of oxygen (Table 1). Alternative terms are sometimes used, including reactive oxidants, oxygen-derived species, and reactive species, which is expanded to include other reactive derivatives of, for example, sulfur, nitrogen, and chlorine. However, "reactive oxygen species" is my preference, as the first alternative is not strictly correct because species such as superoxide can act as reductants, the second loses the notion of reactivity, and the latter definition becomes so broad as to cover most molecules. The initial species generated by oxygen reduction as well as their secondary reactive products are generally considered as ROS. Although there are radicals (e.g., thiyl or carbon-centered radicals) that do not strictly fit into this classification, their interactions frequently involve oxygen and link them to the overall ROS network.

The advantage of considering ROS in a broad context is that many of the species included in the definition are derived from one another or exist in equilibrium, so it is often not possible to consider one in isolation. However, it is equally important that "ROS" not be considered as a single entity. As discussed below, individual ROS vary widely in their reactivity and do not necessarily react with the same targets. So although the term

Table 1 Major reactive oxygen species (ROS) in biology.

Radical		Non-radical
Superoxide	$O_2^{\bullet-}$	Partially reduced oxygen
Hydroxyl	$OH^{\bullet}$	Hydrogen peroxide
		H_2O_2
Phenoxy	$PhO^{\bullet}$	Oxygenated species
Alkoxy	$RO^{\bullet}$	Singlet oxygen
Hydroperoxyl	$ROO^{\bullet}$	Hydroperoxide
Semiquinone	$O=Ph-O^{\bullet-}$ ($SQ^{\bullet-}$)	Hypochlorous acid
Carbonate	$CO_3^{\bullet-}$	Hypobromous acid
		Hypothiocyanous acid
		Halogenated species ^a
		Chloramines
		Bromamines
		Reactive nitrogen species
Nitric oxide	$NO^{\bullet}$	Peroxynitrite
Nitrogen dioxide	$NO_2^{\bullet}$	$ONOO^-$

R, alkyl; Ph, phenyl.

^aHOCl, HOBr, and HOSCN can also be classified as halogenated (or pseudohalogenated) species.

is appropriate for describing a general class of compounds, grouping all ROS together is counterproductive for understanding mechanisms. This is not uncommon, and can result in unrealistic roles being proposed for the involvement of ROS in biological phenomena.²

2 HISTORY

The existence of free radicals as chemical species was recognized over a hundred years ago and the process of rancidity, or lipid peroxidation, has been known for centuries (see **The History of Free Radical Chemistry**). Major developments in the biology of free radicals began around the 1950s. Largely through the application of research from the rubber industry to food science (see **Basic Concepts on Radical Chain Reactions**), the free radical chain reaction of lipid peroxidation was recognized, and from the intense research activity generated around nuclear energy, the fundamental role of radicals in radiation chemistry was recognized. The relevance of these mechanisms to living organisms was first highlighted by two pioneering publications. In 1954, Rebecca Gershman, Daniel Gilbert, and colleagues³ published their classic paper "Oxygen poisoning and X-irradiation: A mechanism in common" and in 1956 Denham Harman⁴ proposed his free radical theory of aging. These ideas stimulated others to consider free radical processes as potential

pathological mechanisms.^{5,6} However, it was the discovery of the enzyme superoxide dismutase (SOD) by Fridovich and McCord⁷ in 1969, which really opened up the field. The existence of an enzyme that breaks down superoxide radicals led to the realization that free radicals are widely generated in biological systems and the finding that organisms require SOD to survive in an aerobic environment⁸ added weight to the proposal that oxygen radicals are responsible for the toxic effects of oxygen. Furthermore, SOD became available as a powerful tool for investigating their role. It was a surprise at the time to discover that the biological reactivity of superoxide is modest, and although deleterious reactions have been identified, the nature of its toxicity is still debated today.

There have been substantial advances since then, especially in the understanding of how free radicals and other ROS react with different classes of biomolecules and how these reactions inflict biological damage. The field has also moved in an unexpected direction from the original concept that free radicals are unwanted toxins to be disposed of at all costs, as it became realized that organisms generate ROS in regulated cellular processes. A number of seminal findings have influenced this way of thinking. First, it was shown that white blood cells (neutrophils) intentionally produce hydrogen peroxide⁹ and superoxide¹⁰ to kill microorganisms. While ROS still act as toxins in this role, observations that exposure to low levels of superoxide

and/or hydrogen peroxide induce positive responses such as cell growth and differentiation, as initially highlighted by Burdon,¹¹ led to the realization that ROS are not strictly deleterious. This view was reinforced by the finding that the NADPH oxidases that produce superoxide in phagocytic cells are widely expressed in other cells and are responsive to growth factors and hormones.^{12,13} Numerous investigators have extended these findings and redox regulation of cell signaling is currently a very active research field.¹⁴ Another notable (Nobel prize winning) discovery that revolutionized physiology was that the free radical gas, nitric oxide, is generated endogenously and regulates numerous metabolic processes.^{15,16}

For all this scientific endeavor and knowledge acquisition, there are still uncertainties about the role of ROS in biology. Although excess production of free radicals is known to be damaging and antioxidant defense mechanisms are essential to protect against them, there are relatively few cases (mainly relating to specific toxicities) where free radicals or other reactive oxidants have been shown to cause a particular pathology or disease. Similarly, health benefits through pharmacological intervention have been largely unrealized.

3 OXYGEN AND EVOLUTION OF LIFE

ROS are intimately linked to the evolution of life on earth.¹⁷ The early atmosphere in which anaerobes evolved was strongly reducing, with most of the oxygen tied up as water. From this environment arose photosynthetic organisms capable of harnessing light energy to convert water to oxygen, and oxygen gradually accumulated. Aerobes that could use the energy released by metabolic reduction of oxygen to water through respiration then developed. However, photosynthesis and respiration are not perfect at interconverting oxygen and water directly, and some partially reduced intermediates (superoxide and hydrogen peroxide) are released. Without systems for handling these reactive species, aerobic organisms would not have survived. Even when there was no molecular oxygen, ROS would have been generated through processes such as UV radiation-induced breakdown of water. An intriguing proposal is that the development of catalase-like molecules using the abundant iron in the environment was critical for early life

forms to survive their deleterious effects.¹⁸ In this scenario, antioxidant mechanisms would have preceded the accumulation of oxygen in the atmosphere and been vital for the initial development of aerobic life. So controlling the effects of ROS could be considered a trade-off for the advantages of metabolizing oxygen, and an extensive array of antioxidant systems have developed for this purpose.

4 BIOLOGICAL SOURCES OF REACTIVE OXYGEN SPECIES

There are a number of cellular processes that generate free radicals and other ROS. Major sites of ROS generation are depicted in Figure 1.

4.1 Mitochondria

Mitochondrial respiration is a major biological source of ROS.¹⁹ Although most of the oxygen consumed by mitochondria is reduced directly to water by cytochrome oxidase, some electrons do leak out of the electron transport chain. Oxygen is reduced to superoxide, which is released into the mitochondrial matrix. It is often reported that up to 5% of the oxygen consumed is converted to superoxide. However, this is probably an overestimate because many of these measurements have been made using methods that promote superoxide release and thus distort the system.¹⁹ The main site of superoxide formation is complex I (NADH-ubiquinone oxidoreductase) under conditions where the ratio of NADH : NAD is high or where conditions favor reverse electron transport (Figure 2). The reaction of oxygen with the ubisemiquinone radicals generated from complex III (ubiquinone-cytochrome reductase) is another, probably less significant source, as are other mitochondrial enzyme systems such as α -ketoglutarate dehydrogenase. As in other situations where superoxide is produced, hydrogen peroxide is also formed either by spontaneous dismutation or in a reaction catalyzed by SOD (1).



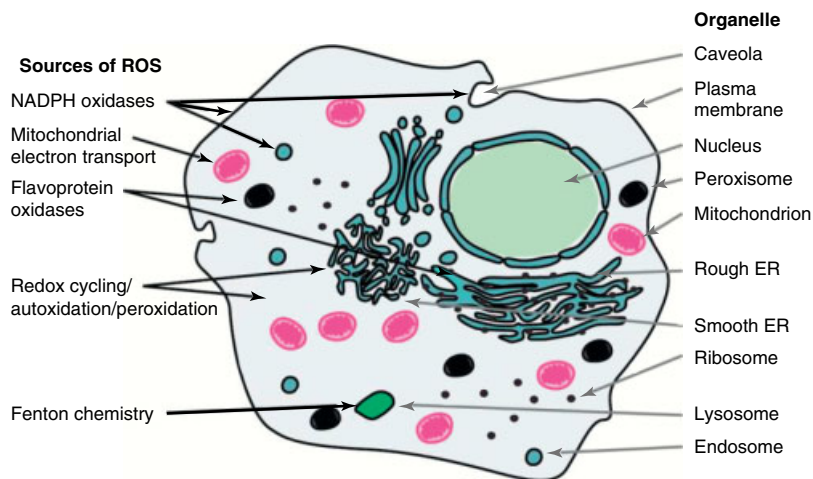


Figure 1 Prototype animal cell showing sites of generation of reactive oxygen species.

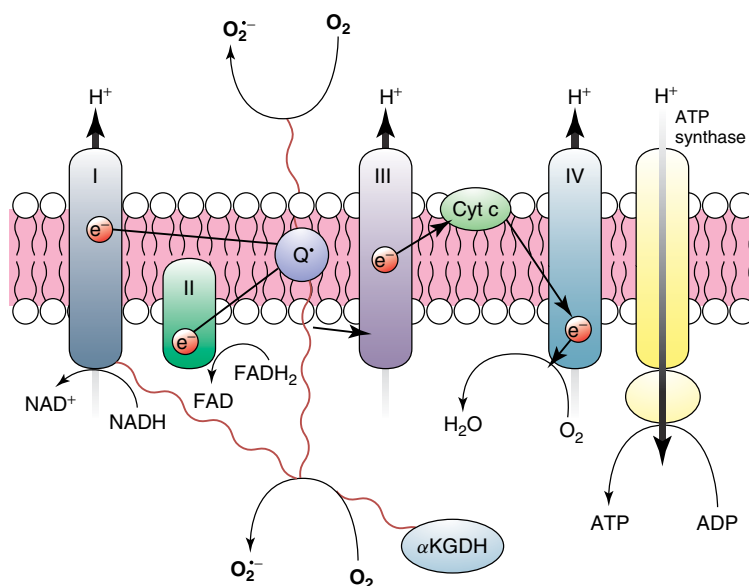


Figure 2 Sites of ROS generation during mitochondrial electron transport. Complex I (NADH-ubiquinone oxidoreductase) oxidizes NADH using coenzyme Q (Q) as an electron acceptor in a reversible reaction. Complex II (succinate-ubiquinone oxidoreductase) oxidizes succinate to fumarate using CoQ as an electron acceptor. Complex III (ubiquinone-cytochrome c oxidase) oxidizes CoQ using cytochrome c (C) as an electron acceptor. Complex IV (cytochrome c oxidase) is the site of reduction of oxygen to water. The reactions at complexes I, III, and IV are coupled with the translocation of protons out of the matrix to generate a transmembrane potential, which is used by the F₁F₀-ATPase to generate ATP. α-KGDH, α-ketoglutarate dehydrogenase.

4.2 NADPH Oxidases

Important biological source of superoxide and hydrogen peroxide, particularly within the context of cell signaling, are the NADPH oxidases (NOXs).

These are a family of multiprotein complexes that catalyze the transfer of electrons from NADPH to oxygen to produce superoxide.²⁰ The prime function of these enzymes is understood to be the production of superoxide (or hydrogen peroxide). There

are five NOX family members, each containing a cytochrome b and a flavoprotein but with different regulatory subunits, cellular localization, and modes of activation.²¹ There are also two DUOXs, which are related proteins termed *dual oxidases* because they also contain a peroxidase domain (which may or may not be active).²² DUOX activity in the thyroid gland is required to provide the hydrogen peroxide used by thyroid peroxidase for hormone synthesis. NOXs are present in animals, plants, and fungi, and have diverse physiological functions.¹³ Most release superoxide directly and it dismutates to give hydrogen peroxide; in others (e.g., NOX4) hydrogen peroxide is formed from the superoxide before it leaves the active site.²³ NADPH oxidases are membrane associated,²⁴ and an important aspect of their cell biology is that electron flow is directional. Thus NADPH is oxidized in the cytoplasm and superoxide is released on the external side of the membrane. This may be to the outside of the cell, or if the membrane is internal, as is the case for the neutrophil phagosome (see below), into the encapsulated organelle (Figure 3a).

4.2.1 Phagocytes

Until recently, the only known NADPH oxidase (now designated NOX2 isoform) was in phagocytic cells (neutrophils and monocytes), where it is required for killing microorganisms.^{26,27} When these cells ingest microorganisms (phagocytosis), NOX2 is activated to generate a high flux of superoxide radicals into the phagosomal space (Figure 3a). In neutrophils, most of the hydrogen peroxide (formed by dismutation of superoxide) reacts with myeloperoxidase which is also released into the phagosome. Myeloperoxidase, and the related peroxidase in eosinophils,²⁸ oxidize halide ions as well as a wide range of more traditional peroxidase substrates. The most significant reaction of myeloperoxidase in the phagosome is with chloride to give hypochlorous acid.^{29,30} Although the precise mechanism of killing is not fully understood, hypochlorous acid is the neutrophil's most effective antimicrobial oxidant.²⁶ The directionality of NOX activity (Figure 3a) means that transfer of electrons occurs across the membrane to oxygen in the phagosomal space. This creates a charge imbalance that

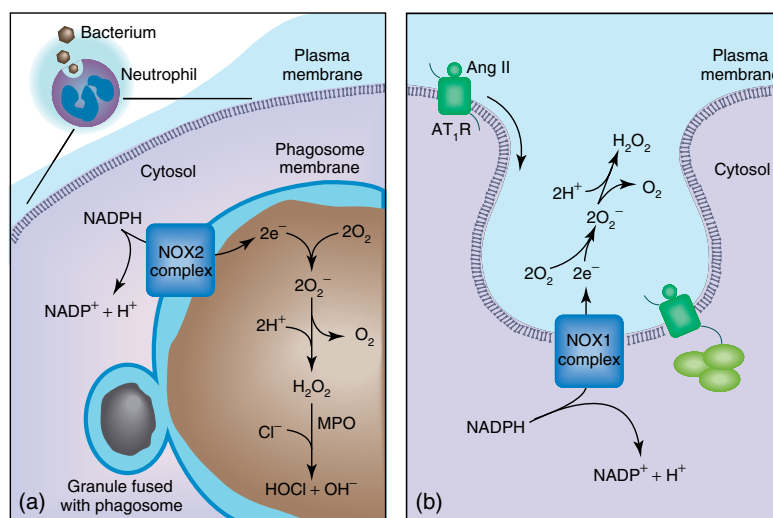


Figure 3 Oxidant generation by NADPH oxidases. (a) Neutrophil phagosome following ingestion of a bacterium. The NADPH oxidase (NOX2) is activated on the phagosomal membrane; electrons are transported from NADPH across the membrane to oxygen to generate superoxide radicals that dismutate to hydrogen peroxide. Degranulation releases (along with other proteins) myeloperoxidase, which generates hypochlorous acid. (b) Proposed mechanism for oxidant generation from receptor-mediated NOX activation illustrated for NOX1 in angiotensin II-activated smooth muscle cells. Receptor activation causes components of the NOX complex to assemble in regions of the membrane (in this case caveoli). Intracellular NADPH is consumed and superoxide is generated on the external surface.²⁰ [Reproduced from Ref. 25. © Nature Publishing Group, 2008.]

must be compensated, mainly by proton movement through voltage-gated channels.³¹ An interesting proposal is that this electrogenic effect, rather than oxidant production accounts for the antimicrobial effect of NOX2, by creating a favorable ionic environment for other antimicrobial agents released into the phagosome.^{32,33} However, this view has been challenged and the bulk of evidence strongly favors an oxidative killing mechanism.^{26,31} Nevertheless, the consequences of electron translocation across the membrane due to NOX activity need further clarification.³⁴

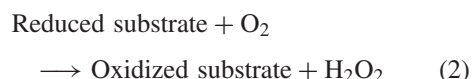
NOX activation can be induced by other stimuli in the absence of phagocytosis, with the reactive oxidants released into the surroundings of the cells.³⁵ This could be considered the downside of oxidative killing as many biological molecules are vulnerable to attack by neutrophil oxidants and excessive production in chronic inflammatory conditions can result in oxidative damage to host tissue.^{36–38}

4.2.2 Non-Phagocytic Cells

NOX activity in other cell types is generally at a much lower capacity than in phagocytes, and rather than having an antimicrobial function, is involved in cell signaling.^{20,27} Although some NOXs are constitutively active, activation is mostly receptor-mediated. Depending on the isoform, organism, and cell type, activation can be by hormones, cytokines, shear stress, or growth factors,^{39–41} and have diverse effects including cell growth and differentiation, production of inflammatory mediators, hyphal growth in fungi, and root hair growth in plants.^{13,42} Where cell localization studies have been performed, NOX assembly has been shown to occur at specific membrane sites, such as in caveolae (as in Figure 3b), lipid rafts, or endosomes.^{20,23,24,43} Superoxide should therefore be generated extracellularly or within the endosome. The implication is that oxidant action also occurs at localized sites in the cell. Studies with hydrogen peroxide-specific probes are starting to provide some direct evidence for this.⁴⁴ As discussed below, there is still uncertainty about how superoxide or hydrogen peroxide transmits signals associated with NOX activation. The prevailing view is that thiol proteins are the major targets and that redox changes link to phosphorylation pathways of signal transduction.

4.3 Flavoprotein Oxidases

Hydrogen peroxide is generated in reactions catalyzed by a range of flavoprotein oxidases, in equimolar amounts to the substrate that they oxidize (2).



Many of these enzymes, for example, acyl-CoA oxidase, polyamine oxidase, urate oxidase, xanthine oxidase, plant glycolate and sulfide oxidases, are present in peroxisomes.^{45,46} These organelles contain most of the cellular catalase, and therefore have a high capacity to break down hydrogen peroxide, but any that escapes could still be a major peroxide source for the rest of the cell. Peroxisomes also contain other antioxidant enzymes including SOD, so in different situations could act as a source or sink for ROS.⁴⁵

Other significant sources of hydrogen peroxide are the flavoprotein oxidases (such as ERO1) present in the endoplasmic reticulum (ER).⁴⁷ These proteins are required for oxidative folding of exported proteins and catalyze the oxidation of Cys residues by molecular oxygen to form protein disulfide bonds (Figure 4).⁴⁸ With a 1 : 1 stoichiometry per disulfide, large amounts of hydrogen peroxide could theoretically be produced.⁴⁹ Although this has not yet been detected directly, a rate of ~ 1 mM/min can be calculated for antibody-producing plasma cells.⁵⁰ How the ER handles hydrogen peroxide, and whether any is released into the cytoplasm, are questions that are currently being addressed. One possibility is that it is consumed by peroxiredoxin 4, which is also localized in the ER.⁵¹ Thus, hydrogen peroxide formation by flavoproteins in the ER or peroxisomes occurs without requiring an external stress or stimulant and in some situations these organelles could be the major cellular site of peroxide generation. How this activity relates to peroxide generation from NADPH oxidases during cell signaling is an important question that is yet to be resolved.

4.4 Heme Protein Autoxidation

Superoxide and/or hydrogen peroxide is produced by other oxygen-utilizing proteins. For example,

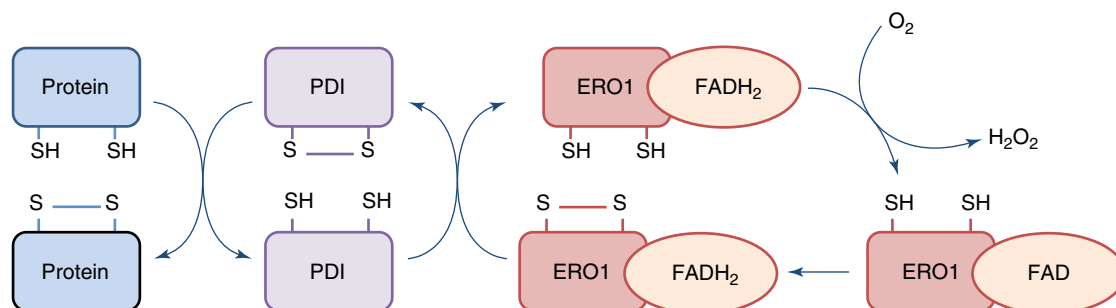


Figure 4 Proposed mechanism for hydrogen peroxide formation during oxidative protein folding in the endoplasmic reticulum. ERO1, endoplasmic reticulum oxidoreductin 1; PDI, protein disulfide isomerase.

autoxidation of heme proteins such as hemoglobin (Hb; 3), myoglobin, or nitric oxide synthase results in release of the bound oxygen as superoxide.^{52,53} The hemoglobin in the erythrocyte is estimated to autoxidize at a rate of a few percent of per day, so is an appreciable source of superoxide in these cells.



4.5 Radiation

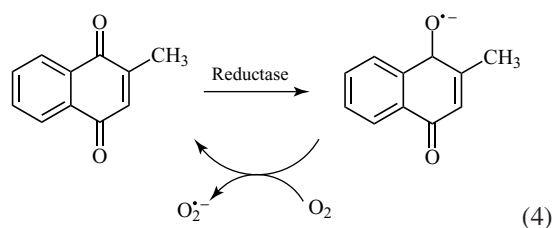
Free radicals are produced on exposure of biological systems to ionizing or UV radiation and are directly or indirectly responsible for the toxicity of such exposure. As described in more detail elsewhere,⁵⁴ the primary target for ionizing radiation is water, which is split into hydroxyl radicals, hydrogen atoms, and hydrated electrons. The latter two species are strongly reducing and short lived and in aerobic solution react primarily with oxygen to give superoxide. Although direct attack of the radiation can also generate radicals on macromolecules such as DNA (see **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA and Understanding DNA Radicals Employing Theory and Electron Spin Resonance Spectroscopy**), the majority of the biomolecular damage is due to hydroxyl radicals, superoxide, and secondary products.

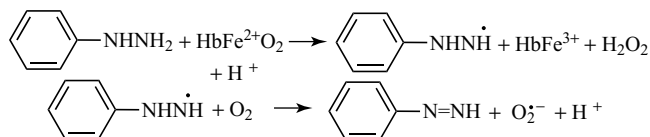
Photochemical ROS generation by UV radiation is particularly important for photoinduced damage to the skin and eye in mammals,⁵⁵ and in the plant chloroplast during photosynthesis.⁵⁶ Most photochemistry occurs via photosensitizers (e.g., chlorophyll, porphyrins) which are converted to

an excited state, whereas lower wavelength UV radiation can form radicals on target molecules directly. As discussed elsewhere,^{1,55,56} ROS generation occurs by energy transfer to oxygen to give singlet oxygen (type I mechanism) or via a radical (type II) mechanism that produces superoxide and other reactive species.

4.6 Drugs and Xenobiotics

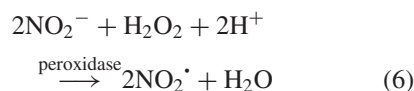
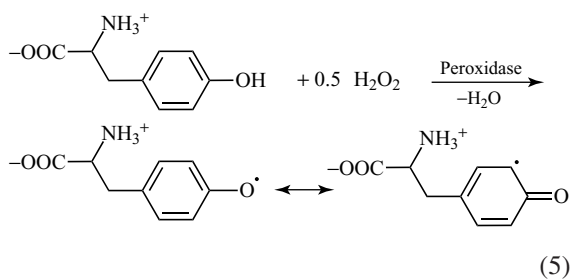
Metabolic oxidation or reduction to free radicals is a common toxicological mechanism for a wide spectrum of drugs and xenobiotics. Quinones and related species are reduced by flavoenzymes such as cytochrome *P*450 reductase, ferredoxin reductase, or xanthine oxidase to generate semiquinone-like species.^{57,58} These radicals commonly react with oxygen to generate superoxide and the parent compound, in a process known as *redox cycling*.⁵⁹ Reducing equivalents are supplied by the cosubstrate of the enzyme (usually NADPH) and the xenobiotic effectively catalyzes the reduction of oxygen to superoxide. Examples of redox cycling agents are the herbicide paraquat, menadione (4), the anticancer drug doxorubicin, and the diabetogenic compound alloxan.^{60–63}





Scheme 1 Reaction of phenylhydrazine with oxyhemoglobin.

Other compounds, including phenols and aromatic amines, are oxidized to radicals by peroxidases such as myeloperoxidase or lactoperoxidase. Endogenous compounds, including tyrosine (5), serotonin, urate, nitrite (6), and ascorbate are good peroxidase substrates.^{64,65} Polyphenols, such as the flavonoids, that are commonly classified as dietary antioxidants also react with peroxidases to form radicals,⁶⁶ and such pro-oxidant reactions could counteract their radical-scavenging antioxidant activity in some situations. Drugs such as phenothiazines and clozapine are oxidized by myeloperoxidase and radical-mediated injury can contribute to their adverse side reactions.^{67,68} Polycyclic hydrocarbons, carcinogens, and benzene can also be activated by cytochrome *P*450 to phenolic derivatives which are oxidized by peroxidases to their phenoxyl radicals.^{69,70} Heme proteins, such as hemoglobin and cytochromes, can also act as peroxidases.^{71,72} As these proteins tend to be abundant, their reactions are biologically relevant even though much less efficient.



Heme proteins and transition metal ions also promote free radical formation by catalyzing auto-oxidation reactions. These reactions, along with hydroxyl radical production (see later), are important mechanisms in metal toxicity. Interactions with hemoglobin give rise to some of the most clear-cut

cases of oxidative stress-related disease.^{52,73} The prototype reaction is with phenylhydrazine, which is oxidized by the heme-bound oxygen initially to give the hydrazyl radical, ferric heme, and hydrogen peroxide (Scheme 1). The radical can then react with oxygen to generate superoxide and these species plus a series of secondary products cause oxidative damage to the erythrocyte. They can be handled by normal erythrocytes, but individuals with an inherited deficiency of the enzyme glucose-6-phosphate dehydrogenase are unable to generate the reducing equivalents (NADPH) needed for the effective removal of hydrogen peroxide and reversal of oxidative changes. They suffer from severe hemolytic anemia if they take antimalarial drugs such as primaquine (where a metabolite is the active agent), sulfanilamides, dapsone, and other substituted aromatics.⁷⁴ Some individuals are particularly susceptible to fava beans, which contain the readily oxidizable hydroxypyrimidines, divicine, and isouramil.^{75,76}

5 PROPERTIES OF REACTIVE OXYGEN SPECIES

Individual ROS differ in their chemical and physical properties. Some are strong and others weak oxidants; some are radicals and undergo one-electron reactions, whereas others are non-radical species that cause two-electron oxidation; they vary in their membrane permeability and in their ability to be scavenged by individual antioxidants. Therefore, the biological impact of ROS production will depend on what species are produced and where. The picture is complex, because many of these species are derived from one another and many of the reactions are reversible (Figure 5), but for a mechanistic understanding of biological processes, it is important to decipher what specific ROS are involved.

For the most part, ROS act as oxidants. However, because the direction of any redox reaction depends on the reduction potentials of the couples involved,

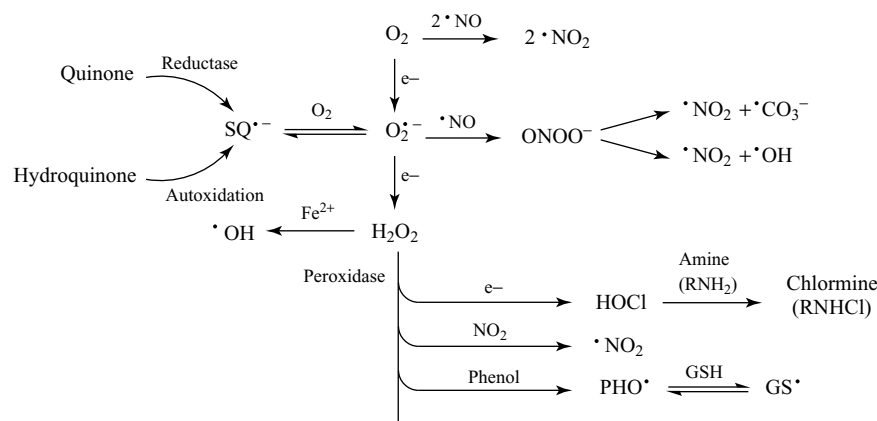


Figure 5 Interplay of physiologically relevant reactive oxygen species. The scheme covers most reactive species (or representatives of a class) and selected routes of generation or interconversion. Abbreviations as in Table 1. One-electron oxidants (radicals) are shown in red and two-electron oxidants in blue. [Reproduced from Ref. 25. © Nature Publishing Group, 2008.]

a species (superoxide, for example) can be an oxidant in some situations and a reductant in others. A more detailed description of the relevant thermodynamics can be found elsewhere (Ref. 77 and **Redox Properties of Radicals**) but in brief, for a reaction to proceed, there must be a negative change in the Gibbs free energy (ΔG). This is related to the difference in reduction potential of the two couples ($\Delta G = -nF\Delta E$, where E is the reduction potential, F the Faraday constant, and n the number of electrons involved). Under any set of conditions, E is a function of the standard reduction potential (E° , or often more conveniently expressed as $E^{o'}$ at pH 7) and the reactant and product concentrations. It is described by the Nernst equation (T temperature, R the gas constant, F Faraday constant, $2.303 RT/F = 0.059$ at 278°K).

$$\text{For } A + ne \longrightarrow B \quad E(V) = E^\circ + 2.303RT/nF \log[B]/[A]$$

(and at 278°K ; $n = 1$) $= E^\circ + 0.059 \log[B]/[A]$

As a general guideline for a reaction between two redox couples, the couple with the higher $E^{o'}$ will act in an oxidizing direction. In Table 2, hydroxyl radicals are the most oxidizing, and radicals higher up the table are more likely to act as oxidants. An alkoxyl radical will oxidize a phenol for example. However, as reactant and product concentrations also influence the direction of a reaction, under some conditions (e.g., if products are rapidly removed), a radical lower down the table can act as the oxidant.

Table 2 One-electron reduction potentials of a selection of biologically relevant free radicals.

Radical couple	Reduction potential ($E^{o'}$) V
$\text{OH}^\bullet, \text{H}^+/\text{H}_2\text{O}$	2.31
$\text{CO}_3^{\bullet-}, \text{H}^+/\text{HCO}_3^-$	1.78
$\text{RO}^\bullet/\text{RO}^-$	~ 1.60
$\text{NO}_2^\bullet/\text{NO}_2^-$	1.04
$\text{O}_2^{\bullet-}/2\text{H}^+/\text{H}_2\text{O}_2$	0.94
$\text{PhO}^\bullet, \text{H}^+/\text{PhOH}$	0.90
$\text{CysS}^\bullet/\text{CysS}^-$	0.92
$\text{ROO}^\bullet, \text{H}^+/\text{ROOH}$	0.77–1.44
Catechol $\text{SQ}^{\bullet-}, \text{H}^+/\text{catechol}$	0.53
Quercetin $\text{SQ}^{\bullet-}, \text{H}^+/\text{quercetin}$	0.33

Species are listed in an approximate order of decreasing reactivity. Standard reduction potentials ($E^{o'}$) are at pH 7, relative to normal hydrogen electrode, and are from Refs 77 and 78. Abbreviations or formulae for radicals are from Table 1. Note that $\text{O}_2^{\bullet-}$ is in equilibrium (pK_a 4.8) with the hydroperoxyl radical ($\text{HO}_2^\bullet$); $E^{o'}$ 1.06 V and that $\text{O}_2^{\bullet-}$ ($\text{O}_2/\text{O}_2^{\bullet-}$ $E^{o'} -0.33$ V) and semiquinones can also act as reductants. Reduction potentials of different phenoxyl radicals and semiquinones vary depending on substituents.

Furthermore, thermodynamics only tell whether a reaction is feasible, not whether it will occur within a reasonable time frame. This depends on the activation barrier that must be overcome, which is reflected in the reaction kinetics (Figure 6).

5.1 Radical Reactions

Biologically relevant ROS include both radicals and two-electron (non-radical) oxidants (Table 1 and

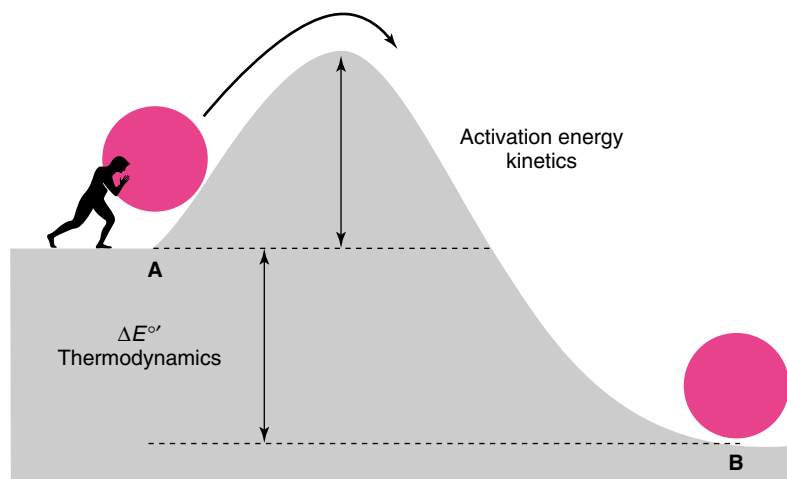


Figure 6 Energy diagram illustrating kinetic versus thermodynamic considerations.

Figure 2). Radicals are not necessarily more reactive than non-radicals, but because the reaction of one radical with a non-radical generates another radical, they have the capacity to undergo chain reactions such as lipid peroxidation (see **Lipid Peroxidation**). Radical reactions are also more likely to be inhibited by phenolic antioxidants such as vitamin E and flavonoids, or ascorbic acid. As well as being a measure of oxidizing strength of a radical, one-electron reduction potential (as in Table 2) is a reasonable reflection of its reactivity because the activation energy for radical reactions is low.

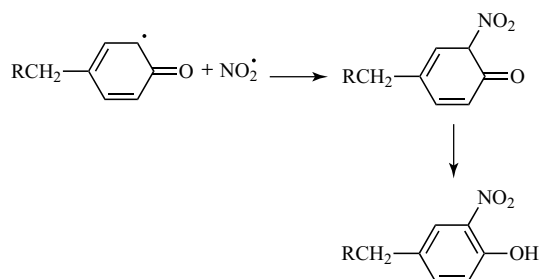
The stronger the oxidant, the less discriminating it is. Hydroxyl radicals, for example, can oxidize DNA bases (see **Oxidatively Generated Nucleobase Modifications in Isolated and Cellular DNA**), aliphatic and aromatic amino acid residues (see **Oxidative Damage to Proteins**), sugars, and many other biomolecules.¹ Carbonate radicals are also capable of oxidizing many of these substrates.⁷⁹ These radicals are formed in the reaction of hydroxyl radicals or peroxy nitrite (see Section 5.2.2) with the carbon dioxide that is prevalent in physiological fluids, and from the peroxidase activity of metalloenzymes such as Cu/Zn SOD.^{79–81} Carbonate radicals are perhaps under-rated players in free radical biology.

Radicals with lower reduction potential, such as nitrogen dioxide, are more restricted but they can react with polyunsaturated lipids and the more oxidizable amino acids, cysteine, methionine, tyrosine, and tryptophan. Phenoxyl radicals vary in

oxidizing ability depending on their ring substituents.⁸² Polyphenols are more readily oxidized and form less energetic radicals that react poorly with these substrates,^{78,83} hence their ability to act as radical-scavenging antioxidants. Semiquinone radicals generally act as reductants and as noted above, reaction with oxygen leads to redox cycling and superoxide production.

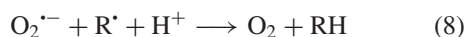
Among the most sensitive biomolecules for radical attack are sulfur centers (Cys and Met residues), redox-active transition metals, and polyunsaturated lipids.^{1,84,85} These reactions do not require a highly oxidizing radical and can result in lipid peroxidation (see **Lipid Peroxidation**) and modifications that affect protein structure and activity. Oxidation can inactivate metalloproteins, and convert the metal into a secondary reactive species. More detail on these reactions and their consequences is presented in **Radical-Based Damage of Sulfur-Containing Amino Acid Residues and Oxidative Damage to Proteins**.

An important property of radicals is that they readily undergo reactions with other radicals. As examples, carbon-centered radicals react with diatomic oxygen (classified as a radical because of its two unpaired electrons) and radical recombination terminates the chain reaction of lipid peroxidation. The propensity for ascorbyl radicals to disproportionate to ascorbate and dehydroascorbate is key to ascorbate being an effective radical scavenger. Semiquinones also disproportionate, and phenoxyl radicals dimerize to give species such as



Scheme 2 Main route to nitrotyrosine.

dityrosine. Reaction of tyrosyl radicals with nitrogen dioxide (Scheme 2) is the major route to nitrotyrosine, and the very rapid reaction of nitric oxide with superoxide (7) is a mechanism for regulating nitric oxide levels and for forming the strong oxidant peroxynitrite.^{15,86}



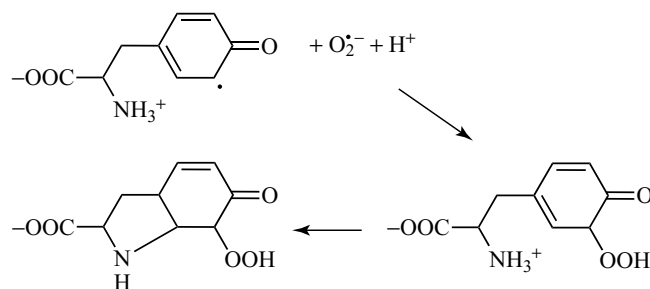
Superoxide also reacts rapidly with other radicals.⁸⁷ These reactions can occur either by electron transfer to repair the parent compound (8) or addition. Addition reactions produce hydroperoxides, as shown for tyrosine (Scheme 3). In this case, the initial product undergoes conjugate addition with the α -amino group to give a reasonably stable hydroperoxide.^{88–90}

5.1.1 Superoxide

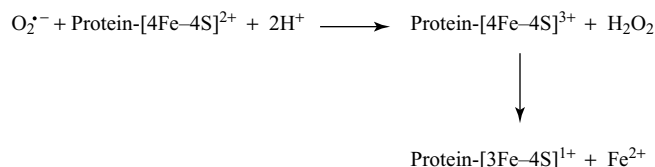
Superoxide can act as an oxidant and reductant. It is an unusual radical because in spite of its reduction

potential of 0.94 V, it oxidizes relatively few biological compounds. This is partly explained by its anionic charge-limiting reactivity with electron-rich centers and by its ready dismutation.¹⁷ Its protonated form, the perhydroxyl radical (pK_a 5.5), is a stronger oxidant. Superoxide reacts with ascorbate at an appreciable rate,⁹¹ and slowly oxidizes thiols such as reduced glutathione (GSH).⁹² Several mechanisms have been proposed to explain its toxicity.^{93,94} The best established is inactivation of iron/sulfur proteins such as aconitase and the dehydratases required for the synthesis of branched chain amino acids.^{94–96} One-electron oxidation by superoxide inactivates the enzymes and releases iron and hydrogen peroxide which can cause further injury (Scheme 4).^{97,98} These reactions are fast (rate constants $>10^6 \text{ M}^{-1} \text{ s}^{-1}$) and highly selective for superoxide.^{95,96} Oxidation of an iron/sulfur center is also employed by bacteria to upregulate resistance genes in response to sublethal superoxide. In this case, a [2Fe–2S] protein, SoxR, is oxidized, and a change in conformation transactivates the transcription factor, SoxS.⁹⁹

Another potentially detrimental reaction of superoxide is with nitric oxide to give peroxynitrite (7). This reaction has a rate constant of $\sim 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ and can compete with SOD-catalyzed dismutation.⁸⁶ Peroxynitrite (Section 5.2.2) is a reactive and damaging oxidant that is implicated in a range of pathologies.^{15,100} However, there is debate about whether sufficient peroxynitrite is generated physiologically for it to be a major toxic species^{15,101} and the reaction may be more relevant for modulating signaling by NO.^{102,103} Addition reactions with other radicals, such as the tyrosyl radical in the active site of ribonucleotide reductase, may also contribute to superoxide toxicity.^{87,104}

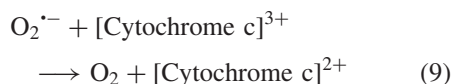


Scheme 3 Superoxide addition to tyrosyl radical to form hydroperoxide.



Scheme 4 Superoxide-mediated inactivation of iron–sulfur proteins.

SOD accelerates superoxide breakdown, but contrary to popular belief, does not necessarily increase the amount of hydrogen peroxide produced. Dismutation converts half the superoxide to hydrogen peroxide, regardless of whether or not it is catalyzed (1). SOD will only increase this amount if it prevents a reaction in which superoxide acts as a reductant or forms an addition product (such as 9 and 7) and does not generate hydrogen peroxide. If it prevents superoxide acting as an oxidant (e.g., as in Scheme 4), the amount of hydrogen peroxide produced would halve.



5.1.2 Nitric Oxide

Although a free radical, nitric oxide reacts slowly if at all with biological oxidants and reductants.¹⁵ It forms nitroso complexes with iron centers (as in its physiological role of activating guanylate cyclase) and is oxidized by oxyhemoglobin to nitrate or nitrite (10). This reaction is rapid and is the main route of removal from blood. Myeloperoxidase has also been shown to catalyze the removal of NO,¹⁰⁵ although this reaction may be mediated by other radical products of the enzyme.



Other major reactions of nitric oxide are addition reactions with other radicals including oxygen (11), superoxide (7), thiyl radicals (12), phenoxyl radicals,^{106–111} Nitrosothiol formation on protein thiols is emerging as an important cell regulatory mechanism.^{112,113} NO itself does not react directly with thiols but (12) provides a plausible mechanism

for nitrosothiol formation. Equation (11) involves an initial, reversible reaction between two NO molecules then reaction of the product with oxygen. The kinetics are therefore third order and it is poorly favored at low reactant concentrations.¹¹¹ It may have greater relevance in lipophilic environments where oxygen and nitric oxide are more soluble.¹¹⁴



5.1.3 Thiyl Radicals

Thiols are favored targets for a wide range of radical species. Radical scavenging by GSH is an important antioxidant defense, and oxidation of cysteine residues is also a mechanism for regulating the activity of thiol proteins. As discussed in more detail in **Radical-Based Damage of Sulfur-Containing Amino Acid Residues**, the initial product is a thiyl radical (as in 13 for a generic radical R[•] and GSH). Thiyl radicals are themselves good oxidants and undergo a range of reactions including abstraction of hydrogen from protein residues and initiation of lipid peroxidation.^{115,116} They also undergo rapid reaction with another thiolate anion to form the disulfide radical anion (14). This reaction is an equilibrium that converts an oxidizing into a strongly reducing radical. In the presence of oxygen, it is driven in the forward direction to give the disulfide plus superoxide as final products (15). Physiologically, this is a major decay route for thiyl radicals. Alternatively, if the thiyl radical has limited access to another thiol, it can react with oxygen to form a peroxy radical (16) and a range of secondary products. Combination of two thiyl radicals to give the disulfide is generally not favored but can occur if oxygen is limiting. In

the presence of nitric oxide, nitrosothiol formation (12) is also possible. Thiyl radicals are readily scavenged by ascorbate.^{115,117}



In considering the role of GSH (or other thiols) as a radical scavenger, it is noteworthy that (13) is an equilibrium that in many cases lies to the left.¹¹⁵ On these grounds, GSH does not appear to have the qualities of a good radical-scavenging antioxidant. The reason why it is effective is that oxygen removes the disulfide radical anion via (15). Thus, oxygen enables GSH to act as a good scavenger without the buildup of potentially damaging thiyl radicals. The reaction also channels radicals into a pathway that leads to superoxide, which can be considered as a radical sink.¹¹⁶ This sequence provides an elegant mechanism for a single enzyme (SOD) to bring about radical removal.

5.2 Two-Electron Oxidants

The two-electron oxidants that are most relevant to biology are hydrogen peroxide, organic hydroperoxides, peroxyxynitrite, and the hypohalous acids. Although the strength of these oxidants is dictated by their reduction potential, kinetic considerations are more dominant in determining reactivity. Hydrogen peroxide, for example, has a higher reduction potential than hypochlorous acid (E° values of 1.77 and 1.50 for reduction to water and chloride, respectively), but reactions of hydrogen peroxide require much higher activation energy and rates are correspondingly slower. Rate constants for reaction with GSH (Table 3) give an indication of the relative reactivities of two-electron oxidants. As with radicals, thiol groups are among their most favored targets. The initial product is the sulfenic acid (or sulfenyl halide) which can undergo a range of secondary reactions that are not necessarily the same as for radical pathways.^{118,119}

Table 3 Relative reactivity of two-electron oxidants based on rate constants for reaction with GSH.

Oxidant	Rate constant ($\text{M}^{-1} \text{s}^{-1}$)
HOCl	3×10^7
HOBr ^a	1×10^7
HOSCN	8×10^4
ONOO ⁻	700
Chloramines	100–700
H ₂ O ₂	0.9

Rate constants are at pH 7 and are from Refs 120–125.

^aMeasured for *N*-acetylcysteine.

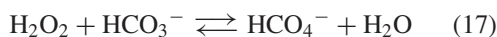
5.2.1 Hydrogen Peroxide

Under physiological conditions, hydrogen peroxide reacts poorly or not at all with most biological molecules, including low molecular weight antioxidants. It reacts slowly with typical thiols.¹²⁰ Its main reactions are with seleno-, thiol, or heme peroxidases and other transition metal centers to give both radical and non-radical species (Figure 5). Reactions with glutathione peroxidases, peroxiredoxins and ascorbate peroxidase are important for detoxification, whereas the radicals and other secondary products generated by metalloproteins, along with products of Fenton chemistry (Section 6.1), are major contributors to the biologically damaging effects of hydrogen peroxide.¹⁷ Cell signaling and oxidative stress responses to hydrogen peroxide are generally considered to involve direct reactions with specific thiol proteins.^{126–128} However, there are kinetic constraints on many of these reactions (Section 7.1) and radicals and other secondary peroxidation products may be involved in transmitting signals.

Organic peroxides are generally similar to hydrogen peroxide in their substrate preferences. They react readily with reduced or oxidized transition metal centers to generate alkoxyl or peroxy radicals, respectively and react directly with thiols. For some peroxiredoxins, they are better substrates than hydrogen peroxide, whereas for others, the reactivity is reversed. Based on data in Ref. 129 it would appear that amino acid hydroperoxides react slightly faster than hydrogen peroxide with GSH.

Hydrogen peroxide reacts with bicarbonate to form peroxymonocarbonate (17), which is approximately 100 times more reactive than free hydrogen peroxide.⁷⁹ This reaction could be biologically important as a mechanism for enhancing hydrogen

peroxide reactivity. However, the reaction is an equilibrium that lies to the left and the forward step is slow. So although this could be the case for pre-existing peroxydicarbonate, its rate of formation would quickly become limiting.



5.2.2 Peroxynitrite

The chemistry of peroxynitrite is complex and is well covered in recent reviews.^{15,86,111} Although peroxynitrite can act as a two-electron oxidant, its most favored biological reaction is with carbon dioxide (as shown in Figure 5) to form carbonate and nitrogen dioxide radicals. Most of its physiological effects are likely to be due to these secondary radicals. If carbon dioxide is limiting, peroxynitrite breaks down to hydroxyl radicals and nitrogen dioxide (see Figure 5). It is sufficiently reactive to oxidize thiols directly but at physiological concentrations, the reaction is a combination of direct and radical-mediated oxidation.¹³⁰ Peroxiredoxins have unusually high reactivity and should react directly with peroxynitrite.¹³¹

5.2.3 Hypohalous Acids

Hypohalous acids are generated from their corresponding halides (or in the case of hypothiocyanous acid from the pseudohalide, thiocyanate) by the mammalian peroxidases, myeloperoxidase, eosinophil peroxidase, and lactoperoxidase (as shown for chloride in Figure 5). These reactive oxidants mediate many of the biological effects of the peroxidases.^{30,37} They vary in oxidizing ability: hypochlorous > hypobromous > hypothiocyanous acid.^{132–134} The preferred substrates of hypochlorous acid are thiols and methionine residues, which react with rate constants greater than $10^7 \text{ M}^{-1} \text{ s}^{-1}$.^{121,135} Hypochlorous acid oxidizes numerous other substrates and also undergoes chlorination reactions, for example with tyrosine to form chlorotyrosine,¹³⁶ unsaturated lipids and NAD^+ to form chlorohydrins,^{137,138} and nucleotides to form chlorinated bases.¹³⁹ Chlorination reactions are much slower than oxidations but give rise to distinctive products that are useful biomarkers.^{140,141}

Hypobromous acid undergoes comparable reactions to hypochlorous acid, although the difference in reaction rate between oxidations and brominations is not as great as for hypochlorous acid.¹³³ Hypothiocyanous acid is capable of oxidizing thiols but undergoes few other biological reactions.^{122,134,142}

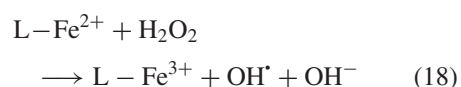
Hypochlorous and hypobromous acids react with amine groups to form chloramines and bromamines (Figure 5).^{143,144} Rate constants for these reactions are about 100-fold less than for thiols,^{123,133} but the biological prevalence of amine groups on free amino acids and proteins plus the fact that the products are also oxidants, mean that chloramines and bromamines are likely to mediate many of the effects of the parent hypohalous acids. Both are two-electron oxidants that are less reactive than their parents and more selective for sulfur centers. Chloramines can react with a further HOCl molecule to form dichloramines (RNCl_2), which are more reactive but less stable than the monochlorinated species.^{145,146}

6 TRANSITION METALS

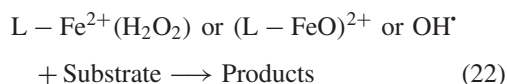
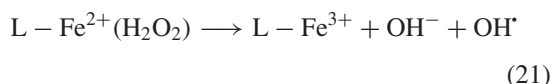
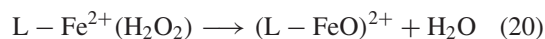
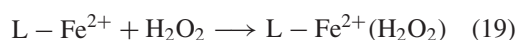
Redox-active transition metals such as iron and copper are key participants in the biological chemistry of ROS. By donating or accepting a single electron, they both generate and remove radical species. Metalloproteins, for example peroxidases, SODs, catalases, act as pro-oxidants and antioxidants. Low molecular weight metal complexes are also important initiators of radical reactions, through Fenton-type reactions with hydrogen peroxide and as autooxidation catalysts.

6.1 Fenton Chemistry

The Fenton reaction has been much studied as a source of hydroxyl radicals and initiator of biological damage.^{94,147–149} In its simplest form, it can be written (where iron is complexed to ligand L) as



Fenton chemistry strictly involves iron and the name originates from observations by Fenton in the 1880s that a mixture of acidified iron and hydrogen peroxide generates a strong oxidant. The term *Fenton-like* is also used to describe comparable reactions of other transition metals such as copper. Over the years, there has been considerable debate as to whether the product is indeed the hydroxyl radical or a higher oxidation state of the metal (such as ferryl $[\text{FeO}]^{2+}$ or Cu(III) complexes). Product analyses and competition kinetic studies have been carried out with a variety of iron chelates and detector systems and led to differing conclusions.^{147,150,151} There is no simple answer, but the situation can be summed up as follows.^{148,152} On thermodynamic grounds, (18) is unlikely to occur as shown.¹⁵³ More likely is an inner sphere mechanism in which there is an initial formation of a ferrous peroxide (Fe(IV)) complex (reaction 19), which can convert to a ferryl species (20), breakdown to give hydroxyl radicals (equation 21), or directly oxidize a substrate (22).



In biological media, iron and copper exist as complexes either with small molecules such as citrate or ATP or bound to macromolecules. The rate of (19) varies depending on the nature of the chelator. The extent to which the initial complex undergoes (20) or (21) as against reacting directly with a substrate also depends on the chelator as well as the nature of the target. So in different circumstances, one or all three of the reactive species may act in (22) as the Fenton oxidant. This is extremely difficult, if not impossible, to distinguish kinetically. However, the initial complex and the ferryl species are both strong oxidants, so regardless of which species is involved, the products from a particular substrate are likely to be similar. Therefore, in most situations, the reactive species is best described as the Fenton oxidant.

An important variation of this reaction is where the metal is bound to a biological molecule that may itself be oxidizable, in which case, site-localized oxidation by the bound Fenton oxidant can occur. Examples of this are copper-catalyzed oxidation of DNA, and protein oxidation by an iron/ascorbate system.^{154,155}

Transition metal ions are present physiologically at low concentrations. Therefore, sustained production of Fenton oxidants requires the oxidized metal to be recycled. Although this was once thought to be an important role for superoxide, in what is commonly referred to as the superoxide-driven Fenton reaction or Haber–Weiss reaction, other reductants such as ascorbate are better able to perform this function.¹⁵⁶

Chelation or sequestration of transition metals to limit their redox activity (such as iron in transferrin or ferritin) is an important protective mechanism against oxidative damage.⁹⁴ However, these metals are in a dynamic state in cells, where low micromolar concentrations of non-protein bound iron can be measured.^{157,158} A major site of iron availability is the lysosome, where metalloproteins are degraded and the low pH enhances both its stability and reactivity.¹⁵⁹ These organelles are an important site for biological damage due to Fenton chemistry and protective effects of chelators, such as desferrioxamine, may be largely attributed to complexation of lysosomal iron.¹⁶⁰

7 KINETICS AND THE IDENTIFICATION OF BIOLOGICAL TARGETS

Each of the ROS described above has been shown to react with numerous individual biomolecules when studied in isolation. Not all of these will be relevant in a more complex biological context, as some will be outcompeted by other more reactive targets. The key factors are how fast a target reacts with the oxidant (defined by the rate constant) and its concentration. Thus, a constituent with a high rate constant may not be favored if its abundance is low. The fraction (F) of an oxidant reacting with one substrate (A) in competition with n other substrates is described by the simple kinetic expression (where k_a and k_n are the rate constants for substrates A and S_n).

$$F = k_a[A]/\Sigma k_n[S_n] \quad (23)$$

This relationship can be used to predict what reactions an oxidant is likely to undergo. It has been used to analyze reactions of nitric oxide, superoxide, and peroxynitrite under various conditions^{111,161} and to identify likely the targets for hypochlorous acid in the neutrophil phagosome and plasma.^{133,162} As described below and by Stone,¹⁶³ kinetic modeling can also identify cellular thiol proteins that are likely the targets for hydrogen peroxide.

Simple kinetic analysis also enables the effectiveness of antioxidants to be assessed. It demonstrates that realistic concentrations of ascorbate can inhibit radical reactions in plasma, but dietary polyphenolics cannot reach sufficiently high concentrations to compete with the ascorbate already present.¹⁶⁴ It also shows that it is impossible for any compound to act as an effective hydroxyl radical scavenger *in vivo*. Most compounds react with hydroxyl radicals with rate constants in the $10^9 \text{ M}^{-1} \text{ s}^{-1}$ range. So even the best scavenger, with a rate constant at the upper limit of $\sim 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, could not reach a high enough concentration for its $k[\text{S}]$ to impact on the sum of $k_n[\text{S}_n]$ for all the physiological substrates present.

While kinetic analyses are valuable for identifying major oxidant targets, minor reactions should not be ignored if they impart a gain of function to the target. For example, DNA modification may in quantitative terms make a negligible contribution to the overall reactions of a radical, but by introducing a mutation to a single base, its effects could be far reaching. Alternatively, an unfavorable reaction that inhibits an enzyme by only a few percent is unlikely to have functional consequences.

7.1 Thiol Proteins as Targets for Hydrogen Peroxide

Reversible oxidation of thiol proteins is an important mechanism in cell signaling.^{14,165–167} Redox signals can be initiated by exogenous hydrogen peroxide, and in many instances receptor-mediated signaling is proposed to be due to endogenously generated hydrogen peroxide. However, there is uncertainty about which thiol proteins are directly targeted by hydrogen peroxide and how redox signals are transmitted. Kinetic modeling provides insight into potential mechanisms. Hydrogen peroxide reacts with the thiolate anion rather than the protonated

thiol, so a low $\text{p}K_a$ imparts have higher reactivity at neutral pH. Reaction rates with low molecular weight thiols decrease with increasing $\text{p}K_a$, but their thiolates all have similar rate constants ($\sim 20 \text{ M}^{-1} \text{ s}^{-1}$).¹²⁰ A minority of proteins including protein tyrosine phosphatases (PTPs) and peroxiredoxins have low $\text{p}K_a$ thiols (5–6 compared with 8.8 for GSH). Rate constants that have been measured for PTPs are similar or less than 10-fold higher than for low molecular weight thiolates¹⁶³ and few other cellular proteins have been shown to react faster.¹⁶⁷ An exception is the peroxiredoxins, which are a family of highly abundant thiol proteins that react exceptionally rapidly with hydrogen peroxide (rate constants in the 10^5 – $10^7 \text{ M}^{-1} \text{ s}^{-1}$ range).^{131,168–171}

Modeling a simple system containing these proteins, GSH, and glutathione peroxidase at estimated cell concentrations gives a clear picture (Figure 7). The peroxiredoxin and seleno-glutathione peroxidase (which has a slightly higher reactivity but lower abundance than the peroxiredoxins) trap almost all the peroxide, a tiny proportion reacts directly with GSH and the PTPs compete poorly even with GSH. Thus a low $\text{p}K_a$ is not on its own sufficient for a cellular protein to be oxidized by hydrogen peroxide and in homogeneous conditions, the low $\text{p}K_a$ PTPs and related enzymes that are widely considered as peroxide targets in cell signaling would not be competitive kinetically. The situation in a real cell, where there are thousands of proteins in different compartments, is much more complex. Although catalase is largely confined to peroxisomes, it is likely to have some role by removing hydrogen peroxide that diffuses into these organelles. For other proteins to be direct targets, it would seem that they would need to have reactivity approaching that of a peroxiredoxin. At least in mammalian cells, no other thiol proteins with this reactivity have been identified.

Oxidation of thiol proteins, including PTPs, has been observed during cell signaling.^{174,175} One possible explanation is that oxidation is indirect, and highly reactive proteins such as peroxiredoxins act as hydrogen peroxide sensors.^{127,165,166,176} Peroxiredoxins, as reviewed elsewhere,¹⁶⁸ undergo reversible oxidation to disulfides, and can be “hyperoxidized” at the active site Cys to a sulfinic acid. Their main function is usually considered to be peroxide-removal as part of the cell’s antioxidant defense,^{168,177–179} but a plausible alternative is that

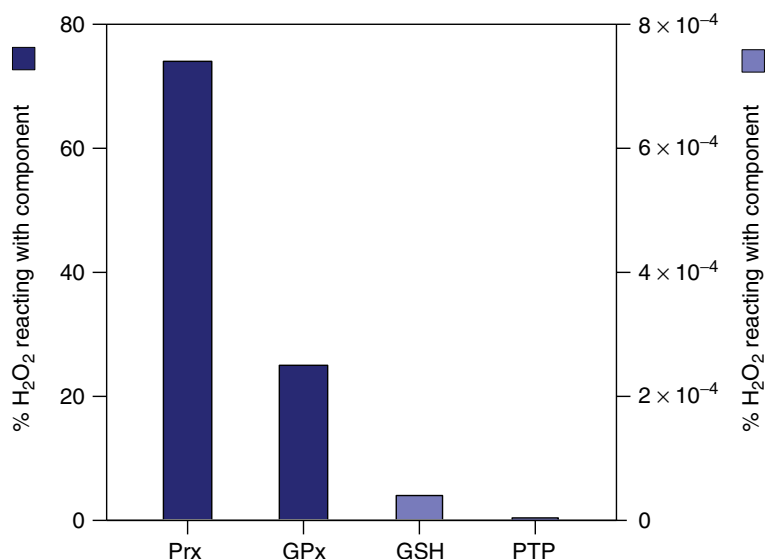


Figure 7 Competition for hydrogen peroxide between typical peroxiredoxin (Prx), seleno-glutathione peroxidase (GPx), protein tyrosine phosphatase (PTP), and GSH at estimated cellular concentrations. Concentrations and rate constants used are GSH 2 mM and $0.89 \text{ M}^{-1} \text{ s}^{-1}$,¹²⁰ Prx 20 μM , $2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$,¹⁶⁹ PTP 0.1 μM , $20 \text{ M}^{-1} \text{ s}^{-1}$ (PTP1B),¹⁷² or $160 \text{ M}^{-1} \text{ s}^{-1}$ (Cdc25B).¹⁷³ Concentrations are approximations assuming a total cellular protein concentration of 250 mg/ml, average molecular weight of 25–50 kDa, so that a component that makes up 0.1% of total protein would be 5–10 μM . Note that GSH and PTP relate to right-hand axis which is 10 000 times amplified.

they trap hydrogen peroxide and transmit its oxidizing capacity to other proteins. Such a mechanism has been observed in yeast where members of the peroxiredoxin family are initially oxidized by hydrogen peroxide, then transfer oxidizing equivalents via a mixed disulfide to the transcription factor YAP1 or a stress-activated MAP kinase.^{180,181} Proteins that interact with mammalian Prx1 may do so through such a mechanism.¹⁷⁶

8 DIFFUSION AND COMPARTMENTALIZATION

Cells and tissues are not homogeneous, and an important consideration is whether an oxidant will act locally or is able to diffuse from the site of generation and act at a distance. This will depend on (i) whether it is sufficiently reactive to be consumed by substrates in the immediate vicinity and (ii) whether limited membrane permeability will restrict it to the compartment in which it is generated. Even if ROS generation is localized to a particular organelle or localized membrane site, it does not

necessarily follow that the oxidant will react at that site.

8.1 Membrane Permeability

Superoxide has low membrane permeability and only limited ability to pass through anion channels^{182–184} so its reactions are largely restricted to the compartment where it is generated. On the other hand, hydrogen peroxide can diffuse through cell membranes, and aquaporins may facilitate this transfer.¹⁸⁵ Hydrogen peroxide concentration gradients across membranes do exist, however, due to differing consumption rates on either side.¹⁸⁶ Membrane permeability of other ROS depends on charge. Peroxynitrite (pK_a 6.6) and hypochlorite (pK_a 7.5), for example, are not freely diffusible but readily permeate membranes in their protonated form.^{187,188}

An interesting conundrum is how the superoxide or hydrogen peroxide generated by NADPH oxidases exert their effect. Because they are generated on the external cell surface or within an organelle

(Figure 3b), they must traverse the membrane in order to interact with an intracellular target. This is a major restraint for superoxide. However, endosomal generation could favor reactions with targets present in the endosome.^{43,189} Hydrogen peroxide would be less constrained to a compartment such as an endosome. Even though extracellular hydrogen peroxide could enter the cell, it would also diffuse in other directions and its effects would not be localized to the generation site.

8.2 Diffusion Distances

The distance a reactive species travels before it is consumed is determined by the concentrations of available substrates and the rate constants of these reactions. It decreases as the concentration(s) of reactive substrates increase and is described by the relationship (where k_n and S_n are as described for competition kinetics, l is the distance over which the oxidant drops from an initial concentration of C_0 to C , D is its diffusion coefficient¹⁹⁰)

$$\ln C/C_0 = l/\sqrt{\Sigma k_n[S_n]}/D \quad (24)$$

D is not known for cellular milieu, but for small reactive species is estimated to be not greatly less than for aqueous solution.

This expression can be used to estimate how far a species is likely to diffuse from where it is generated in the presence of particular substrate(s) and to assess whether site-localized action could occur within a cell. GSH is typically present in cells at millimolar concentrations and reacts with most radicals and two-electron oxidants. A comparison of how far various oxidants can diffuse in the presence of 2-mM GSH (Figure 8) shows that reactive radicals and non-radical species such as hypochlorous acid are restricted to act locally, but hydrogen peroxide and peroxynitrite are able to diffuse beyond the dimensions of a typical 10–20 μm diameter cell.²⁵

Diffusion of hydrogen peroxide in the presence of other potential cellular targets can also be modeled. Peroxiredoxins at typical cell concentrations of 10–50 μM are reactive and abundant enough to limit its range between 50% and 10% of the cell diameter. Glutathione peroxidases are less abundant but their high reactivity would restrict the peroxide to a similar range. Other thiol proteins such as PTPs would not restrict diffusion to within the diameter of the cell and therefore should not undergo selective oxidation at the site of peroxide generation. This analysis does not therefore support the proposal that site-localized oxidation of other thiol proteins could occur if peroxiredoxins were inactivated.^{177,179,193} An association between oxidant generator and target that facilitates transfer of the oxidant or

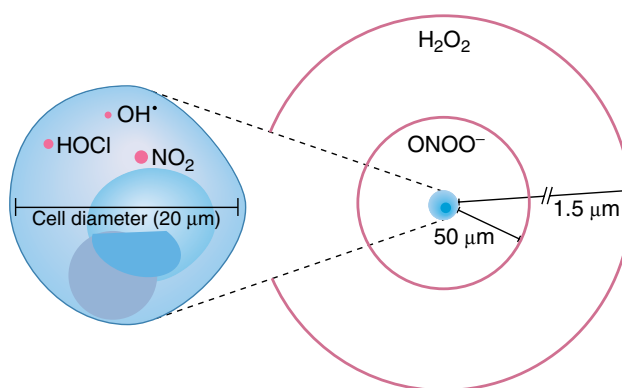


Figure 8 Estimated diffusion distances of selected oxidants in the presence of a nominal cellular GSH concentration of 2 mM, relative to the diameter of a generic cell (20 μm). The cell is scaled down 10-fold from left to right to illustrate that distances for peroxynitrite and hydrogen peroxide are greater than its diameter. The distance over which the oxidant concentration drops to a tenth has been taken as its diffusion distance. Rate constants ($\text{M}^{-1} \text{s}^{-1}$) for each oxidant reacting with GSH are 3×10^7 for NO_2 ¹⁹¹; 700 for peroxynitrite¹²⁴; 3×10^7 for hypochlorous acid¹²¹; 1×10^{10} for hydroxyl radicals.¹⁹² [Reproduced from Ref. 25. © Nature Publishing Group, 2008.]

confinement to a compartment that excludes other reactive substrates would be needed for this to occur.

9 FREE RADICAL SCAVENGING AND ANTIOXIDANT DEFENSE

In a biological context, an antioxidant is defined as a substance that delays, prevents, or removes oxidative modification to a target molecule.¹ Antioxidant activity is not a generic property of a substance, but will depend on context and what particular oxidant is responsible for the process under study. For example, many compounds (e.g., polyphenols, vitamin E) are excellent radical scavengers but react poorly with two-electron oxidants. Most commonly used “antioxidants” are ineffective scavengers of hydrogen peroxide. If a reaction is inhibited by *N*-acetylcysteine, for example, this would indicate that it is not directly mediated by hydrogen peroxide.

A scavenging reaction is protective only if the product is less reactive or damaging than the initial species. This is not always the case with radical reactions where scavenging of one radical generates another. Vitamin E is a good lipophilic antioxidant because the tocopheroxyl radical has low reactivity and can be removed by radical–radical reactions. However, in lipoprotein particles where opportunities for recombination are limited, it promotes lipid peroxidation (tocopherol-mediated peroxidation¹⁹⁴) unless it is scavenged by a secondary antioxidant such as ascorbate.

The main physiological radical-scavenging antioxidants in the aqueous phase are ascorbate and GSH. Ascorbate is effective because it reacts with a wide spectrum of radicals to generate ascorbyl radicals, and these disproportionate in preference to undergoing other reactions. As discussed in Section 5.1.3, radical scavenging by GSH and other thiols is effective only because cells have an efficient mechanism for removing oxidizing and potentially damaging thiyl radicals. Comparing ascorbate and GSH, the lower reduction potential of ascorbate makes it the better one-electron reductant. Ascorbate can also intercept thiyl radicals,¹¹⁵ and in cells has been predicted to play the major role.¹¹⁷ Synergy has been seen between ascorbate acting as the main scavenger and GSH recycling the dehydroascorbate formed.¹⁹⁵ In cultured cells,

which contain little or no ascorbate, scavenging by thiols should be more dominant and redox reactions could be different from in ascorbate-replete tissues.

Synergism is equally relevant for dietary or pharmacological antioxidants. Even though compounds such as polyphenolics and carotenoids are good radical scavengers, dietary intake is unable to increase tissue concentrations sufficiently to impact on total radical-scavenging capacity.¹⁶⁴ To act as radical-scavenging antioxidants (and it should be noted that this mode of action is debatable), they would need to accumulate at a site of radical generation, or act synergistically to facilitate radical transfer to more abundant species such as ascorbate or GSH.

10 CONCLUSIONS: A CONTINUUM OF BIOLOGICAL DAMAGE, OXIDATIVE STRESS, AND REDOX REGULATION

From the early days of radiation chemistry, it was realized that free radicals and other ROS are capable of damaging and killing living organisms. Many deleterious reactions with biological molecules have been characterized. Numerous chemicals generate radicals as a result of metabolic activation, and release of superoxide and hydrogen peroxide by the mitochondrial electron transport can cause oxidative stress to the cell. In some cases, free radical generation has been linked to toxicity. Animals and plants also produce ROS to combat invading pathogens. However, many cells generate superoxide or hydrogen peroxide not as toxins but for the purpose of cell signaling or metabolic regulation.

So instead of the original view that ROS are strictly damaging and antioxidants are required to protect against this damage, it is now appreciated that there is a continuum of oxidative damage, oxidative stress, and redox regulation. Clearly, certain reactive oxidants can be directly damaging or cytotoxic. However, lesser damage or exposure to less reactive species can activate stress responses. The ultimate result may still be cell death, for example by apoptosis, but the response may also upregulate expression of proteins involved in protective pathways such as antioxidant activity, DNA repair, xenobiotic detoxification, and chaperone activity. At the other end of the spectrum,

ROS can regulate the activity of oxidant-sensitive enzymes involved in cell metabolism, growth, and development. In this context, antioxidants, including enzymes such as SODs or glutathione peroxidases, need to be considered as regulators of this redox activity and not strictly for ROS removal.

There is still much to be discovered about how different responses to ROS integrate. It is simplistic to think just in terms of overall ROS exposure and we need to know what particular species are being generated in any situation, how much, and where the oxidants are located. It is also important to know what specific reactions are responsible for oxidative damage, stress responses, and redox regulation. There is extensive information available on the biomolecular modifications caused by individual oxidants, but which of these should be considered as direct damage and which as initiators of stress responses is not so clear-cut. Some stress response mechanisms are well characterized, such as the activation of the bacterial transcription factors oxyR and SoxS by hydrogen peroxide and superoxide, respectively.⁹⁹ Although information is still lacking on the molecular sites of oxidation, activation of the transcription factor Nrf2 by various oxidants and electrophiles is well established as a mechanism for upregulating protective proteins.¹⁹⁶ However, there are still large gaps in our knowledge of the oxidant-sensitive targets that initiate cell signaling responses, which oxidants they respond to, and how NADPH oxidase activation links into signaling pathways.

Location and quantification are important considerations for understanding how endogenously generated ROS act in cells or tissues. Reliable data are critically needed on how much superoxide or hydrogen peroxide is released by mitochondria, NADPH oxidases, and other enzyme systems. Development of methods that can provide this information is a high priority. Although site-localized production of ROS within cells clearly occurs, there are few cases where it has been established that the oxidant also act locally.⁴⁴ There are also unanswered questions regarding how a cell that is apparently generating significant amounts of hydrogen peroxide in the peroxisomes or the ER can respond to what would be expected to be more modest generation generated during signal transmission. These questions are starting to be addressed with the development of specific

oxidant-sensitive probes and detection methods that can follow events in live cells,^{197–199} and through characterizing the reactions that specific radicals and non-radical oxidants undergo in complex biological situations.

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Fundamentals of Controlled/Living Radical Polymerization

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1 INTRODUCTION

Commercial success of radical polymerization (RP) originates in minimal requirements for purification of monomers and solvents, convenient reaction conditions employed (typically room temperature to 100 °C, ambient pressure), large range of radically polymerizable monomers, and their facile copolymerization. Approximately 50% of all synthetic polymers are currently made via RP processes. The range of monomers is larger than that for any other chain polymerization because radicals are tolerant to many functionalities, including acidic, hydroxy, and amino groups. RP is not affected by water and protic impurities and can be carried out in bulk, solution, aqueous suspension, emulsion, dispersion, and so on. In conventional RP, high molecular weight (MW) polymers are formed at early stages of the polymerization, and neither long reaction times nor high conversions are required, in sharp contrast to step-growth polymerization.

However, RP has some limitations, especially in comparison with ionic processes that provide facile routes to living polymers. For a polymerization to be considered “living,” the contribution of chain breaking reactions such as termination and transfer should be negligible. Although transfer is not a major issue in RP when the appropriate conditions are applied, termination is much more difficult to be avoided and is a major limitation of

RP. In contrast to ionic reactions, in which cations or anions do not react via bimolecular termination, radicals terminate with a diffusion-controlled rate. In order to form high MW polymers, the relative probability of such termination must be minimized. This is accomplished by running RP at very low concentrations (from ppb to ppm) of propagating radicals. The concentrations of growing species are thus much lower in RP than in carbanionic or ring-opening polymerizations. In RP, a steady concentration of radicals is established by balancing the rate of termination with that of initiation. The rate of propagation is much faster than the rate of initiation/termination (as required to keep radical concentration low). Therefore, chains are continuously generated and it is not possible to prepare (co)polymers with controlled architecture by conventional RP. As discussed in other articles (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications and Kinetics of Polymerizations**), in RP, a propagating radical reacts with monomer approximately every 1 ms and chains typically terminate after ≈ 1 s, during which time high MW polymer is formed (degree of polymerization (DP) ≈ 1000). At any given moment of the polymerization, the number of growing chains which can be functionalized or chain-extended is very small (i.e., $<0.1\%$), unlike in ionic living polymerization, which is essentially carried out with instantaneous initiation and without chain breaking reactions.

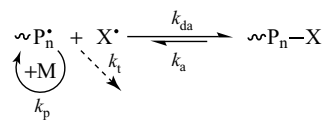
Thus, it has not been possible to prepare well-defined (co)polymers via conventional RP. However, new approaches that exploit equilibria between growing radicals and dormant species have been recently developed to minimize the proportion of terminated chains in RP. Such controlled RPs with reversible deactivation (controlled/living radical polymerization (CRP), IUPAC recommends the term *controlled reversible-deactivation radical polymerization*) are mechanistically similar to conventional RP methods and proceed through the same reactive intermediates. However, the proportion of terminated chains in CRP is dramatically reduced from >99.9% to circa less than 10% and sometimes even less than 1%. Since termination cannot be entirely avoided in CRP, these systems are never living at a level of anionic polymerization. However, the degree of control is often sufficient to attain many desirable material properties.

In this article, the fundamentals of controlled RP are first summarized and followed by the brief description of stable free radical polymerization (SFRP), atom transfer radical polymerization (ATRP), and reversible addition–fragmentation transfer (RAFT), as an example of degenerative transfer (DT) processes. All CRP systems enable the synthesis of many well-defined copolymers with novel architectures, compositions, and functionalities. These features and some possible applications of these materials are not discussed here, as they are covered in detail in articles devoted to particular polymerization methods (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**, **Nitroxide-Mediated Polymerization and its Applications**, **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**, and **Sb, Bi, Te, and I-Transfer Polymerization and Applications**).

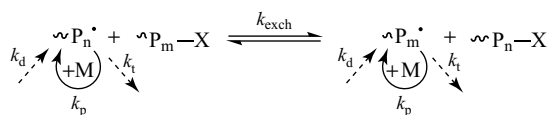
2 CONTROLLED REVERSIBLE-DEACTIVATION RADICAL POLYMERIZATION

2.1 General Concepts

Controlled synthesis of polymeric materials requires minimization of chain breaking reactions and simultaneous growth of all chains. A prerequisite



Scheme 1



Scheme 2

of fast initiation and very slow termination seems to disagree with the fundamental principles of RP, in which steady state of radical concentration is achieved by equal rates of initiation and termination. However, such a scenario was realized by the development of controlled/“living” systems in which the active propagating radicals are intermittently formed. This concept, originally applied to cationic ring-opening polymerization,¹ was later successfully extended to carbocationic systems.²

A dynamic equilibrium between propagating radicals and various dormant species is the most important feature of all CRP systems.^{3,4} There are two types of equilibria. Radicals may be reversibly trapped in a deactivation/activation process, according to Scheme 1 or they can be involved in a degenerative exchange process (Scheme 2).

The first approach is more widely used and relies on the persistent radical effect (PRE).^{5,6} In systems obeying the PRE, newly generated radicals are rapidly trapped in a deactivation process (with a rate constant of deactivation, k_{da}) by species X (which is typically a stable radical such as a nitroxide^{7,8} or an organometallic species such as a cobalt porphyrine^{9,10}). The dormant species are activated (with a rate constant k_a) either spontaneously/thermally, in the presence of light, or with an appropriate catalyst (as in ATRP)^{11,12} to reform the growing centers. Radicals can propagate (k_p) and also terminate (k_t). However, persistent radicals (X) cannot terminate with each other but only (reversibly) cross-couple with the growing species (k_{da}). Thus, every act of termination between growing radicals is accompanied by the irreversible accumulation of X. Its concentration

progressively increases with time, following a peculiar one-third power law.^{4–6} The growing radicals then predominantly react with X, which is present at >1000 times higher concentration, rather than with themselves. As the concentration of X increases with time, the concentration of radicals decreases (as the equilibrium in Scheme 1 becomes shifted toward the dormant species) and the probability of termination is diminished.

In systems based on the PRE, a steady state of growing radicals is established through the activation–deactivation process but *not* through initiation–termination. Because initiation can be much faster than termination, it essentially gives rise to the simultaneous growth of all chains. In contrast, systems that employ DT are *not* based on the PRE. They follow typical RP kinetics with slow and continuous radical supply (e.g., with the rate constant of decomposition of thermal initiator, k_d) and termination (k_t). The transfer agent is at much larger concentration than radical initiator and thus formally plays the role of a dormant species.

Good control over MW, polydispersity, and chain architecture in all CRP systems requires fast exchange between active and dormant species. Ideally, a growing radical should react with only a few monomer units before it is converted back into a dormant species. Consequently, it would remain active only for a few milliseconds and would return to the dormant state for a few seconds or longer. The growth of a polymer chain may consist, for example, of ~1000 periods of ~1-ms activity, interrupted by ~1000 periods of ~1-min dormant states. The lifetime in the active state is thus comparable to the lifetime of a propagating chain in conventional RP (~1000 ms, i.e., ~1 s). However, because the entire propagation process in CRP may take ~1000 min or ~1 d, this facilitates various synthetic procedures, such as functionalization or chain extension, block copolymerization, and so on. Also, simultaneous growth of all chains enables multidirectional growth of chains and preparation of stars, combs, molecular brushes, and other complex architectures.¹³

2.2 Similarities and Differences between RP and CRP

Since RP and CRP proceed via the same radical mechanism, they exhibit similar chemo-, regio-, and

stereo-selectivities and can polymerize a similar range of monomers. If RP and CRP are carried out with the same rate, the absolute amount (concentration) of terminated chains is similar (not exactly the same, due to chain length-dependent termination (CLDT)), because concentrations of radicals are similar. However, in RP, essentially all chains are dead, but in CRP, dead chains form only a small fraction (<10% of all chains) due to a large amount of dormant species. Nevertheless, several important differences between CRP and RP exist and are summarized below.

1. The lifetime of growing chains is extended from ~1 s in RP to more than 1 h in CRP. This is done by the involvement of dormant species and intermittent reversible activation.
2. In RP, a steady-state radical concentration is established with similar rates of initiation and termination, whereas in CRP systems based on the PRE (ATRP and SFRP), a steady radical concentration is reached by balancing the rates of activation and deactivation.
3. In conventional RP, initiation is slow and a relatively large fraction of free radical initiator is often left unconsumed at the end of the polymerization. In most CRP systems, initiation is fast and all chains start growing at essentially the same time, ultimately enabling control over chain architecture.
4. In RP, nearly all chains are dead, whereas in CRP, the proportion of dead chains is usually <10%.
5. Polymerization in CRP is often slower than in RP, but this does not necessarily have to be the case. Rates may be comparable, especially if the targeted MW in CRP is relatively small.
6. In conventional RP, termination predominantly occurs between long chains and constantly generated new chains. In CRP systems based on the PRE (ATRP and SFRP), at the early stages, all chains are short (most probable termination), but as they become much longer, the termination rate significantly decreases. In DT processes (e.g., RAFT), new chains are constantly generated by a small amount of conventional initiator, and therefore, termination is more likely.
7. There are also several degrees of control molecular architecture unique for CRP. This includes preparation of polymers with predetermined

MW and designed MW distribution and complex architectures.

8. Use of multifunctional initiators provides new avenues to concurrent and multidirectional growth of polymer chains in CRP, resulting in well-defined star, graft, or even brush macromolecules. These special features enable formation of many hybrid materials. Such architectures are not available from RP.
9. Copolymerization of comonomers with different reactivity ratios results in mixture of copolymers with different composition due to continuous drift in comonomer feed in RP. In CRP, the same copolymerization results in novel gradient copolymers with essentially identical structure among all chains.
10. Chain capping agents from dormant species in CRP can be used for subsequent functionalization and formation of heterotelechelic or homotelechelic polymers. In CRP, end functionalities can be incorporated only via transfer reactions.

3 HOW FAST CAN A CRP BE CONDUCTED WITH PRESERVED CHAIN END FUNCTIONALITY?

Faster RP requires higher concentration of radicals, which in turn results in more pronounced termination. Therefore, chain end functionality (CEF) and control are progressively lost at higher polymerization rate in any CRP. Nevertheless, there is some confusion about how fast can any CRP be with sufficiently preserved CEF? Can we have ultrafast polymerization leading to ultrahigh MW and with preserved "livingness"? Which are the most important parameters that influence fraction of dead chains versus polymerization rate to the largest extent? Does this fraction depend on the mechanism of polymerization (e.g., ATRP vs RAFT)? Kinetic modeling will help to answer these questions.

Independently of the mechanism of exchange between active and dormant species, propagation and termination steps are the same in any RP. The rate of propagation (R_p) is proportional to the propagation rate constant (k_p), the concentrations of monomer ($[M]$), and propagating radical ($[R^*]$) as

expressed in (1), where t is the polymerization time:

$$R_p = -\frac{d[M]}{dt} = k_p[M][R^*] \quad (1)$$

According to (1), for the same monomer, faster polymerization requires higher $[R^*]$. However, increased radical concentration also results in faster bimolecular termination:

$$R_t = \frac{d[T]}{dt} = 2k_t[R^*]^2 \quad (2)$$

where k_t is the termination rate constant and $[T]$ is the concentration of the dead chains resulting from radical termination. Thus, the unavoidable penalty for faster polymerization (i.e., higher radical concentration) is progressively higher proportion of terminated chains and loss of livingness. Nevertheless, very fast CRPs with preserved control or functionality have been claimed in literature.^{14,15} The fraction of extendable chains is defined by preserved CEF. Consequently, for any CRP a minimal time is required to preserve a specific value of CEF. This time primarily depends on the type of monomer (propagation rate constant and termination rate constant), targeted DP (DP_T), initial monomer concentration, and targeted monomer conversion.

Retention of CEF is needed for synthesis of various telechelic polymers, segmented copolymers, and, especially, block copolymers.

3.1 Dead Chain Fraction in CRP

In CRP systems, linear first-order kinetic plots are often observed, indicating constant radical concentration, due to either steady state by equal rates of initiation and termination (DT systems) or balanced rates of activation and deactivation and negligible termination for PRE systems. At constant $[R^*]$, the integration of (1) gives the relationship between polymerization time (t), monomer conversion (p), and $[R^*]$:

$$\ln(1 - p) = -k_p[R^*]t \quad (3)$$

The concentration of terminated chains can be calculated by the integration of (2):

$$[T] = 2k_t[R^*]^2t \quad (4)$$

The combination of (3) and (4) yields the concentration of terminated chains as a function of time and conversion:

$$[T] = \frac{2k_t[\ln(1-p)]^2}{k_p^2 t} \quad (5)$$

The DP_T is defined as the ratio of initial monomer concentration, $[M]_0$, to the concentration of living polymers, $[P-X]$ (equal to initiator concentration, $[R-X]_0$, for quantitative initiation). Hence, the dead chain fraction (DCF) can be expressed by the following equation:

$$DCF = \frac{[T]}{[R-X]_0} = \frac{2DP_T k_t [\ln(1-p)]^2}{[M]_0 k_p^2 t} \quad (6)$$

To simplify calculations, the decrease in the number of chains by bimolecular combination (corresponding to quantitative disproportionation) is neglected. Thus, the DCF defines the fraction of living chains lost from the initial living chains. Knowing DCF, one can calculate the CEF by the following equation:

$$CEF = 1 - DCF \quad (7)$$

Equation (6) indicates that there are several potential strategies that can be employed to decrease the fraction of dead chains: reducing the rate of polymerization (larger t), quenching the reaction at lower monomer conversion (smaller p), targeting lower DP_T , using higher initial monomer concentration (larger $[M]_0$), or choosing monomers with an inherently lower value of $k_t/(k_p)^2$. In the following discussion, we will individually discuss all parameters involved in (6) and determine how they influence CEF.

3.2 Minimal Polymerization Time in CRP

Since (6) includes six parameters, it is convenient to fix some parameters and test how the remaining one or two parameters affect the DCF. For example, in the bulk polymerization of methyl methacrylate (MMA) at 80 °C ($k_t = 9.00 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $k_p = 1300 \text{ M}^{-1} \text{ s}^{-1}$, and $[M]_0 = 9.34 \text{ M}$) the effect of polymerization time, monomer conversion, and DP_T on DCF can be correlated. DCF is inversely

proportional to polymerization time when targeting a certain DP_T and a specific degree of conversion:

$$DCF = C_1 t^{-1}, C_1 = \frac{2DP_T k_t [\ln(1-p)]^2}{[M]_0 k_p^2} \quad (8)$$

In (8), C_1 is a constant when every parameter except t is fixed. Figure 1 illustrates the relationship of DCF and the polymerization rate in two ways. In Figure 1a, three different DP_T s are targeted at 60% conversion, while Figure 1b illustrates effect of different degrees of conversion for a targeted $DP_T = 500$. Both procedures show a similar trend that a reduced fraction of dead chains, or increased livingness, can be achieved by slowing down the polymerization. Both higher DP_T and higher conversion give larger value for C_1 . However, curves for higher DP_T or higher conversion give steeper slope than the lower values. For example, in Figure 1a, the DCF decreased with polymerization time and this decrease was the most significant for $DP_T = 1000$. Figure 1a shows that targeting $DP_T = 1000$ at 60% conversion in 15 h leads to 18% of dead chains ($CEF = 82\%$). Also, to preserve 95% of chains at 60% conversion while targeting poly(methyl methacrylate) (PMMA) with $DP_T = 500$ requires 27 h. In addition, for $DP_T = 500$ and conversion 80%, reaction performed within 15 h leads to 27% of dead chains.

3.3 Influence of Conversion on DCF

DCF is also affected by conversion as shown by the following equation:

$$DCF = C_2 [\ln(1-p)]^2, C_2 = \frac{2DP_T k_t}{[M]_0 k_p^2 t} \quad (9)$$

Polymerization targeting a certain DP_T will lose more living chains when achieving higher conversion within the same time. Figure 2 illustrates this in two ways, using again MMA bulk polymerization at 80 °C, as an example. According to Figure 2, targeting 70% conversion in 40 h leads to 6% of dead chains for $DP_T = 500$. For $DP_T = 1000$ with 30-h targeted polymerization time, the reaction only loses 5% of living chains at 50% conversion.

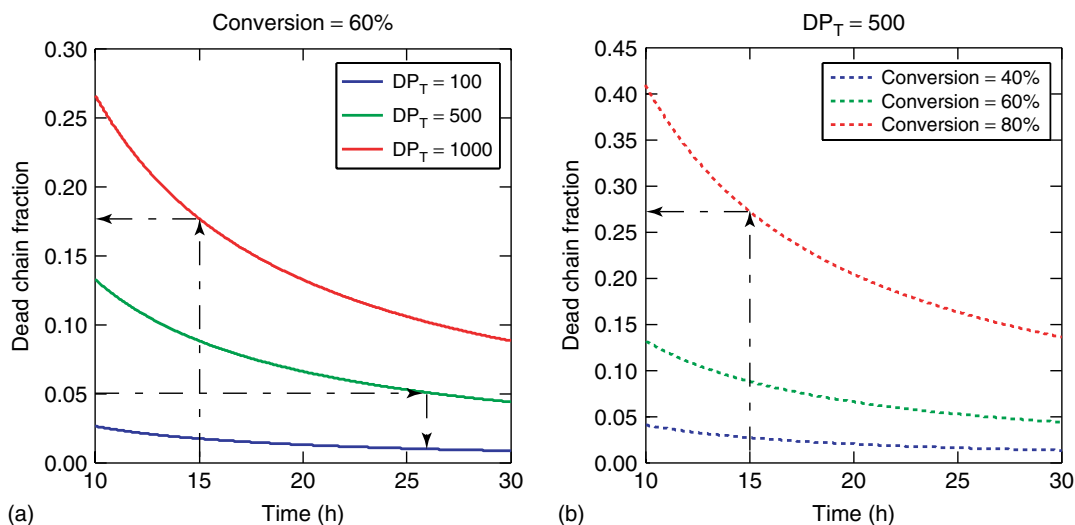


Figure 1 Plots of DCF versus polymerization time for bulk polymerization of MMA at 80 °C. (a) Three different DP_T s at 60% conversion and (b) three different conversions for $DP_T = 500$. [Reprinted with permission from Ref. 14. American Chemical Society.]

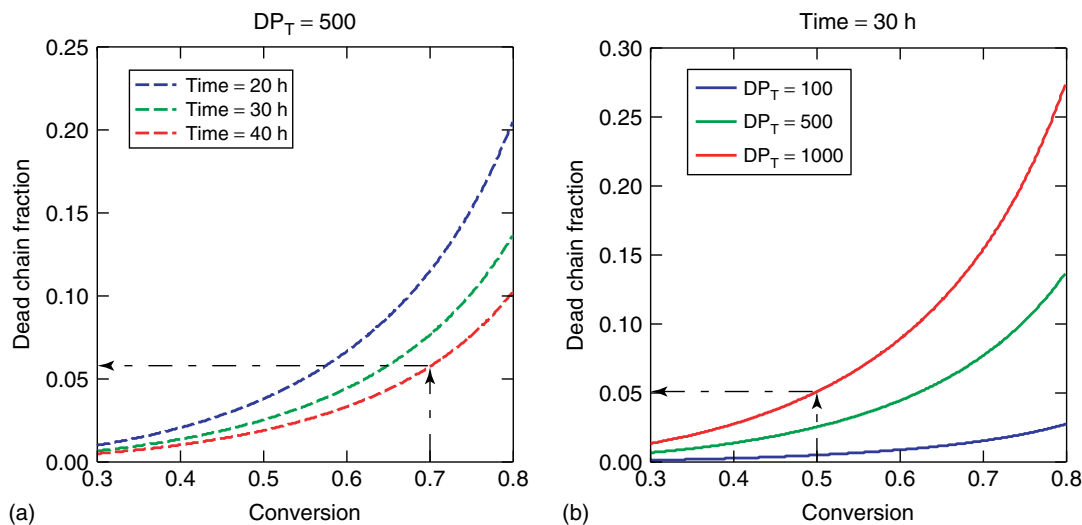


Figure 2 Plots of DCF versus conversion for bulk polymerization of MMA at 80 °C. (a) Three different rates of polymerization for $DP_T = 500$ and (b) three different DP_T values in 30 h. [Reprinted with permission from Ref. 14. American Chemical Society.]

3.4 Influence of DP_T on DCF

To retain the same CEF at the same conversion, the systems with higher DP_T require slower rate of polymerization. The relationship between DCF and DP_T (10) for bulk polymerization of MMA at 80 °C is illustrated in Figure 3. The linear slopes decrease with polymerization time but increase

with conversion. Figure 3a shows that 89% CEF can be preserved when targeting $DP_T = 800$ and achieving 60% conversion within 20 h. Reaching 80% conversion within 30 h results in 16% of dead chains when targeting $DP_T = 600$:

$$DCF = C_3 \times DP_T, C_3 = \frac{2k_t[\ln(1-p)]^2}{[M]_0 k_p^2 t} \quad (10)$$

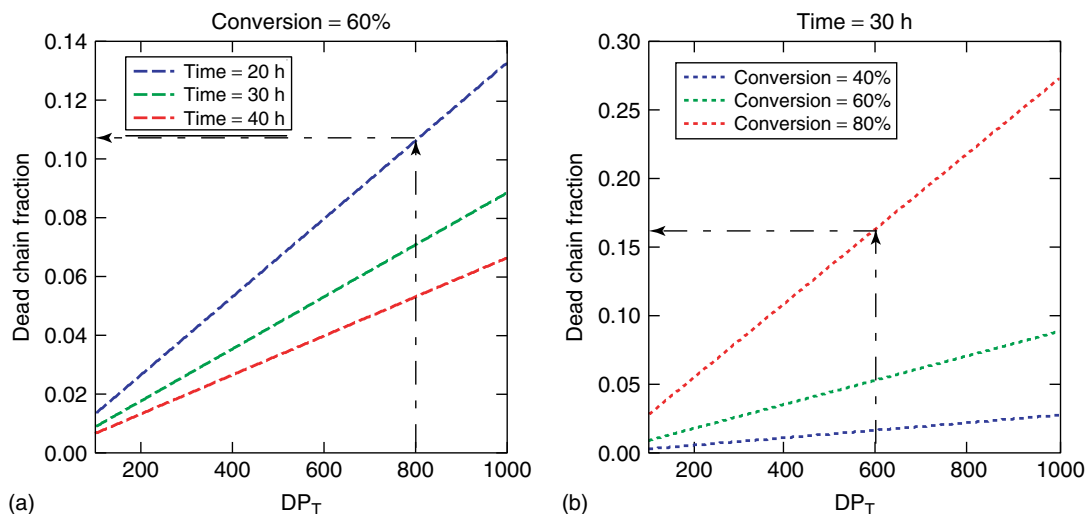


Figure 3 Plots of DCF versus DP_T for bulk polymerization of MMA at 80 °C. (a) Three different rates of polymerization at 60% conversion and (b) three different conversions reached in 30 h. [Reprinted with permission from Ref. 14. American Chemical Society.]

3.5 Preparation of Polymers with a Specific DP

A polymer with the same specific DP can be prepared by targeting higher DP_T at lower conversion or targeting lower DP_T at higher conversion. Which approach provides lower DCF within the same time? Both higher DP_T and higher conversion lead to more dead chains at the same polymerization rate. Since DP can be expressed as the product of DP_T and conversion, that is, $DP = DP_T \times p$, (6) converts to

$$DCF = \frac{2DP_T k_t}{[M]_0 k_p^2 t} \frac{[\ln(1-p)]^2}{p} \quad (11)$$

In (11), the second term of the product ($[\ln(1-p)]^2/p$) is an increasing function of p . Since the first term in the equation contains two rate constants and three fixed values, it remains constant and DCF increases with p . Hence, the combination of higher DP_T and lower conversion gives less dead chains when targeting a certain polymer DP within the same polymerization time.

Figure 4 shows an example of the DCF formed during formation of PMMA with different DPs. In this plot, every point on the three-dimensional surface stands for one polymerization reaction stopped within 5 h. In three curves, the product of conversion and DP_T is a fixed value. Along the

same curve, the desired DP does not change, while the trend of DCF obeys the above conclusion. For instance, to synthesize PMMA with $DP = 60$, one could target $DP_T = 75, 100$, and 150 , but stop the reaction at 80, 60, and 40% conversion, respectively. Based on the data in Figure 4, those three systems will generate polymers with DCF = 12.3, 5.3, and 2.3%, respectively. Thus, synthesis of $DP_T = 150$ at 40% conversion gives five times lower DCF than aiming at $DP_T = 75$ at 80% conversion in preparation of PMMA with $DP = 60$.

3.6 Influence of Initial Monomer Concentration on DCF

Previous example showed that polymerization diluted by monomer is better controlled. Can dilution by solvent also provide better control? The addition of a solvent may sometimes be necessary to improve the solubility of the polymer or catalyst or to control the viscosity of the system. The role of the solvent is not the same as that of the monomer and (12) shows that solvent is not a good diluent for decreasing DCF because it actually reduces $[M]_0$, correspondingly increasing DCF:

$$DCF = \frac{C_4}{[M]_0}, C_4 = \frac{2DP_T k_t [\ln(1-p)]^2}{k_p^2 t} \quad (12)$$

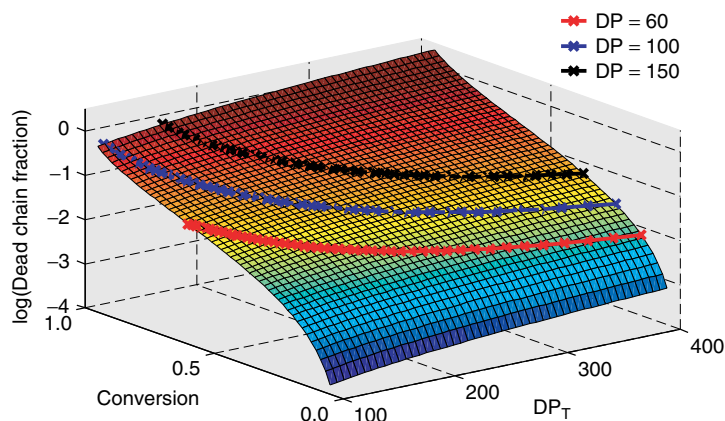


Figure 4 Plot of logarithmic value of DCF versus conversion and DP_T for PMMA for three different desired DPs. Conditions: 80 °C, bulk polymerization, 5 h. [Reprinted with permission from Ref. 14. American Chemical Society.]

In comparison with bulk polymerization, when the monomer is diluted by solvent, the radical concentration must increase in order to maintain the same polymerization rate. This causes more termination at the same rate of polymerization. Figure 5 shows the DCF after 10 h for a MMA polymerization conducted at 80 °C targeting $DP_T = 500$. At the same conversion, bulk polymerization always gives a lower DCF. Selecting the point at 70% conversion from each of these three curves, bulk polymerization generates only 7.7% of dead chains, while the other two DCFs are 11.5 and 15.3%, respectively.

3.7 Effect of k_t and k_p Values on DCF and Minimal Polymerization Time

The above conclusions are universal for any CRP. Higher CEF requires slower polymerization, higher monomer concentration, lower DP_T , and stopping polymerization at lower conversion. However, the relationship between “how fast” and “how living” a CRP is, strongly depends on the polymerized monomers and more specifically on k_p and k_t values. Equation (13) shows that lower $k_t/(k_p)^2$ value gives less dead chains under specific condition (constant C_5), thus low k_t and high k_p are both desired:

$$DCF = C_5 \frac{k_t}{k_p^2}, \quad C_5 = \frac{2DP_T[\ln(1-p)]^2}{[M]_0 t} \quad (13)$$

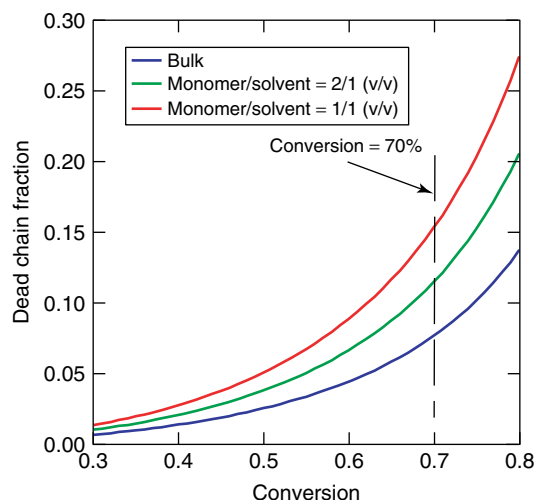
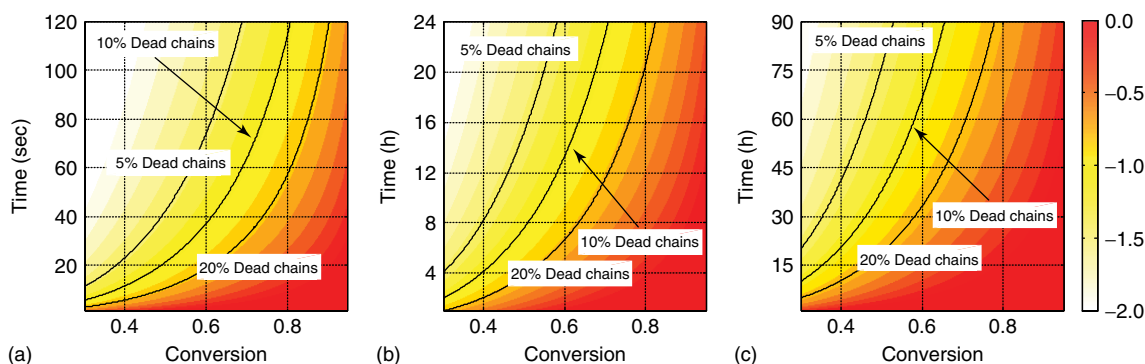


Figure 5 Comparison of DCFs for three different initial monomer concentrations. Conditions: 80 °C, $[MMA]_0/[R-X]_0 = 500/1$, 10 h. [Reprinted with permission from Ref. 14. American Chemical Society.]

In RP, termination is often a diffusion-controlled process and difference between termination rate constants for various monomers is not large, although it depends on chain length and conversion. However, propagation rate constants depend strongly on monomer structure. For example, at 80 °C, the k_p of styrene (St) is circa twice smaller than that of MMA but nearly two orders of magnitude smaller than that of methyl acrylate (MA). Table 1 shows corresponding rate constants and values for 90% preservation of CEF for these three

Table 1 Minimal time for the polymerization of MA, MMA, and St with CEF = 90%.^a

Monomer	k_p (M ⁻¹ s ⁻¹) ^b	k_t (M ⁻¹ s ⁻¹) ^b	DP _T = 500		DP _T = 100	
			$p = 60\%$	$p = 90\%$	$p = 60\%$	$p = 90\%$
MA	47 400	1.10×10^8	37 s	4 min	7 s	1 min
MMA	1 300	9.00×10^7	13.3 h	83.9 h	2.7 h	16.8 h
St	665	1.10×10^8	2.8 d	17.5 d	0.6 d	3.5 d

^a Conditions: 80 °C, [M]₀/[R-X]₀ = DP_T/1, bulk polymerization.^b k_p and k_t values were obtained or estimated from the literature.^{16–20} k_t value is the sum of k_{tc} (the combination rate constant) and k_{td} (the disproportionation rate constant).**Figure 6** Contour maps for DCF as a function of conversion and polymerization time for different monomers. (a) MA, (b) MMA, and (c) St Conditions: 80 °C, [M]₀/[R-X]₀ = 500/1, bulk polymerization. Scale bar represents the logarithmic value of DCF.

monomers. Three “contour maps” are plotted in Figure 6 for the bulk polymerization of MA, MMA, and St, targeting the same DP_T = 500 at 80 °C. Each contour corresponds to the logarithmic value of DCF and three solid lines show the relationship between reaction time and conversion for DCF = 5, 10, and 30%. For example, it is possible to prepare poly(methyl acrylate) (PMA) with 90% preserved CEF for DP_T = 500 at 60% conversion in 37 s. However, as highlighted by bold entries in Table 1, the same control requires 13 h for PMMA and 2.8 d for polystyrene (PS)! The other entries show the effect of DP_T for 500 and 100 values for PMA at 90% conversion. The former requires 50 min but the latter only less than 1 min. Finally, the other entries show that the same CEF = 90% for PS and DP_T = 100 requires 3.5 d at 90% but only 0.6 d at 60% conversion.

3.8 Evaluation by CLDT

The “maps” shown in the figures were constructed for constant values of termination rate coefficients.

However, since termination is diffusion limited, it depends on viscosity and chain length. Thus, the CLDT rate coefficients strongly depend on both conversion and DP.²⁰ The effect of CLDT rate coefficient was analyzed as a function of DP and conversion for bulk polymerization of MMA and MA at 80 °C.^{21,22} Figure 7 provides a more accurate evaluation of DCF of PMMA by integrating the CLDT data. The system with DP_T = 500 (Figure 7a) does not show a significant difference compared to the non-CLDT evaluation. However, in the DP_T = 5000 system (Figure 7b), the curves for specific DCFs display a dramatic drop in termination reactions, which means that much faster polymerization can be conducted for a system with a high DP_T. For example, to preserve 90% CEF at 50% conversion targeting PMMA with DP_T = 5000, it requires 40 h, which is nearly twice shorter time than that predicted by non-CLDT.

Although the required rate of polymerization for acceptable CEF depends on the type of monomer, there are some other possibilities of decrease $k_t/(k_p)^2$ via tuning various reaction conditions. For example, an increase in temperature results in an

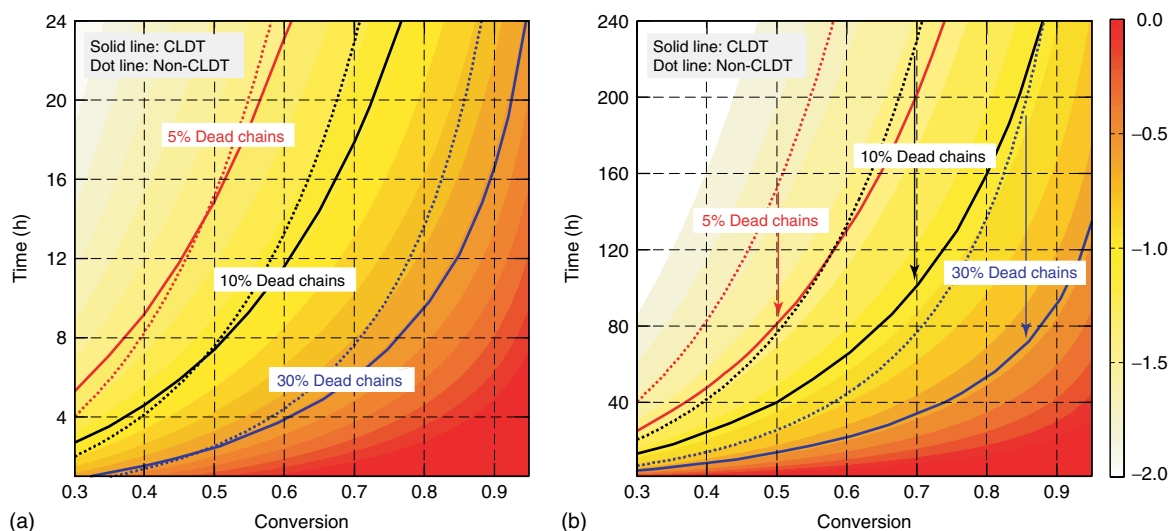


Figure 7 Plots comparing DCF of PMMA computed with and without CLDT. (a) $DP_T = 500$ and (b) $DP_T = 5000$. Conditions: 80°C , $[M]_0/[R-X]_0 = 500/1$, bulk polymerization. Scale bar represents the logarithmic value of DCF. [Reprinted with permission from Ref. 14. American Chemical Society.]

increase in the polymerization rate without a significant loss of CEF since higher temperature increases k_p much more than k_t , due to lower activation energy of termination compared to that of propagation. However, there is a limit in temperature increase due to chain transfer (e.g., acrylates), self-initiation (e.g., St), and depropagation (e.g., methacrylates). Pressure is another important parameter.²³ Radical propagation has a negative volume of activation, while termination has a positive one and higher pressure not only enhances k_p but also reduces k_t . This strategy has been successfully applied to synthesize high MW polymers by activators generated by electron transfer (AGET) ATRP²⁴ and RAFT polymerization.^{25–28}

3.9 CEF in CRP Systems Involving Extra Radical Initiators

There are several CRP processes relying on DT mechanism, such as RAFT polymerization, that employs radical initiators (e.g., azobisisobutyronitrile (AIBN)). To this category also belong the initiators for continuous activator regeneration (ICAR) ATRP. The radical initiators continuously generate new chains. Thus, there are two populations of living chains, those generated from the original (macro)initiator R-X and newly generated, also

extendable chains I-X and I-P-X. The R group may play an important role. It can be the first block in a block copolymer, and it can represent a surface in surface-initiated CRP, natural product in bioconjugates, or a specific functionality in telechelics. Thus, although I-X and I-P-X species can grow, they will not contain an important R moiety. Therefore, it is useful to define two types of CEF in the systems involving radical initiators. The first definition is similar to the general case for CRP, which is the fraction of all extendable chains (P-X), and the second one describes the fraction of chains with dual functionality (R-P-X). Since extendable species include initiator and living polymer, to simplify the following discussion, we define [R-P-X] as the total concentration of dual functionalized chains, including R-P-X chains and original initiator R-X. Similarly, [I-P-X] contains I-P-X chains and newly generated initiator I-X. Thus, [P-X] is the sum of [R-P-X] and [I-P-X].

Since ICAR ATRP and other DT processes (as RAFT polymerization) follow similar kinetics, the results provide more general conclusions for all DT systems. ICAR ATRP (or RAFT) is accelerated in the presence of increased concentration of radical initiators. However, although such systems, also named as hybrid ATRP¹⁵, result in faster polymerization, they also result in a larger loss of CEF. The number of polymer chains with dual

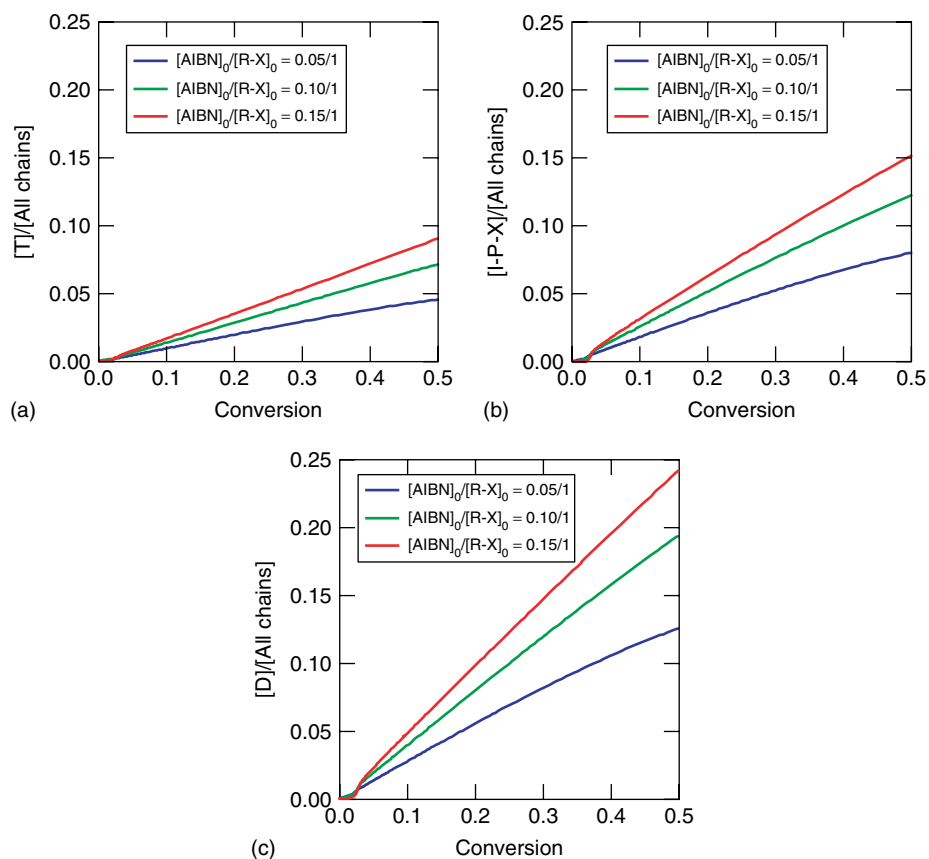


Figure 8 Plots of DCF in ICAR ATRP. (a) Fraction of termination chains, (b) fraction of α -I group-terminated extendable chains, and (c) fraction of all dead chains. Conditions: 60 °C, $[St]_0/[EtBrIB]_0/[CuBr_2]_0/[TPMA]_0/[AIBN]_0 = 200/1/0.01/0.01/x$ ($x = 0.05, 0.10, 0.15$), $St/acetoneitrile = 2/1$ (v/v) ($R-X = EtBrIB$). [Reprinted with permission from Ref. 14. American Chemical Society.]

α , ω -functionality drops significantly with increased radical initiator concentration.

$[T]$ is still defined as the concentration of terminated chains, including those forming between two polymeric radicals, between one polymeric radical and one initiator radical ($I^{\bullet}$ or $R^{\bullet}$). $[D]$ is defined as the concentration of all types of dead chains, including nonextendable chains and those extendable chains possessing an α -I group. Thus, a new definition for DCF is expressed by the following equation:

$$DCF = \frac{[D]}{[\text{All chains}]} = \frac{[T] + [I-P-X]}{[\text{All chains}]} \quad (14)$$

In ICAR and RAFT systems, the number of extendable chains does not change, since lost $R-X$ and $R-P-X$ chains are replenished by $I-X$ and $I-P-X$

chains. Figure 8a and b shows the fractions of terminated chains and α -I group-terminated extendable chains. The increase in $[AIBN]_0$ increases all types of dead chains (all chains except $R-X$ and $R-P-X$ ones), as illustrated in Figure 8c. Thus, although formally, concentration of extendable chains does not change, with 15% AIBN, there are already 9% of terminated chains at 50% conversion and also only 76% of chains with dual-CEF left!

The difference in CEF between CRP with and without radical initiator can be compared using ICAR ATRP and normal ATRP. In order to provide a fair comparison, specific conditions were chosen for these two polymerizations to proceed at a similar rate. Under these conditions, the differently defined CEF values are shown in Figure 9. The CEF in Figure 9a is defined as the fraction of extendable chains among initial living chains. For normal

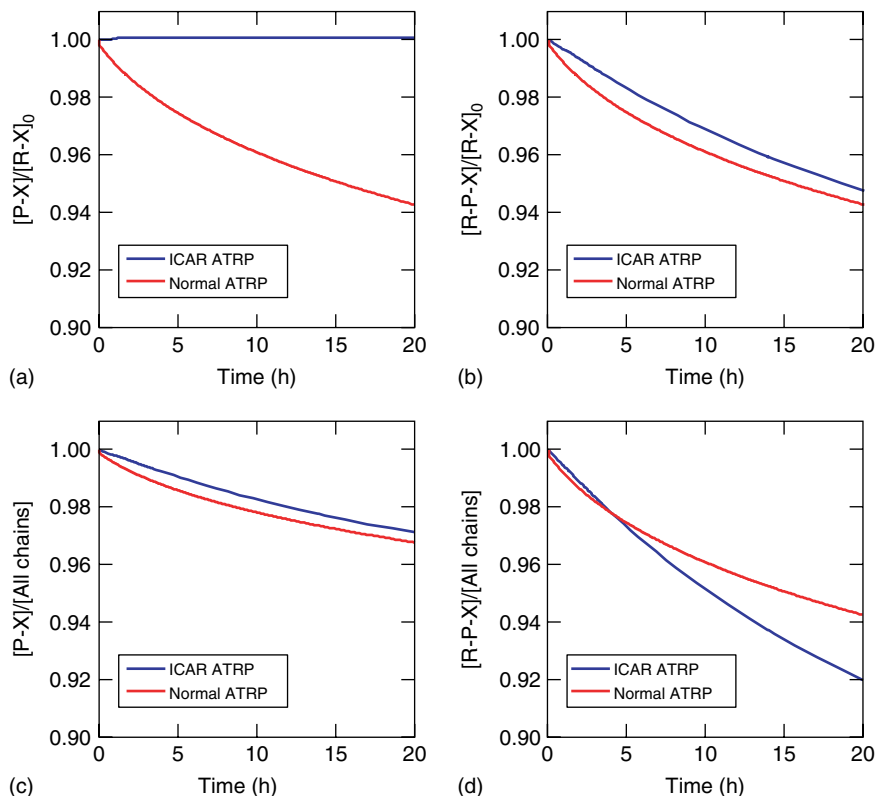


Figure 9 Comparison of CEFs in ICAR ATRP, and normal ATRP according to different CEF definitions. (a) Fraction of extendable chains among initial living chains (initiator), (b) fraction of dually functionalized chains among initial living chains, (c) fraction of extendable chains among all chains, and (d) fraction of dually functionalized chains among all chains. Conditions: ICAR ATRP, 60 °C, $[St]_0/[EtBrB]_0/[CuBr_2]_0/[TPMA]_0/[AIBN]_0 = 200/1/0.01/0.01/0.05$, $St/acetoneitrile = 2/1$ (v/v); normal ATRP, 60 °C, $[St]_0/[EtBrB]_0/[CuBr]_0/[CuBr_2]_0/[PMDTA]_0 = 200/1/0.945/0.055/1$, $St/acetoneitrile = 2/1$ (v/v) (PMDTA: N,N,N',N'',N'' -pentamethyldiethylenetriamine; R-X = EtBrB). [Reprinted with permission from Ref. 14. American Chemical Society.]

ATRP, the concentration of extendable chains decreases due to unavoidable termination reactions, leading to the accumulation of persistent radicals (CuX_2/L). However, according to the conservation of X groups and steady state in ICAR ATRP, every lost X through termination is replenished from a newly generated radical. Thus, the number of extendable chains does not decrease. Figure 9b presents the fraction of dually functionalized chains among initial living chains. The curve for normal ATRP is similar to the one in Figure 9a, as every P-X chain in normal ATRP is terminated with α -R group. Although concentration of extendable chains in ICAR ATRP is constant, due to the replacement of some R-P-X and R-X by I-X and I-P-X, the curve is lower than that in Figure 9a.

The ICAR ATRP curve in Figure 9b is higher than the one for normal ATRP because the termination in ICAR ATRP also involves I-P' species, while the termination in normal ATRP only leads to the decrease in [R-P-X]. Figure 9c illustrates the fraction of extendable chains among all chains present. In a normal ATRP, [all chains] decreases through bimolecular combination and the curve is higher than the corresponding one in Figure 9a. However, in an ICAR system, new chains are gained from the radical initiators and the increase in [all chains] is faster than its decrease caused by combination. Although the number of extendable chains is kept constant, the increase in [all chains] decreases their fraction in final product. The CEF (defined by (14)) shown in Figure 9d is the fraction

of dually functionalized extendable chains among all chains. The decrease in dual-CEF in ICAR system is faster than that in normal ATRP because of newly generated chains.

4 PERSISTENT RADICAL EFFECT

SFRP and ATRP systems are characterized by unusual nonlinear semilogarithmic kinetic plots that obey a peculiar power law. This kinetics was first elegantly explained by Fischer,⁵ who introduced the concept of the PRE in both organic reactions and macromolecular systems. As mentioned before, stable persistent radicals do not terminate, and hence, their concentration progressively increases with the reaction time, shifting the equilibrium in Scheme 3 toward the dormant species. Fischer, and later Fukuda, derived precise kinetic equations to correlate the amount of evolved persistent radical as a function of the overall equilibrium and termination rate constants.^{5,29}

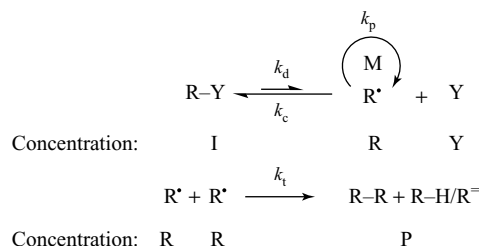
The essence of the PRE can be more clearly explained for systems not complicated by propagation (k_p) and CLDT. Such a simplified system, shown in Scheme 3, consists of three elementary reactions: dissociation (activation) of the alkoxyamine R-Y (k_d), cross-coupling (deactivation) of the transient radical R with persistent radical Y (k_c), and termination of two transient radicals to form product P (k_t).

In this case, the rates of formation of the persistent radical and of loss of the transient radical are given by (15) (the term $2k_t$ is used to be consistent with the earlier published papers):

$$\begin{cases} \frac{dR}{dt} = k_d I - k_c RY - 2k_t R^2 \\ \frac{dY}{dt} = k_d I - k_c RY = \frac{dR}{dt} + 2k_t R^2 \end{cases} \quad (15)$$

The two coupled differential equations were solved analytically by Fischer and independently by Fukuda. They proposed that the increase in concentration of deactivator (Y) should be proportional to $t^{1/3}$ and the loss of transient radical (R) proportional to $t^{-1/3}$ according to the following equation:

$$\begin{cases} Y = (6k_t K_{eq}^2 I_0^2)^{1/3} t^{1/3} \\ R = \left(\frac{K_{eq} I_0}{6k_t} \right)^{1/3} t^{-1/3} \end{cases} \quad (16)$$



Scheme 3

The dependence for the persistent radical Y should be valid in the time interval defined by (17), and (18) should be fulfilled:

$$t_L = \frac{4\sqrt{k_t} K_{eq}}{3I_0^{1/2} k_d^{3/2}} < t < t_U = \frac{I_0}{48K_{eq}^2 k_t} \quad (17)$$

$$K_{eq} < I_0 k_c / 16k_t \quad (18)$$

The dependences described in (15), derived by Fischer and Fukuda, used initial concentration of the initiator (I_0) rather than the actual one, I . However, initiator concentration constantly decreases with the progress of the reaction in all radical systems. It is therefore more accurate to use the actual concentration of the initiator to derive the kinetic equations for transient and persistent radicals, especially when the reactions proceed to higher conversion. A new equation for the evolution of persistent radical during the quasi-equilibrium stage was therefore derived.^{6,30} The derivation is based on the stoichiometric requirement that the amount of persistent radical is equivalent to the number of dead chains, that is, $I_0 - I = Y$, and the assumption that change in the persistent radical concentration is much higher than that for the propagating radicals ($dY/dt \gg -dR/dt$) after quasi-equilibrium is established.

Using variable I , the integration of (3) leads to the following expression:

$$\frac{I_0^2}{I_0 - Y} + 2I_0 \ln \frac{I_0 - Y}{I_0} - (I_0 - Y) = 2k_t K_{eq}^2 t \quad (19)$$

where the persistent radical concentration (Y) is the only variable on the left-hand side of the equation. In a new function $F(Y)$, the only variable is Y:

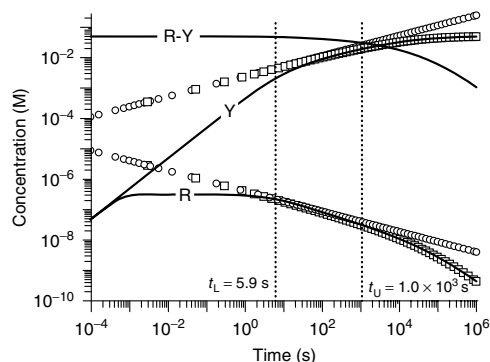


Figure 10 Evolution of concentrations of all species (solid lines) and concentrations of persistent radical predicted from equation (20) (□) and Fischer's equation (○); $k_d = 0.01 \text{ s}^{-1}$, $k_c = 5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $k_t = 2.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $I_0 = 0.05 \text{ M}$. $K_{eq}(\text{calc.}) = 2.0 \times 10^{-8} \text{ M}$. [Reprinted with permission from Ref. 30. Copyright 2006 American Chemical Society.]

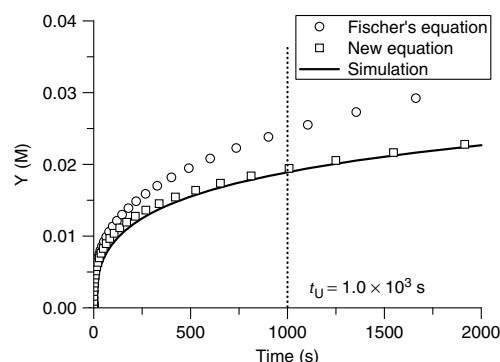


Figure 11 Simulated and calculated concentrations of persistent radical derived from equation (20) and Fischer's equation; $k_d = 0.01 \text{ s}^{-1}$, $k_c = 5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $k_t = 2.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $I_0 = 0.05 \text{ M}$. $K_{eq}(\text{calc.}) = 2.0 \times 10^{-8} \text{ M}$. [Reprinted with permission from Ref. 30. Copyright 2006 American Chemical Society.]

$$F(Y) = \frac{I_0^2}{I_0 - Y} + 2I_0 \ln \frac{I_0 - Y}{I_0} - (I_0 - Y) \quad (20)$$

A plot of $F(Y)$ versus t provides a straight line with a slope $2k_t K_{eq}^2$. The equilibrium constants for SFRP could be then calculated as $K_{eq} = (\text{slope}/2k_t)^{1/2}$.

The new equations were compared with Fischer's original equations. Calculated values of Y using both equations are plotted versus time together with simulated values in Figure 10. They correspond to alkoxyamine based on St and N-tert-butyl-N-[1-diethylphosphono(2,2-dimethylpropyl)]nitroxide (DEPN) (1-phenylethyl-DEPN) at 120°C .³¹ The data calculated from the new equation match perfectly the simulation once the system reaches quasi-equilibrium, while the plot from Fischer's equation deviates from the simulated values. The apparent deviation ($>30\%$) at long reaction times is illustrated on a linear timescale (Figure 11).

As shown in Figures 10 and 11, Fischer's equation is valid only for a short time period. This period (40–400 s) is much shorter than the time range proposed by Fischer (5.9– 1.0×10^3 s).⁵ The new equation does not have an “upper time limit” and is valid from the moment the system reaches quasi-equilibrium.

This treatment can also be applied to ATRP.⁶ Based on the stoichiometric requirement, that is, $I_0 - I = C_0 - C = Y$ and the assumption

$\frac{dY}{dt} \gg -\frac{dR}{dt}$, new equations were derived for Y as shown in the following equation:

$$\begin{aligned} \text{For } C_0 \neq I_0 \left(\frac{I_0 C_0}{C_0 - I_0} \right)^2 & \left(\frac{1}{C_0^2 (I_0 - Y)} \right. \\ & + \frac{2}{I_0 C_0 (C_0 - I_0)} \ln \left(\frac{I_0 - Y}{C_0 - Y} \right) \\ & \left. + \frac{1}{I_0^2 (C_0 - Y)} \right) = 2k_t K_{ATRP}^2 t + c' \end{aligned}$$

$$\begin{aligned} \text{where } c' &= \left(\frac{I_0 C_0}{C_0 - I_0} \right)^2 \\ & \times \left(\frac{1}{C_0^2 I_0} + \frac{2}{I_0 C_0 (C_0 - I_0)} \ln \frac{I_0}{C_0} + \frac{1}{I_0^2 C_0} \right) \end{aligned} \quad (21)$$

Thus, a new function $F(Y)$ (where Y is the only variable) can be used to calculate K_{ATRP} :

$$\begin{aligned} F(Y) &= \left(\frac{I_0 C_0}{C_0 - I_0} \right)^2 \\ & \times \ln \left(\frac{1}{C_0^2 (I_0 - Y)} + \frac{2}{I_0 C_0 (C_0 - I_0)} \right. \\ & \left. \times \left(\frac{I_0 - Y}{C_0 - Y} \right) + \frac{1}{I_0^2 (C_0 - Y)} \right) \end{aligned} \quad (22)$$

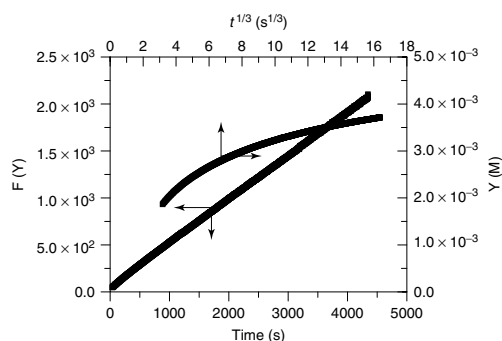


Figure 12 Comparison of the determination of K_{ATRP} using (23) ($F(Y)$ vs t) and the original Fischer's equation ($[Y]$ vs $t^{1/3}$): $[\text{Cu}^{\text{I}}\text{Br}/\text{TPMA}]_0 = [\text{EtBrIB}]_0 = 5 \text{ mM}$, in MeCN at 22°C . [Reprinted with permission from Ref. 6. Copyright 2006 American Chemical Society.]

A plot of $F(Y)$ versus t should be a straight line and the equilibrium constant for the reaction can be calculated from the slope ($K_{\text{ATRP}} = \sqrt{\text{slope}/2k_t}$), with the intercept of c' .

An even simpler equation was derived for the equimolar case:

$$\begin{aligned} \text{For } C_0 = I_0 \\ \frac{C_0^2}{3(C_0 - Y)^3} - \frac{C_0}{(C_0 - Y)^2} + \frac{1}{C_0 - Y} \\ = 2k_t K_{\text{ATRP}}^2 t + c'' \\ \text{where } c'' = \frac{1}{3C_0} \end{aligned} \quad (23)$$

The function $F(Y)$ is now defined as follows:

$$F(Y) = \frac{C_0^2}{3(C_0 - Y)^3} - \frac{C_0}{(C_0 - Y)^2} + \frac{1}{C_0 - Y} \quad (24)$$

A plot $F(Y)$ versus t should be a straight line and the equilibrium constant can be calculated from the slope ($K_{\text{ATRP}} = \sqrt{\text{slope}/2k_t}$), with an intercept of c'' .

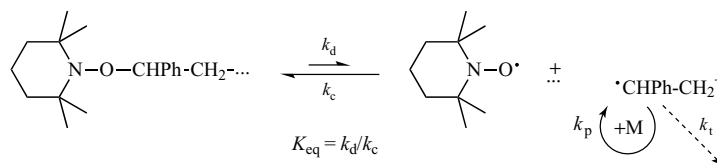
The validity of the newly derived equations over a range of conditions was confirmed by experiments carried out for systems with K_{ATRP} ranging from $\sim 10^{-9}$ to as high as $\sim 10^{-6}$ for both nonequimolar and equimolar reactions. When determining the K_{ATRP} , high conversion to X-Cu(II) may be reached. The concentration range of Cu(I) species (C_0) is limited due to its relatively low solubility.

Therefore, an excess of initiator (I_0) over Cu^I species (C_0) was used for reactions with relatively small K_{ATRP} (slow reactions), while equimolar concentrations of I_0 and C_0 were used for reactions with relatively large K_{ATRP} (fast reactions). A typical plot for a reaction with an equimolar concentration of I_0 and C_0 is shown in Figure 12.⁶ The plot is straight with the intercept identical to the expected one ($c_{\text{exp}} = 66.5$, $c_{\text{th}} = 66.5$), giving $K_{\text{ATRP}} = 9.65 \times 10^{-6}$. On the other hand, the plot with $Y \sim t^{1/3}$ shows a pronounced curvature ($K_{\text{ATRP}}(\text{ini}) = 3.58 \times 10^{-6}$, $K_{\text{ATRP}}(\text{final}) = 1.95 \times 10^{-7}$, $K_{\text{ATRP}}(\text{av}) = 4.74 \times 10^{-7}$). The values of K_{ATRP} were obtained for several nonequimolar and equimolar reaction systems using this methodology.

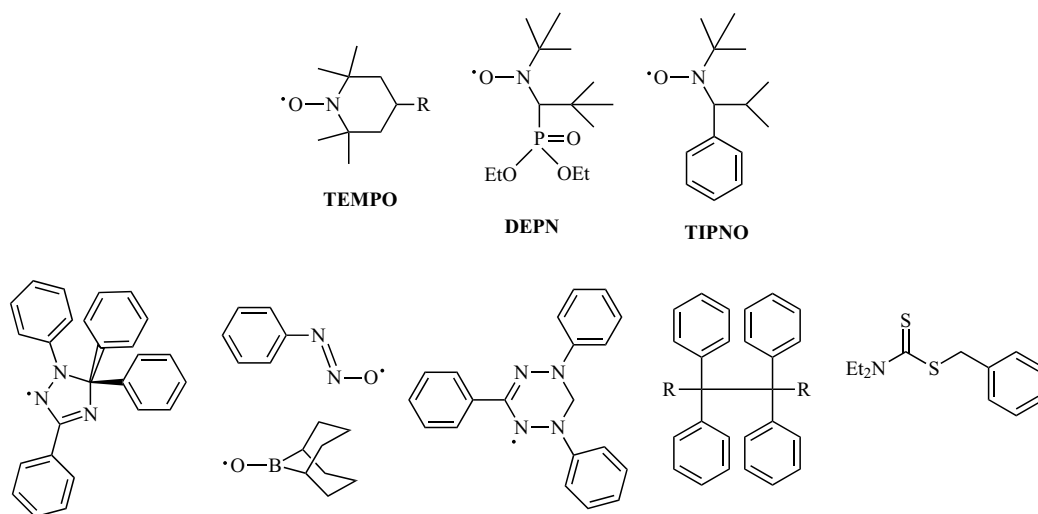
5 SFRP: NITROXIDE-MEDIATED POLYMERIZATION AND ORGANOMETALLIC RADICAL POLYMERIZATION SYSTEMS

SFRP and, more specifically, nitroxide-mediated polymerization (NMP) (see **Nitroxide-Mediated Polymerization and its Applications**)^{7,8} (IUPAC recommends the term *aminoxyl-mediated polymerization*) or organometallic radical polymerization (OMRP)^{9,10} systems rely on the reversible homolytic cleavage of a relatively weak bond in a covalent species to generate a growing radical and a less reactive species (usually the persistent radical, but can also be species with an even number of electrons).^{10,32} This species should react reversibly only with growing radicals and should *not* react among themselves or with monomers to initiate the growth of new chains, and they should *not* participate in side reactions such as the abstraction of β -H atoms.

Nitroxides (aminoxyl radicals) were originally employed as stable free radicals in the polymerization of (meth)acrylates.³³ The field of NMP gained momentum after the seminal paper by Georges *et al.*,⁷ who used 2,2,6,6-Tetramethylpiperidyl-1-Oxyl (TEMPO) as a mediator in St polymerization (Scheme 4). TEMPO and substituted TEMPO derivatives form relatively strong covalent bonds in alkoxyamines that have very low equilibrium constants in NMP (ratio of rate constants of dissociation (activation) and coupling (deactivation), $k_d/k_c = K_{\text{eq}} = 2.0 \times 10^{-11}$



Scheme 4



Scheme 5

M at 120 °C for PS)⁴ and therefore require high polymerization temperatures.

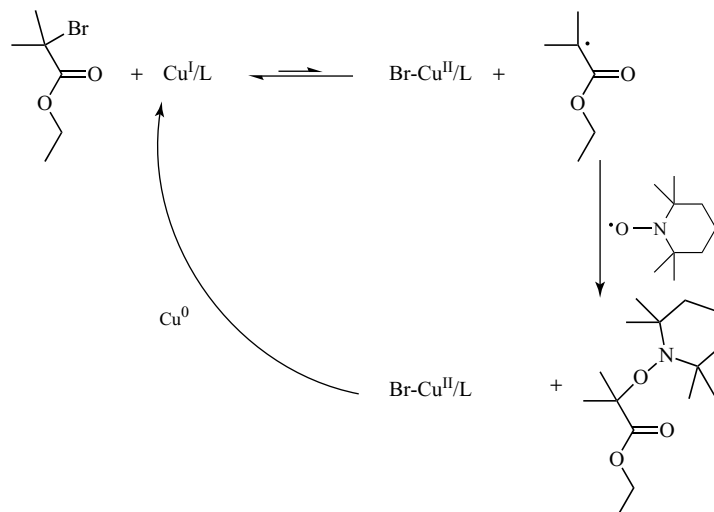
Subsequently, other nitroxides were synthesized that provide a range of C–O bond strengths.^{8,34,35} DEPN³⁶ (also known as *SG-1*) and 2,2,5-tri-methyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO)³⁷ in Scheme 5 contain a H-atom at the α -C. Such nitroxides were originally predicted to be unstable and were expected to quickly decompose. However, the stability of both DEPN and TIPNO is sufficient to control the polymerization of many monomers and a slow decomposition may reduce their accumulation. Polymerization can also be accelerated in NMP systems by a constant radical flux, for example, using slowly decomposing free radical initiators.³⁸ Other systems employing this concept were developed utilizing triazolyl radicals,³⁹ boronyloxy radicals,⁴⁰ and bulky organic radicals such as thermolabile alkanes,⁴¹ (Scheme 5). Alkyl dithiocarbamates, originally used by Otsu *et al.*,^{42,43} undergo homolytic cleavage when irradiated by UV light and can mediate polymerization following an SFRP mechanism. However, the

dithiocarbamyl radicals not only cross-couple but also dimerize and initiate polymerization.

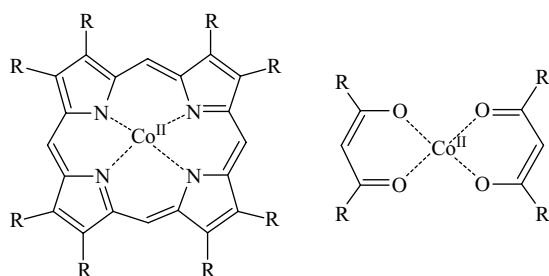
The exploitation of alkoxyamines was originally limited by a lack of efficient synthetic procedures for their preparation, procedures that often resulted in low yields and a wide range of byproducts.^{8,44} However, several versatile techniques have since been developed that involve the controlled generation and trapping of carbon-centered radicals, including single electron transfer reactions associated with ester enolates⁴⁵ and enolate anions.⁴⁶ Another simple method involves halogen abstraction from alkyl halides by a Cu catalyst via atom transfer radical addition and subsequent trapping of the alkyl radical by an excess of nitroxide persistent radical (Scheme 6).⁴⁷

5.1 OMRP Systems

The OMRP of MA with Co porphyrine,⁹ one of the most successful CRP systems, leads to well-defined high MW polyacrylates and has been



Scheme 6



Scheme 7

recently extended to poly(vinyl acetate), though it also includes the DT steps.⁴⁸ However, similar compounds in polymerization of methacrylates act as very efficient catalytic chain transfer agents.⁴⁹ More recently, Co(acac)₂ derivatives were used to control the polymerization of vinyl acetate and *N*-vinylpyrrolidone.^{50,51} Other transition metal complexes (of Mo,⁵² Os,⁵³ Cr,⁵⁴ and Fe^{55,56}) can act as SFRP moderators (Scheme 7). Some of these complexes may also participate in ATRP equilibria (vide infra).¹⁰

5.2 Monomers and Initiators

The range of polymerizable monomers by NMP includes St, various acrylates, acrylamides, dienes,

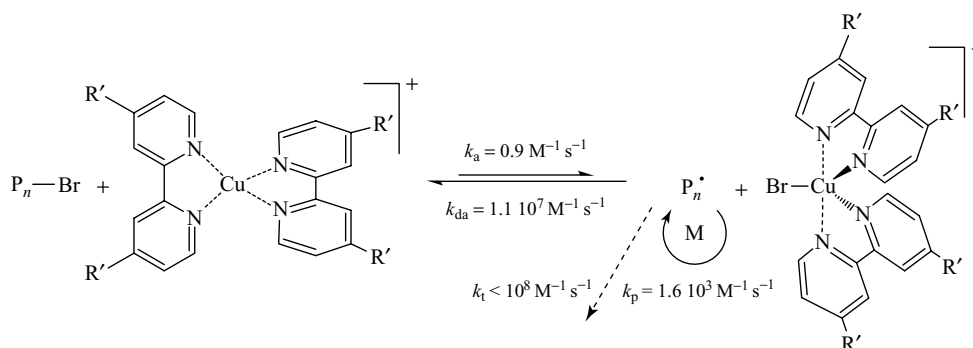
and acrylonitrile. Monomers forming less stable radicals such as vinyl acetate have not yet been successfully polymerized via NMP because of too low values of K_{eq} , but they were successfully polymerized by OMRP. Disubstituted alkenes such as methacrylates that form more sterically hindered tertiary radicals show difficulties in control by NMP owing to very slow deactivation and/or disproportionation.⁵⁷ Copolymerization with St improves the control.⁵⁸

5.3 General Conditions

The bond dissociation energy (BDE) of most nitroxides and alkoxyamines in NMP is relatively high, and therefore, high temperatures are required. The polymerization of St can be successfully mediated with TIPNO and DEPN at $T > 80^\circ\text{C}$, but with TEMPO, the temperature usually exceeds 120°C . All solvents used in RP can also be employed in NMP. NMP has been successfully used in aqueous systems under homogeneous, emulsion, and miniemulsion conditions.^{59–61} Range of temperatures in OMRP is much larger and temperatures are lower than that in NMP.¹⁰

5.4 Controlled Architectures

NMP has been applied to the synthesis of various homopolymers, statistical, gradient, block, and graft



Scheme 8

copolymers. Star, hyperbranched, and dendritic structures have also been prepared.^{8,35} The range of MWs attainable in NMP is quite large, although transfer can limit MWs at elevated temperatures. Also, nitroxides may abstract β -H atoms and lead to elimination and a loss of functionality in some systems. OMRP was mostly used for synthesis of linear homopolymers, but there are also examples of more complex architectures.

6 ATOM TRANSFER RADICAL POLYMERIZATION

ATRP (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**)^{11,12,62–67} is currently the most widely used CRP technique. This originates from the commercial availability of all necessary ATRP reagents, including transition metal compounds and ligands used as catalysts as well as alkyl halide initiators and also the large range of monomers polymerizable by this technique under a wide range of conditions.

The basic working mechanism of ATRP involves homolytic cleavage of an alkyl halide bond R-X (or macromolecular P_n -X) by a transition metal complex Mt^n/L (such as $CuBr/bpy_2$). This reaction generates reversibly (with the activation rate constant, k_a) the corresponding higher oxidation state metal halide complex $X-Mt^{n+1}/L$ (such as $CuBr_2/bpy_2$) and an alkyl radical $R^\bullet$ (a representative example of this process is illustrated in Scheme 8).^{12,68} $R^\bullet$ can then propagate with a vinyl monomer (k_p), terminate by coupling and/or disproportionation (k_t), or

can be reversibly deactivated by $X-Mt^{n+1}/L$ (k_{da}). Radical termination is diminished as a result of the PRE^{5,6} that ultimately shifts the equilibrium toward the dormant species (activation rate constant $\ll$ deactivation rate constant). The values of the rate constants in Scheme 8 refer to St bulk polymerization at 110 °C.^{69–72}

One important difference between SFRP and ATRP is that kinetics and control in ATRP depends not only on the persistent radical ($X-Mt^{n+1}/L$) but also on the activator (Mt^n/L). MWs are defined by the $\Delta[M]/[RX]_0$ ratio and are not affected by the concentration of the transition metal species. The polymerization rate increases with initiator concentration (P-X) and is proportional to the ratio of concentrations of activator and deactivator:

$$R_p = -d[M]/dt = k_p[M[P^\bullet]] \\ = k_p[M(k_a[P-X][Mt^n/L])/(k_{da}[X-Mt^{n+1}/L])] \quad (25)$$

The synthesis of polymers with low dispersities and predetermined MWs requires a sufficient concentration of deactivator. Dispersities decrease with monomer conversion (p) and concentration of deactivator but increase with the k_p/k_{da} ratio. In the absence of any irreversible chain breaking reactions, dispersities are also lower for higher targeted MW, that is, for lower $[RX]_0$.^{73,74}

$$M_w/M_n = 1 + 1/DP_n \\ + [(k_p[RX]_0)/(k_{da}[X-Mt^{n+1}/L])] \\ \times (2/p - 1) \quad (26)$$

ATRP proceeds via an inner sphere electron transfer (ISET) process, that is, atom transfer. A hypothetical outer sphere electron transfer (OSET, also named as a single electron transfer living radical polymerization)⁷⁵, that is, a two-step pathway through radical anions or dissociative OSET was estimated to be $\sim 10^{10}$ times slower than ISET for model bromoacetonitrile and CuBr/tris[(2-pyridyl)methyl]amine (TPMA) system.⁷⁶ However, under certain conditions, a reduction or oxidation of radicals to carbanions or carbocations by transition metal complexes can occur as a side reaction.^{77,78} Therefore, the appropriate selection of an initiator and catalyst will not only depend on the monomer or targeted molecular architecture but should also be made with respect to plausible side reactions. ATRP with alkyl iodides and dithioesters or trithiocarbonates may also proceed by concurrent DT mechanism, depending on the catalyst and structure of the reagents involved.^{79–84}

6.1 Monomers

The list of monomers successfully homopolymerized by ATRP is quite extensive and includes various substituted styrenes,⁸⁵ (meth)acrylates,^{86–88} (meth)acrylamides,^{89,90} vinyl pyridine,⁹¹ acrylonitrile,⁹² vinyl acetate,⁹³ vinyl chloride,⁹⁴ and others.¹² Nitrogen containing monomers as well as certain dienes can present challenges in ATRP as monomer or polymer complexation to the catalyst can render it less active. Some nitrogen containing monomers can also retard polymerization by displacing the terminal halogen of a growing chain or participating in transfer. Nonpolar monomers such as isobutene^{95,96} and α -olefins^{97–99} were successfully copolymerized using ATRP.

ATRP is tolerant to many functional groups such as hydroxy, amino, amido, ether, ester, epoxy, siloxy, and others. All of them have been incorporated into (meth)acrylate monomers and successfully polymerized. One exception is the carboxylic acid group that can protonate amine-based ligands; it must therefore be protected. However, the polymerizations of methacrylic acid at high pH,¹⁰⁰ styrenesulfonic acid, and acrylamide with sulfonic acid functionality have all been successful in the presence of amines.^{101–104}

Since K_{ATRP} depends very strongly on the structure and reactivity of the monomer and RX, specific

catalysts must be used for different monomers. The order of the equilibrium constants in ATRP, acrylonitrile > methacrylates > St $\sim$ acrylates > acrylamides > vinyl chloride > vinyl acetate, differs from those in SFRP and RAFT due to much larger contribution of polar effects.¹⁰⁵ This order should be followed to efficiently prepare block copolymers, that is, polyacrylonitrile (PAN) should be chain-extended with poly(meth)acrylate and not vice versa. However, it is possible to alter this order using a technique known as *halogen exchange*, whereby a macromolecular alkyl bromide is extended with a less reactive monomer in the presence of a CuCl catalyst.^{106–108} The rationale behind “halogen exchange” is that the value of the ATRP equilibrium constant for alkyl chloride-type (macro)initiators is one order of magnitude lower than the alkyl bromides with the same structure. These C–Cl bonds are activated more slowly, and thus, the rate of propagation is decreased with respect to the rate of initiation. This effectively leads to increased initiation efficiency from the added macroinitiator and preparation of a second block with lower dispersity. In this way, block copolymers were successfully prepared from poly(*n*-butyl acrylate) and extended with PAN or PMMA.^{109,110}

6.2 Transition Metal Complexes as ATRP Catalysts

ATRP has been successfully mediated by a variety of metals, including those from groups 4 (Ti¹¹¹), 6 (Mo^{52,112,113}), 7 (Re¹¹⁴), 8 (Fe,^{93,115–119} Ru,^{62,120} and Os^{53,121}), 9 (Rh¹²² and Co¹²³), 10 (Ni^{124,125} and Pd¹²⁶), and 11 (Cu^{11,12}). Cu is by far the most efficient metal as determined by the successful application of its complexes as catalysts in the ATRP of a broad range of monomers in diverse media. The transition metal complex is very often a metal halide, but pseudohalides, carboxylates, and compounds with noncoordinating triflate and hexafluorophosphate anions were also used successfully.¹²⁷

Ligands include multidentate alkyl amines,^{128,129} pyridines,^{130,131} pyridineimines,¹³² phosphines^{115,133}, ethers, or half-metalocene species.¹³⁴ Ligands serve to adjust the atom transfer equilibrium and to provide appropriate catalyst solubility. Since atom transfer proceeds via a reversible expansion of the metal coordination sphere, the system should be flexible enough to assure a very

fast reversible ISET process.¹³⁵ The atom transfer process should dominate over aforementioned side reactions. Although some catalysts are suitable for several types of monomers, other systems may require a specific catalyst and specific conditions.

The redox properties of the catalyst can be adjusted over a very broad range (>500 mV, corresponding to a range of ATRP equilibrium constants spanning eight orders of magnitude).^{76,136} There is an excellent linear correlation between K_{ATRP} and redox potentials of $\text{Cu}^{\text{II}}\text{Br}_2$ complexes with various N-based ligands.

Another important parameter that affects equilibrium constants is halidophilicity, that is, the affinity of halide anions to the transition metal complexes. For example, since $\text{Cu}(\text{II})$ species typically do not form strong complexes with iodide anion, alkyl iodides are less efficient initiators in Cu-mediated ATRP as could be anticipated from their weak BDE.^{70,76}

6.3 Initiators

The broad availability of initiators is perhaps the most significant advantage of ATRP. In fact, many alkoxyamines and RAFT reagents are prepared from activated alkyl halides, that is, ATRP initiators.^{47,137,138} Essentially, all compounds with halogen atoms activated by α -carbonyl, phenyl, vinyl, or cyano groups are efficient initiators. Compounds with a weak halogen–heteroatom bond, such as sulfonyl halides, are also good ATRP initiators.¹³⁹ There are many compounds with several activated halogen atoms which were used to initiate multidirectional growth to form star-like polymers, brushes, and related copolymers. Activated halogens can be incorporated at the chain ends of polymers prepared by other techniques such as polycondensation, cationic, anionic, ring-opening metathesis, coordination, and even conventional radical processes to form macroinitiators. Chain extensions via ATRP from such macroinitiators were successfully used to form novel diblock, tri-block, and graft copolymers.^{69,140,141} Inorganic surfaces (wafers, colloidal particles, fibers, and various porous structures) were functionalized with ATRP initiators to grow films of controlled thickness and density.^{142–144} Also, several natural products were

functionalized with ATRP initiators to prepare novel bioconjugates.^{145–150}

The reactivity of initiators depends *reciprocally* on the R–X BDE.^{76,151}

6.4 Various ATRP Initiating Systems

ATRP can be conducted over a very broad temperature range: from subzero to >130 °C. Reactions have been successful in bulk, organic solvents, CO_2 , water (homogeneous and heterogeneous—emulsion, inverse emulsion, miniemulsion, microemulsion, suspension, precipitation, and dispersion),¹⁵² and even in the gas phase and from solid surfaces.

For very reactive and reducing catalysts (which are naturally air-sensitive), and for polymerization systems, which are difficult to be deoxygenated (water and large vessels), irreversible oxidation of the catalyst by residual oxygen can lead to failed *normal* ATRP. Thus, alternative systems have been developed. *Reverse* ATRP is a convenient method for avoiding such oxidation problems. In this technique, the ATRP initiator and lower oxidation state transition metal activator ($\text{Cu}(\text{I})$) are generated *in situ* from conventional radical initiators and the higher oxidation state deactivator ($\text{Cu}(\text{II})$).^{153,154} The initial polymerization components are less sensitive to oxygen, and yet the same equilibrium between active and dormant species can ultimately be established as in normal ATRP.

There are several other initiation systems described in detail in chapter on ATRP (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). Such as *AGET*^{155–160} and processes with very low amounts of copper (ppm) such as activators regenerated by electron transfer (ARGET),^{161–164} and *ICAR*.¹⁶⁵ *ICAR* very closely resembles RAFT. The role of dithioester in RAFT is played by an alkyl halide in the presence of ppm amounts of copper catalysts. The small amount of radical initiator is responsible for continuing polymerization. If the radical source disappears, RAFT stops and *ICAR* would also stop very quickly.

6.5 Controlled Architectures

ATRP has been successfully used to control topology (linear, stars, cyclic, comb, brushes, networks,

dendritic, and hyperbranched), composition (statistical, blocks, stereoblocks, multiblock copolymers, multisegmented block copolymers, graft, periodic, alternating, and gradient copolymers), and functionalities (incorporated into side chains, end groups (homo- and heterotelechelic), and in many arms of stars and hyperbranched materials).^{166–168} In addition, natural products and inorganics were functionalized via ATRP.^{142,149} ARGET and ICAR allow easy access to polymers with designed MW distribution that lead to materials with novel morphologies such as hexagonally perforated lamellae.¹⁶⁹

7 DEGENERATIVE TRANSFER PROCESSES AND RAFT

Conventional free radical initiators are used in DT processes, and control is assured by the presence of transfer agents (RX) that exchange a group/atom X between all growing chains. This thermodynamically neutral (degenerative) transfer reaction should be fast in comparison to propagation ($k_{\text{exch}} > k_p$). At any instant, the concentration of dormant species $P_n\text{-X}$ is much larger than that of the active species P_n^* (~million times). DPs are defined by the ratio of concentrations of consumed monomer to the sum of concentrations of the consumed transfer agent and the decomposed initiator:

$$DP_n = \Delta[M]/([TA] + f \Delta[I]) \quad (27)$$

One exception is when DT reagents are activated by a catalyst, such as copper complexes. In such a case, all chains are generated from transfer agent (TA) since no radical initiator is used.^{81,84}

If transfer is fast and concentration of the decomposed initiator is much smaller than that of the transfer agent, good control can be obtained. Polydispersities decrease with conversion and depend on the ratio of the rate constants of propagation and exchange, according to the following equation⁷⁴:

$$M_w/M_n = 1 + (k_p/k_{\text{exch}})(2/p - 1) \quad (28)$$

DT processes do *not* operate via the PRE. A steady-state concentration of radicals is established via initiation and termination processes.

The simplest example of DT occurs in the presence of alkyl iodides (see **Sb, Bi, Te, and I-Transfer Polymerization and Applications**).¹⁷⁰

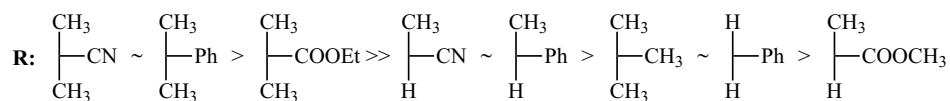
Unfortunately, the rate constants of exchange in these systems are typically three times larger than the rate constants of propagation for most monomers, resulting in polymers with dispersities greater than 1.3. They can be accelerated by classical ATRP catalysts or other compounds. As in reversible chain transfer catalyzed polymerization.¹⁷¹ Exchange is faster in other DT processes employing derivatives of Te or Bi (see **Sb, Bi, Te, and I-Transfer Polymerization and Applications**)^{172–175}; consequently, better control was obtained with these systems.

RAFT polymerization is among the most successful DT processes (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).^{137,176–179} While addition–fragmentation chemistry was originally applied to the polymerization of unsaturated methacrylate esters (prepared by catalytic chain transfer (CCT)),¹⁸⁰ RAFT employs various dithioesters, dithiocarbamates, trithiocarbonates, and xanthates as transfer agents leading to polymers with low dispersities and various controlled architectures. The contribution from termination is slightly different in RAFT than it is in SFRP and ATRP. In the latter two systems, all chains are originally short; as they become long, the probability of termination decreases. However, in DT systems, there is always a small proportion of continuously generated new short chains. They terminate faster than long chains. This also makes the formation of pure block copolymers via typical DT techniques impossible, since low MW initiators always generate new homopolymer chains during the polymerization of the second monomer.

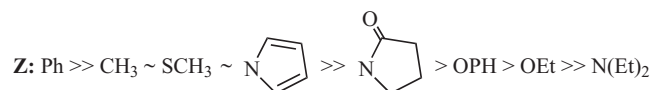
7.1 Monomers and Initiators

DT can be applied to any monomer used in RP unless there is some interference with the transfer agent. For example, dithioesters can decompose in the presence of primary amines. RAFT is also suitable to directly polymerize hydrophilic monomers in aqueous media without any protection group chemistry.^{179,181}

In principle, there is no limitation for the radical initiators, but peroxides may oxidize RAFT reagents.¹⁸² Also, initiator concentrations should be



Scheme 9 Order of R group leaving ability in RAFT.



Scheme 10 Rates of addition decrease and fragmentation increase from left to right for RAFT agents with these Z groups.

sufficiently small to assure that large majority of chains originate from the transfer agents and not from radical initiators.

7.2 Transfer Agents

As discussed earlier, transfer agents should be carefully selected for particular monomers in order to provide sufficiently fast addition and also sufficiently fast fragmentation. Alkyl iodides (and derivatives of Te, Sn, Ge, As, or Bi) should have a leaving group R, which provides a more stable radical. Isobutyrate is good for acrylates, but propionate is not efficient in polymerization of methacrylates. This also has implications on the block copolymerization order.

In the RAFT polymerization of MMA with dithiobenzoates ($\text{S}=\text{C}(\text{Ph})\text{SR}$), the effectiveness of the RAFT agent (i.e., the leaving group ability of R) decreases in the order shown in Scheme 9. Only the first two R groups are successful in preparing PMMA with low dispersity ($M_w/M_n \leq 1.2$) and predetermined MW.^{183,184}

Groups Z in RAFT should be more radical stabilizing for monomers forming more stable growing radicals. For the RAFT polymerization of St, the chain transfer constants were found to decrease in the series shown in Scheme 10.¹⁸⁵

7.3 Controlled Architectures

RAFT and other DT systems can be applied to the synthesis of many (co)polymers with controlled architectures. It should be remembered that there

will always be some contamination from chains resulting from the radical initiators, unless a concurrent ATRP/RAFT is employed.⁸¹

Multifunctional RAFT reagents are usually prepared from multifunctional activated alkyl bromides. RAFT reagents can be attached to polymer chains or surfaces via either the R or the Z group. Attachment via the Z group allows polymer chains to grow (and terminate) in solution. This can reduce cross-linking for multifunctional systems.¹⁸⁶

Statistical, block, stereoblock, alternating/periodic, and gradient copolymers were prepared via RAFT. Many functional monomers were polymerized by RAFT. The dithioester group can be removed by the addition of a large excess of AIBN.¹⁸⁷

8 RELATIVE ADVANTAGES AND LIMITATIONS OF SFRP, ATRP, AND DT PROCESSES

Each CRP system has some comparative advantages/disadvantages. Recent advances in all three techniques have minimized many of the disadvantages, but others need to be still eliminated.

8.1 Stable Free Radical Polymerization

The advantages include: (i) purely organic system for NMP, (ii) applicable to acidic monomers, and (iii) no Trommsdorf effect.

The limitations include: (i) relatively expensive moderators must be used in stoichiometric amounts to the chain end, (ii) some limitation for potentially toxic transition metal compounds used in

stoichiometric amounts for OMRP, (iii) difficult to control for polymerization of disubstituted alkenes such as methacrylates, (iv) difficult to introduce CEF, and (v) relatively high temperatures required for NMP.

8.2 Atom Transfer Radical Polymerization

The advantages include: (i) only catalytic amounts of transition metal complexes (commercially available) are necessary; (ii) many commercially available initiators, including multifunctional and hybrid systems; (iii) large range of monomers (except unprotected acids); (iv) easy end-functionalization; (v) no Trommsdorf effect; and (vi) large range of polymerization temperatures.

The limitations are as follows: (i) transition metal catalyst must often be removed and (ii) acidic monomers require protection.

8.3 RAFT and Other DT Processes

The advantages are as follows: (i) large range of monomers and (ii) minimal perturbation to RP systems.

The limitations are as follows: (i) commercial availability of some transfer agents; (ii) dithioester and other end groups should be removed due to color, toxicity, and potential odor; (iii) primary and secondary amine containing monomers as well as basic polymerization conditions lead to the decomposition of dithioesters; and (iv) range of chain end functionalities is limited.

However, recently some of the limitations have been overcome and others may be avoided in future:

NMP: Control of MMA polymerization can be improved in the presence of either new nitroxides or small amounts of St, allowing formation of block copolymers.^{57,58}

ATRP: AGET allows production of clean block copolymers by starting from an oxidatively stable catalyst precursor and employing reducing agents; ARGET and ICAR have lowered the amount of Cu to low ppm amounts and allowed higher MW polymers to be synthesized^{162,165}; new ligands expanded the range of polymerizable monomers to include vinyl acetate and vinyl chloride^{93,94}; simple replacement of a Br end group by azide has

opened many possibilities for functionalization via click chemistry,^{188–190} including new bioconjugates; halogen exchange¹⁰⁶ has allowed the production of some block copolymers with sequences not available via other processes. Kinetically, ICAR resembles RP (such as RAFT).

In RAFT, dithio end groups could be removed in the presence of large excess of AIBN¹⁸⁷; with the rational design of RAFT reagents, retardation and side reactions can be avoided.¹⁹¹ The convergent growth of chains in multifunctional system can prevent macroscopic gelation.¹⁸⁶ Copper catalyst can prevent formation of new chains and allow formation of purer block copolymers.⁸¹

In all systems, a better understanding of the processes in dispersed media has allowed the reduction in the amount of necessary surfactant, has increased colloidal stability, and has also resulted in the extension of miniemulsion to true emulsion, microemulsion, and inverse miniemulsion systems.^{59,61,152,155,167,179,192–195} It has also allowed to form very high MW polymers under high pressure and also with minimal amount of copper.^{75, 196–200}

9 FUTURE PERSPECTIVES

Precise control over molecular architecture via CRP requires the suppression of chain breaking reactions. The development of CRP enabled the synthesis of new materials for specialty applications and helped construction of a much needed correlation between molecular structure and macroscopic properties. There are several reasons why CRP is currently the most rapidly developing area of synthetic polymer chemistry. They include the large range of polymerizable monomers, the simple reaction set-up and undemanding conditions, unprecedented control for an RP, and large potential market for products made by CRP. However, to reach its full potential, more research is needed in various areas of CRP.

Fundamental mechanistic and kinetic studies on all CRP processes are still very necessary. A deeper understanding of structure–reactivity correlation in NMP may lead to satisfactory control over polymerization of methacrylates. The proper choice of dithioesters will decrease retardation effects of some RAFT reagents. A full comprehension of structural effects for ATRP catalysts could lead to the development of even more active complexes that can be used in smaller amounts. This could minimize the

environmental impact of ATRP chemistry as well as expand the range of polymerizable monomers to include (meth)acrylic acid and α -olefins. Some transition metal complexes participate in both ATRP and SFRP and can potentially even be involved in coordination polymerization. This may open an efficient route to the incorporation of polar monomers into a polyolefin backbone.

Model reactions with low MW analogs and oligomers are needed to evaluate penultimate effects and quantify potential chain breaking reactions. Various additives that can accelerate polymerization and provide enhanced microstructural (tacticity and sequence) control should be evaluated. They can increase stereoselectivity as well as chemoselectivity, which are relatively low for radical processes. Better cross-fertilization between synthetic organic chemistry and polymer chemistry is needed. In the past, achievements in organic chemistry were applied to polymer chemistry. However, recent advances made in polymer chemistry have now benefited organic chemistry, for example, new catalysts developed for ATRP are used for atom transfer radical addition and cyclization and new nitroxides developed for NMP are used in organic synthesis.^{201–204}

A deeper insight into the reaction intermediates and energetic pathways will be possible using new techniques offered by computational chemistry. However, precise computational evaluation requires a large basis set, since many reaction pathways may become dramatically affected by tiny changes in the structure of the substituents. Thus, continued model studies and their correlation with macromolecular systems are very much needed to better understand and optimize the existing processes. Computational chemistry has already helped develop new RAFT reagents and may help discover new mediating systems for SFRP and ATRP. Although current CRP techniques seem to cover all major mechanistic approaches to equilibria between active and dormant species, it is feasible to imagine more efficient stable free radicals, more active transition metal complexes, and better DT agents than currently available. Thus, both a serendipitous and rational search (including leads from computational chemistry and model organic systems) for new mediating agents in CRP should continue.

Most CRP reactions are carried out under homogeneous conditions. However, new possibilities

exist when using dispersed systems (microemulsion, inverse emulsion, precipitation polymerization, etc.). Polymerization in confined space may lead not only to new nanocomposites and hybrids but can potentially facilitate additional control over several facets of the polymerization (less termination, stereocontrol, etc.). Cross-linking reactions in CRP provide networks with very different properties than conventional RP.¹⁹⁹ Higher network uniformity leads not only to better swellability but will also be very important for membranes, drug release, and special separation techniques.

CRP has provided access to nearly all macromolecular architectures available from anionic polymerization. However, there are still a few difficult and challenging structures, including heteroarm star polymers, cyclic polymers, and some others. These challenges can be resolved using multifunctional initiators in CRP or special terminating/capping agents. Precise synthesis of polymers with complex architectures must be evaluated by accurate characterization techniques to determine quantitatively the level of functionality, detect existing imperfections, and exactly describe composition, topology, and microstructure. Novel scattering techniques, modulated thermal analysis, detailed mechanical analysis, more sensitive spectroscopic techniques, multidimensional chromatography, and visualization of individual molecules by atomic force microscopy (AFM) are just a few examples of techniques that help characterize the exact structure of prepared materials. There are many remaining challenges in the characterization of gradient copolymers, including measuring the profile and uniformity of the gradient. This is an important issue (from the point of view of intellectual property) since many copolymers prepared by CRP are inherently different from those prepared by RP.

New polymers with precisely controlled architecture are primarily developed to explore novel properties. Such structure–property correlation is very much needed for many applications. Since macromolecular systems are very large and complex, it is difficult to predict all properties by modeling and computational techniques without input from well-defined macromolecules. The detailed correlation of molecular structure with final properties is still not obvious since many properties will also depend on processing conditions, including the solvent used and its removal conditions, mechanical stresses, and thermal history. The incorporation

of such parameters into simulation will be very beneficial.

Additionally, evaluation of all imperfections and synthetic errors on properties of prepared polymers is needed. This should include the effect of polydispersities and shape of MW distribution. Polymers with higher dispersities may form new morphologies with enhanced curvature and bicontinuous sponge-like systems. They can also allow more flexible processing regimes. In CRP, it will be much more economical to prepare polymers faster, with more termination and with more errors. Therefore, it will be important to understand how these imperfections may affect material properties to optimize cost–performance ratio.

In conclusion, CRP has a very bright future, and it is anticipated that many new products will be introduced to the market within the next several years. The annual value of materials made by CRP was recently projected to reach \$20 billion, corresponding to ~10% of all materials prepared by conventional RP. However, reaching this target will require a joint effort from synthetic polymer chemists, polymer physicists, processing engineers, and marketing specialists.

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Kinetics of Polymerizations

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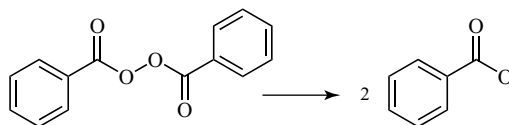
1 INTRODUCTION

1.1 Justification

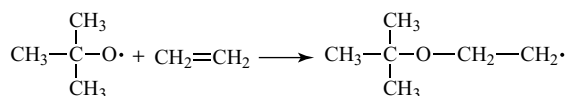
Worldwide, synthetic polymer production amounts to nearly 200 million tons per annum, approximately half of which is via radical means (see **Radical Polymerization in Industry**).¹ That it is tremendously important to have a detailed understanding of the kinetics of such a process—used to make 100 million tons of product per year!—is a matter so obvious that it should not need any laboring. The close connection between plant safety and control of kinetics adds even further to this importance. Indeed, really the only issue here that is not immediately comprehensible is that so many laboratory chemists have become dismissive of the importance of radical polymerization (RP) kinetics. Mostly, such chemists are in pursuit of new materials. They fail to appreciate or admit two things: (i) The material properties of polymers are intimately connected with quantities such as average molar mass and (copolymer) composition that are determined by polymerization kinetics (Section 2). (ii) The commercialization of any process at the very least involves solid knowledge of its kinetics, and in most cases has the stronger requirement that the kinetics must be favorable. Thus one sees that, far from reaction kinetics being irrelevant to the development of new polymeric materials, it plays an indispensable role.

1.2 Fundamental Reactions

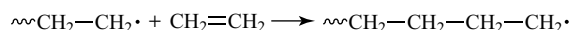
Any description of chemical kinetics must be founded on knowledge of the reactions that occur. Therefore, we begin by illustrating the fundamental reactions of RP. Firstly, there must be a reaction that generates free radicals (see **Overview of Radical Initiation**). Most commonly, this is achieved through thermally induced *decomposition* of a deliberately added chemical *initiator*, for example (di)benzoyl peroxide (BPO):



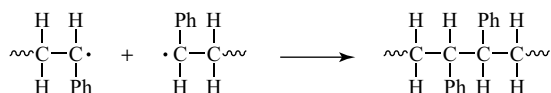
This process is said to produce *primary radicals*. Ideally, these add to monomer, for example, *tert*-butoxy (e.g., from the initiator di-*tert*-butyl peroxide (DTBP)) with ethylene (IUPAC name: ethene):



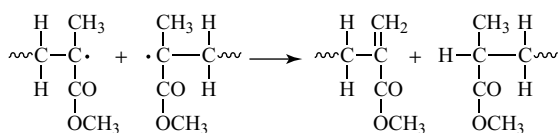
A polymer molecule is formed by the continued occurrence of the addition reaction, a process known as *propagation*:



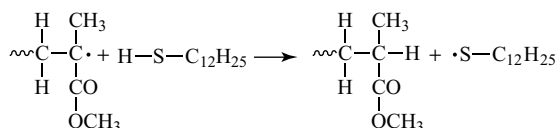
There are three reactions that stop the growth of macroradicals. The most intuitive is *termination* by *combination*, which occurs, for example, in styrene polymerization:⁶



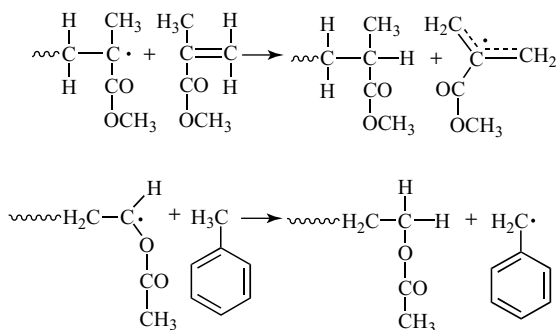
Disproportionation is also a termination reaction in that it results in annihilation of radical activity. It takes place, for example, in polymerization of methyl methacrylate (MMA):⁸



Finally, there are *transfer* reactions, as effected, for example, by a *chain-transfer agent* such as dodecyl mercaptan:



There are quite a few forms of chain transfer to small molecules.^{6,9} Others that are apt to mention here are *chain transfer to monomer*, for example with MMA, and *chain transfer to solvent*, for example with polymerization of vinyl acetate in toluene:¹⁰



All these forms of transfer have in common with termination that they limit polymer growth. However, they are different to termination in that

there is no loss of radical activity *per se*. Ideally the small-molecule radical generated by transfer is like a primary radical in that it adds to monomer and thus initiates the formation of another polymer molecule. This situation is commonly realized; for example, it is the case with the sulfur-centered and monomeric radicals above. However, it is not always the case. For instance, for obvious reasons, the benzyl radical in the example above is relatively stable, and so it retards polymerization by acting as a terminating agent,¹⁰ a process termed *degradative chain transfer*.¹²

1.3 Scope of this Work

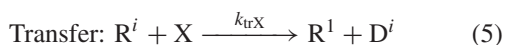
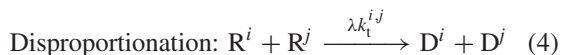
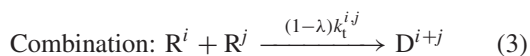
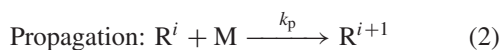
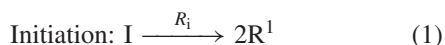
It would take a whole book to do full justice to the topic of radical polymerization kinetics. Since this is only an article in an encyclopedia, our focus must therefore be selective. We will not cover here the kinetics of reversible-deactivation radical polymerization (RDRP),^{13,14} as it is covered elsewhere in this encyclopedia (see **Fundamentals of Controlled/Living Radical Polymerization, Nitroxide-Mediated Polymerization and its Applications, Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications, Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**, and **Sb, Bi, Te, and I-Transfer Polymerization and Applications**). Besides, all the reactions considered here occur also in RDRP systems, the kinetics of which must therefore be built upon the foundations presented in this work. Similarly, our slant will not be exclusively based on kinetic equations, for in another book section one of us has recently approached the topic from that angle.⁵ Rather, we will merely summarize the important equations and ideas in Section 2, before taking a mechanistic line of attack in the remainder of this article, so that the reader hopefully emerges with an understanding of the fundamental processes of initiation, propagation, termination, and chain transfer (Section 1.2), all of which should be expected to occur in any radical polymerization. Finally, we will discuss the reactions of chain transfer to polymer and β -scission. These cannot be considered as fundamental RP reactions, because there are many systems in which they do not occur. However, there is growing realization that these

reactions are far more widespread than previously realized, and that, where they do occur, they have a pivotal impact on kinetics and properties.

2 FOUNDATIONS AND MACHINERY

2.1 Reaction Scheme and Population-Balance Equations

A reaction scheme for the fundamental reactions of Section 1.2 is as follows:



Here I denotes initiator, M monomer, R^i (living) radical of degree of polymerization i , D^i dead polymer of degree of polymerization i , X transfer agent, and k a rate coefficient, the subscript to which signifies the reaction involved.

Recognizing that reactions (1)–(5) are elementary in nature, one may immediately write down from this fundamental scheme the following population-balance equations, where c denotes concentration and t time:

$$\begin{aligned} \frac{dc_{R^1}}{dt} = & R_i + k_{trX}c_Xc_{R^1} - k_p c_M c_{R^1} \\ & - k_{trX}c_Xc_{R^1} - 2c_{R^1} \sum_{j=1}^{\infty} k_t^{1j} c_{R^j} \quad (6a) \end{aligned}$$

$$\begin{aligned} \frac{dc_{R^i}}{dt} = & k_p c_M c_{R^{i-1}} - k_p c_M c_{R^i} - k_{trX}c_Xc_{R^i} \\ & - 2c_{R^i} \sum_{j=1}^{\infty} k_t^{ij} c_{R^j}, \quad i = 2, \infty \quad (6b) \end{aligned}$$

$$\begin{aligned} \frac{dc_{D^i}}{dt} = & 2\lambda c_{R^i} \sum_{j=1}^{\infty} k_t^{ij} c_{R^j} + k_{trX}c_Xc_{R^i} \\ & + (1-\lambda) \sum_{j=1}^{i-1} k_t^{j,i-j} c_{R^j} c_{R^{i-j}}, \quad i = 1, \infty \quad (7) \end{aligned}$$

These equations are the source from which all RP kinetics flow. Before making this clear, some essential points about reactions (1)–(5) in relation to (6) and (7) will be made.

For *initiation*, (1), we use R_i for *rate* of creation of polymerizing radicals, rather than a rate coefficient. This is for two reasons: (i) Initiation may occur in a variety of ways⁶—by homolysis of a thermolabile compound, by photolysis of a photoinitiator, by self-reaction of monomer (so-called self-initiation or autoinitiation), and more besides. (ii) There are always side reactions by which primary radicals are squandered before they can initiate polymerization. For both these reasons, initiation does not lend itself to general formalism in terms of a rate coefficient. In the most common case of employing a thermally decomposing initiator—for example, BPO in Section 1.2—one has

$$R_i = 2fk_d c_I \quad (8)$$

where k_d is the rate coefficient for decomposition of initiator of concentration c_I , and f is the so-called *initiator efficiency*, which is the fraction of primary radicals that actually add to monomer and thus successfully initiate polymerization.

Usually, one form of small-molecule *transfer* will be dominant, and one may just use $f_{tr} = k_{trX}c_X$ for the overall *frequency* of transfer, as in (6) and (7). Where it is the case that several transfer reactions occur to a significant extent, one should just use

$$f_{tr} = \sum_{\text{all } X} k_{trX}c_X \quad (9)$$

in all the equations of this work. The other thing to note about transfer is that it is assumed here to involve quantitative reinitiation of polymerization, that is, formation of a R^1 species. Where this is not the case, for example when one has degradative chain transfer, it is not difficult to adapt the equations of this work appropriately.¹⁵

Rather than explicitly including *combination* and *disproportionation*, reactions (3) and (4), respectively, in (6) and (7) we have equivalently used overall rate coefficients for termination k_t^{ij} , and the fraction of termination by disproportionation λ . The simple interrelations here are as follows:

$$k_t^{ij} = k_{td}^{ij} + k_{tc}^{ij} \quad \text{or} \quad k_t = k_{td} + k_{tc} \quad (10)$$

$$\lambda = k_{td}^{ij} / k_t^{ij} = k_{td} / k_t \quad (11)$$

The subscripts “d” and “c” denote disproportionation and combination, respectively.

Chain-length-dependent termination (CLDT) has been included from the outset in (6) and (7). Because termination is diffusion-controlled,^{16,17} immediate intuition is that a termination rate coefficient k_t should depend on the chain lengths i and j of the two radicals involved; hence the notation $k_t^{i,j}$. Over the last decade, it has become possible to confirm this expectation via a variety of experimental methods,^{18,19} with the result that the reality of CLDT is now beyond dispute,¹⁸ and there is little point in pretending otherwise if one is genuinely interested in understanding RP kinetics.

On the other hand, (6) assumes chain-length-independent *propagation*. This is an approximation. Although chemically controlled rather than diffusion-controlled, the body of evidence suggests that for approximately the first 10 propagation steps, values of k_p are elevated above the long-chain value of a system.¹⁵ However, calculations with such a model for CLDP show that it only has a significant effect on overall kinetics if the number-average degree of polymerization DP_n is approximately 100 or less.²⁰ In the usual instance of making long polymer, this will not be the case. Thus it seems reasonable not to account for CLDP here. Where this is necessary, there exist methods for doing so.^{15,20}

In the preceding two paragraphs, note the important distinction between diffusion-controlled and chemically controlled reactions, that is, (bimolecular) reactions for which the rate-determining step is reactant encounter and surmounting a (chemical) energy barrier, respectively. In order to gain understanding of an RP rate coefficient—indeed any rate coefficient—it is first of all essential to be aware of which type of control is operative.

Results that follow from (6) and (7) for quantities of importance are now presented.

2.2 Conversion of Monomer into Polymer

2.2.1 Rate of Polymerization

From reaction (2), the rate of propagation in RP is

$$R_p = k_p c_M \sum_{i=1}^{\infty} c_{Ri} = k_p c_M c_R \quad (12)$$

where the overall radical concentration c_R is as implicit in this equation. The fact that polymer

chains are long means that most of the monomer is consumed by propagation rather than by reactions that start and stop polymer growth: for example, initiation and transfer. Thus to essentially flawless approximation, (12) also gives the overall rate of monomer consumption, that is, the rate of polymerization.

From (6), one may obtain

$$\begin{aligned} \frac{dc_R}{dt} &= \sum_{i=1}^{\infty} \frac{dc_{Ri}}{dt} = R_i - 2 \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} k_t^{i,j} c_{Ri} c_{Rj} \\ &\equiv R_i - 2 \langle k_t \rangle c_R c_R \end{aligned} \quad (13)$$

Implicit in (13) is the following definition of the overall, or chain-length-averaged, termination rate coefficient $\langle k_t \rangle$:^{21,22}

$$\langle k_t \rangle = \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} k_t^{i,j} \frac{c_{Ri}}{c_R} \frac{c_{Rj}}{c_R} \quad (14)$$

Integration of the well-known (13) yields c_R for use in calculating R_p .

For steady-state polymerization (SSP), one has $dc_R/dt \approx 0$, meaning that

$$c_R = \left(\frac{R_i}{2 \langle k_t \rangle} \right)^{0.5} \quad (15)$$

In practice, this equation is accurate as long as there are no abrupt changes in either the rate of initiation or the rate of termination. In other words, it is widely applicable. Substitution into (12) generates the following signature result for RP kinetics:

$$R_p = -\frac{dc_M}{dt} = k_p c_M \left(\frac{R_i}{2 \langle k_t \rangle} \right)^{0.5} \quad (16a)$$

This rate law—and indeed all the familiar results so far—hold also for CLDT, as is implicit.

One might therefore ask why a fuss is made about CLDT. The answer is that it makes $\langle k_t \rangle$ a variable rather than constant quantity. This may be seen from the following steady-state equation for the situation of negligible transfer, where Γ denotes the gamma function:^{23,24}

$$\begin{aligned} \langle k_t \rangle &= k_t^{1,1} \left[\Gamma \left(\frac{2}{2-\alpha} \right) \right]^{-2} \\ &\times \left[\frac{(2R_i k_t^{1,1})^{0.5}}{k_p c_M} \left(\frac{2}{2-\alpha} \right) \right]^{2\alpha/(2-\alpha)} \end{aligned} \quad (17)$$

Strictly speaking, this result holds only for the *geometric-mean* model for termination:

$$k_t^{ij} = k_t^{1,1} (ij)^{-\alpha/2} \quad (18)$$

This is a two-parameter model for CLDT: $k_t^{1,1}$, the rate coefficient for termination between monomeric radicals, stipulates the *magnitude* of k_t^{ij} values, while α , the exponent for variation of $k_t^{i,i}$ with i , quantifies the *strength* of the CLDT, with $\alpha = 0$ returning chain-length-independent termination (CLIT). There are two issues of interest here: (i) Equation (18) is the only model for CLDT that, when introduced into (6) and (7), delivers closed expressions for $\langle k_t \rangle$ and other overall quantities of interest.²⁵ (ii) Numerical solution of (6) and (7) with various CLDT models reveals that they all give results excellently in accord with (17).^{25,26}

Given the above, one may use (17) in (16a) to obtain the following *generally applicable* rate law for steady-state RP in the absence of large amounts of transfer:²⁷

$$R_p \sim (R_i)^{0.5-b} (c_M)^{1+2b} (k_t^{1,1})^{-0.5-b},$$

where $b = \frac{\alpha}{2(2-\alpha)}$ (19)

For the usual situation of $k_t^{1,1} \sim 1/\eta$,^{17,19,28} the order of R_p with respect to viscosity η is $0.5 + b$. Equation (19) correctly recovers the classical rate-law orders of 0.5 for c_I , 1.0 for c_M , and 0.5 for η : these follow from the CLIT value of $b = 0$. The stronger the CLDT, the stronger the deviations from these values. For example, $\alpha = 0.2$ gives $R_p \sim (c_I)^{0.44} (c_M)^{1.11} \eta^{0.56}$, while $\alpha = 0.5$ gives $R_p \sim (c_I)^{0.33} (c_M)^{1.33} \eta^{0.67}$. Equations (17) and (19) may be used to understand trends in $\langle k_t \rangle$ data and to analyze SSP rate data in order to obtain reliable values of α and $k_t^{1,1}$.^{4,29}

2.2.2 Integrated Rate Laws

In terms of the more common index x of fractional conversion of monomer into polymer, (16a) assumes the following equivalent form:

$$\frac{-d \ln(1-x)}{dt} = k_p \left(\frac{R_i}{2\langle k_t \rangle} \right)^{0.5} \quad (16b)$$

This recommends plotting SSP data as $-\ln(1-x)$ versus t , fitting a straight line, and setting the

slope equal to $R_i^{0.5} k_p / (2k_t^{0.5})$.³⁰ An advantage of (16b) is that it is trivially integrated in the event of R_i , k_p , and k_t all being constant with time. The result is

$$x = 1 - \exp(-K't), \text{ where } K' = Kc_I^{0.5}$$

$$\text{and } K = k_p \left(\frac{fk_d}{\langle k_t \rangle} \right)^{0.5} \quad (20)$$

Here, (8) for R_i has been assumed. An example of using (20) to analyze some data^{2,3} is presented in Figure 1.

Equation (20) accounts for change of c_M with time. It is also unavoidable that c_I changes with time. For a thermally decomposing initiator, c_I will decrease from its initial value, $c_{I,0}$, according to the standard first-order rate law $c_I = c_{I,0} \exp(-k_d t)$. Where there is a significant induction time t_{ind} before polymerization commences, then $c_{I,0} \exp(-k_d t_{\text{ind}})$ should be employed as the value of $c_{I,0}$. Using this expression for c_I in (16b) results in

$$x = 1 - \exp \left\{ \frac{-2K(c_{I,0})^{0.5}}{k_d} \left[1 - \exp \left(\frac{-k_d t}{2} \right) \right] \right\} \quad (21)$$

For $k_d t \ll 1$, this reduces to (20).

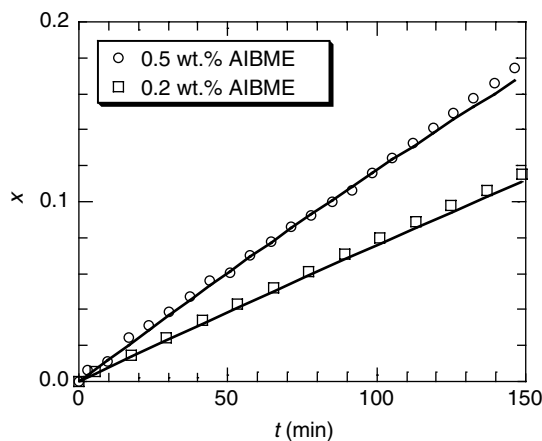


Figure 1 Fractional conversion x as a function of time t over a limited range only for bulk polymerization of methyl methacrylate initiated by 2,2'-azoisobutyromethyl ester (AIBME) at 50 °C. Points: experimental values;^{2,3} curves: (20) with $K \equiv k_p(fk_d/\langle k_t \rangle)^{0.5} = 1.48 \times 10^{-4} \text{ M}^{-0.5} \text{ s}^{-1}$. This is consistent with the known individual rate coefficients for this system, viz. $fk_d \approx 1 \times 10^{-6} \text{ s}^{-1}$,^{2,3} $k_p \approx 500 \text{ M}^{-1} \text{ s}^{-1}$, and $\langle k_t \rangle \approx 1.25 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.⁴

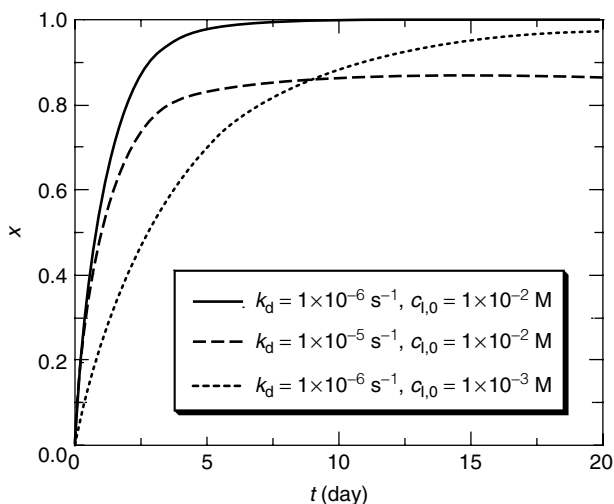


Figure 2 Fractional conversion x of monomer into polymer as a function of time t , as evaluated using (21) with $k_p(fk_d/\langle k_t \rangle)^{0.5} = 1 \times 10^{-4} \text{ M}^{-0.5} \text{ s}^{-1}$ and k_d and $c_{I,0}$ as displayed. The parameter values for the unbroken line correspond most closely to those of the data of Figure 1.

Some evaluations of (21) are presented in Figure 2. These make clear the result from (21) that there is a limiting conversion of $1 - \exp[-2K(c_{I,0})^{0.5}/k_d]$. This is the phenomenon of *dead-end polymerization*, where, because either c_I is too low (meaning there simply are not enough initiator molecules for all monomer to be converted into polymer) or k_d is too high (meaning that the formed chains are too short for all monomer to be incorporated), a system falls appreciably short of 100% conversion. These effects are illustrated in Figure 2. At the same time, Figure 2 also makes clear that for “standard” parameter values, for example, those of the data in Figure 1, declining initiator concentration does not prevent all monomer from being consumed. Generally, one only needs to watch out for this phenomenon at high temperatures, where k_d will be large.

2.2.3 Effects of Conversion on Rate Coefficients

Figure 3 shows the data of Figure 1—both experimental and calculated—extended over the entire range of conversion. It is evident that (20) only functions at low conversion as an accurate description of bulk MMA polymerization at 50 °C. This situation is typical, even if often not as pronounced as in

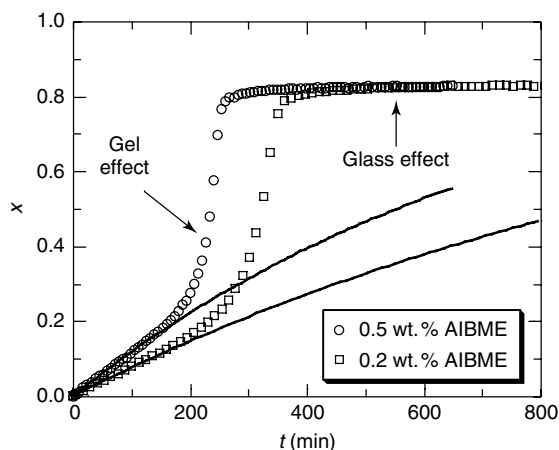


Figure 3 As for Figure 1, except that the *entire range of conversion* is shown. [The Kinetics of Radical Polymerization in Encyclopedia of Polymer Science and Technology, November 2010 in Encyclopedia of Polymer Science and Technology. Copyright 2011, John Wiley & Sons, Inc. This material is reproduced with permission of John Wiley & Sons, Inc.]

Figure 3. It arises because of variation of rate coefficients with conversion, giving rise to the two effects highlighted in Figure 3. These are both important, and will now be discussed.

The *gel effect* is an autoacceleration in rate that may occur at intermediate conversion and is also known as the *Trommsdorff effect* or *Trommsdorff–Norrish effect* in recognition of early workers

to report on it.^{31,32} In fact, these are more appropriate names than gel effect: although there is acceleration in rate, as at the gel point of step-growth polymerization, there is no gel formation. Right from the beginning,³³ it was recognized that this effect must be due to changing $\langle k_t \rangle$: as polymer is formed and a system becomes more viscous, the diffusion-controlled nature of termination means that $\langle k_t \rangle$ decreases, and hence rate increases, as is unmistakable in Figure 3. This in turn leads to increase of the molar mass (Section 2.3). For both these reasons, and additionally that of safety (i.e., avoiding runaway conditions), this effect is tremendously important in the modeling of polymerizations. It will be discussed further in Section 5.3, where data will be presented.

One may not so immediately arrive at a qualitative explanation for the *glass effect*, which sees the polymerization all but cease at high conversion (refer to Figure 3). If this were due to macroradical *termination*, then it would require $\langle k_t \rangle$ to increase markedly, which can be ruled out given that the gel effect is due to the opposite. Similarly, although the glass effect looks quite similar to dead-end polymerization (Figure 2), this can be excluded as the cause for several reasons, the most obvious of which is that the appropriate parameter values for the present case result in *initiator* lasting for several days (Figure 2), as opposed to running out after just hours (Figure 3). Since small-molecule diffusion coefficients become very small as a polymer–solvent system becomes glassy, for many years it was believed that the glass effect is due to the *propagation* reaction becoming diffusion-controlled: the idea is that k_p starts to decrease, and this results in a plummeting rate. There is some truth in this explanation, on two fronts: (i) The conversion of the glass effect always corresponds very closely to that at which a system becomes glassy, so the bestowed name is justified. (ii) Measurements show that k_p does indeed start to decrease around the glass transition point.³⁴ However, the same measurements also show that k_p does not decrease by the many orders of magnitude that are necessary to bring polymerization to a halt. Thus, while propagation does contribute, a more complete explanation for the glass effect is that *initiator efficiency* plunges toward zero: the glassy polymer matrix keeps a pair of geminate primary radicals in the vicinity of each other for so long that they can hardly avoid undergoing recombination.³⁵

The above discussion makes clear that $\langle k_t \rangle$ can be expected to change with conversion potentially right from the beginning of a polymerization, while for systems with a glass transition point, k_p will start changing when this point is reached. It is now recognized that f must depend on system viscosity, and thus it too changes throughout the course of a polymerization,^{36,37} with the change being cataclysmic at the onset of glassy conditions.³⁵ Because (20) and (21) assume that all of $\langle k_t \rangle$, f , and k_p are constant in value, they are therefore of limited utility. Rather, the effects of conversion must be taken into account by computer-based modeling that carries out numerical integration of (6) and (7) with rate parameters varying appropriately with conversion. There are countless examples of such undertakings in the literature.

2.3 Molar Masses

As will become clear, this is not a simple topic. Readers not of a mathematical bent may wish to avert their gaze from the equations, and instead focus on the concepts that follow from them. The reason for including the equations is that they are manageable yet still give a highly effective description.

2.3.1 Instantaneous Molar Mass Distributions

Equation (7) defines the *instantaneous number-chain length distribution*, that is, the relative number of (dead) chains of degree of polymerization i being produced at any instant. While this equation may be used as it stands, it is both convenient and instructive to simplify it. For CLIT ($k_t^{ij} = k_t$) and *steady state*, the result is⁵

$$n_i = F_n(1 - S)S^{i-1} + (1 - F_n)(i - 1)(1 - S)^2S^{i-2} \quad (22a)$$

Here n_i is the instantaneous number *fraction* of dead chains of length i (meaning that the sum of all n_i values equals 1), S is the *probability of propagation* (of a radical), and F_n is the *number*

fraction of chains formed by transfer and disproportionation:

$$S = \frac{k_p c_M}{k_p c_M + k_{trX} c_X + 2k_t c_R} \quad (23a)$$

$$F_n = \frac{k_{trX} c_X + 2\lambda k_t c_R}{k_{trX} c_X + 2\lambda k_t c_R + (1 - \lambda)k_t c_R} \quad (24a)$$

For example, if all dead chains are formed by combination, then $F_n = 0$, while if all dead chains are formed by disproportionation and/or transfer, then $F_n = 1$. Note that (22a) may also be derived via probability arguments.³⁸

In the long-chain limit ($S \rightarrow 1$, equivalent to $\nu \rightarrow \infty$), (22a) becomes⁵

$$n_i = F_n \frac{1}{\nu} \exp\left(\frac{-i}{\nu}\right) + (1 - F_n) i \frac{1}{\nu} \frac{1}{\nu} \exp\left(\frac{-i}{\nu}\right) \quad (22b)$$

The new parameter here, ν , is the average number of events that a radical undergoes before it forms a dead chain:

$$\nu = \frac{k_p c_M}{k_{trX} c_X + 2k_t c_R} = \frac{S}{1 - S} \quad (23b)$$

If there is negligible transfer, then ν equals the so-called *kinetic chain length*.¹² The equation numbering here connotes that ν is just an alternative parameter to S . For example, $S = 0.995$ is equivalent to $\nu = 199$.

Equation (22b) is the celebrated *Schulz–Flory distribution* for the chain-length distribution (CLD) from (radical) polymerization (note that in this article the abbreviation “CLD” has a different meaning to that of these letters in “CLDT”). The exponential functions make it more mathematically transparent than (22a), which is actually the *exact* description. One should remember that these equations assume CLIT and SSP. Conversion from CLD into *molar mass distribution* (MMD, vernacularly termed *molecular weight distribution*) is easy: one just uses $M = M_0 i$, where M_0 is monomer molar mass, leading to $dM = M_0 di$ and $d(\log M) = d(\log i)$. This means that $n_M = n_i / M_0$ and $n(\log i) = n(\log M)$. Analogous relations hold for weight distributions. It is slightly more involved to obtain these distributions. The general relationships are,³⁹ illustrated

in each case for the Schulz–Flory distribution:

$$\frac{in_i}{DP_n} \stackrel{\text{def.}}{=} w_i = F_w \frac{1}{\nu} \frac{i}{\nu} \exp\left(\frac{-i}{\nu}\right) + 0.5(1 - F_w) \frac{1}{\nu} \left(\frac{i}{\nu}\right)^2 \exp\left(\frac{-i}{\nu}\right) \quad (25)$$

$$i w_i \stackrel{\text{def.}}{=} \frac{w(\log_{10} i)}{\ln 10} = F_w \left(\frac{i}{\nu}\right)^2 \exp\left(\frac{-i}{\nu}\right) + 0.5(1 - F_w) \left(\frac{i}{\nu}\right)^3 \exp\left(\frac{-i}{\nu}\right) \quad (26)$$

Here, w is weight fraction (i.e., all distributions are *normalized*), and

$$F_w = \frac{k_{trX} c_X + 2\lambda k_t c_R}{k_{trX} c_X + 2\lambda k_t c_R + 2(1 - \lambda)k_t c_R} = \frac{F_n}{2 - F_n} \quad (24b)$$

is the *weight* fraction of chains formed by transfer and disproportionation (cf. F_n). Notice that $F_w = \lambda$ in the event of negligible transfer (11). Equation (26) gives the size-exclusion chromatography (SEC) MMD, so named because it is the form of MMD delivered by this most common experimental technique. It is therefore this equation that should be used to fit experimental data, as now demonstrated.

The equations above show that from five rate coefficients ($f k_d$, k_p , k_{tc} , k_{td} , and k_{trX}) and three reactant concentrations (c_M , c_I , and c_X), MMD actually depends on only two parameters. Considering first F_w (equivalently, F_n), Figure 4 shows that it determines the *shape* (width and height) of an SEC CLD. Thus the first step in fitting (26) to SEC CLD data is to obtain the optimum value of F_w . Having done this, one varies ν (equivalently, S) until the *position* of the fit is optimized: as illustrated in Figure 5, such variation affects only the location of the SEC CLD. In this way, unique F_w and ν values are yielded. What one can extract from these depends on what else is known. If all else is known, then from ν one can obtain the value of k_t and from F_w the value of λ . For example, for bulk styrene polymerization with a high rate of initiation, one would expect transfer to be insignificant. Thus from the value $F_w = 0.25$ fitted to the styrene data,⁷ one deduces $\lambda = 0.25$, that is, 25% of termination is by disproportionation (24b).

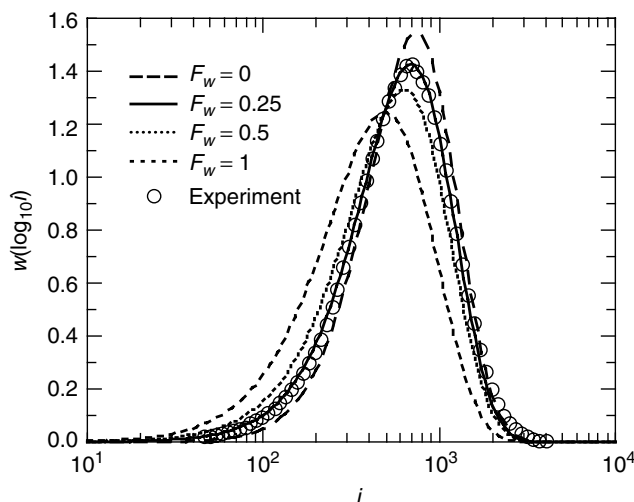


Figure 4 Chain-length distributions presented as $w(\log_{10} i)$, where w is weight fraction and i is chain length. Points: results from a low-conversion suspension polymerization of styrene at 80°C .⁷ Curves: Schulz-Flory distributions calculated using (26) with $\nu = 245$ and different F_w as indicated. This illustrates that F_w determines the MMD shape (see text).

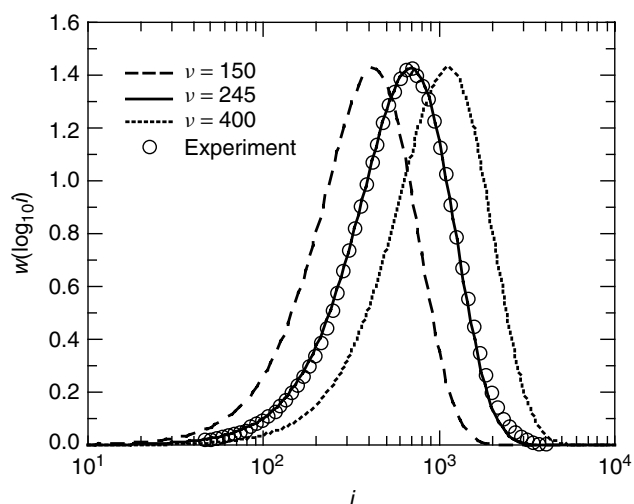


Figure 5 As for Figure 4, except that now $F_w = 0.25$ is held constant and ν is varied, thereby illustrating that the latter parameter determines the MMD position (see text).

There is no denying that (22b) provides a flawless fit to the styrene data that has been used for illustration. However, the value $\lambda = 0.25$ is non-physical in that styrene radicals, being secondary in nature, are known to terminate almost exclusively by combination.⁶ This problem may be solved by allowing termination to be chain-length-dependent. For the geometric-mean model, (18), it has been shown that,

in the absence of transfer, the Schulz-Flory distribution becomes⁴⁰

$$n_i = F_n C i^{-0.5\alpha} \exp(-C' i^p) + (1 - F_n) A^2 p i^{1-\alpha} \exp(-A i^p) \quad (27)$$

Here $C = (2R_i k_t^{1,1})^{0.5} / (k_p c_M) = 1/\nu$ (where ν is now for CLDT, cf. (23b) for CLIT), $p = 1 - (\alpha/2)$,

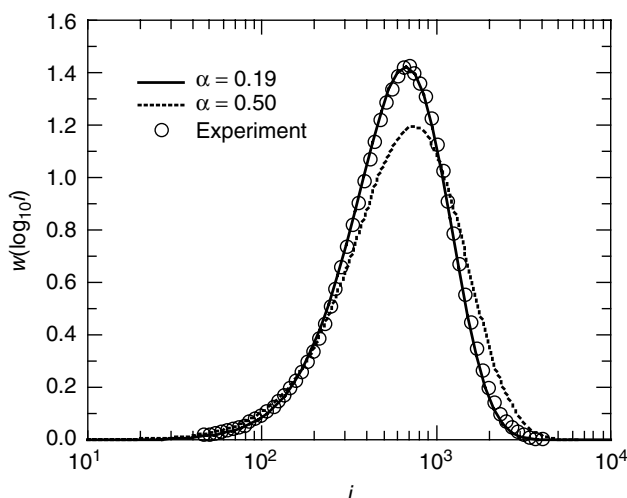


Figure 6 As for Figure 4, except that now the curves are calculated from (27)—that is, allowing chain-length-dependent termination—using $F_w = 0$ (100% combination) together with $\alpha = 0.19$ ($\nu = 135$) and $\alpha = 0.5$ ($\nu = 65$) as indicated. These different ν values were chosen so that $DP_n = 425$ in both cases. [The Kinetics of Radical Polymerization in Encyclopedia of Polymer Science and Technology, November 2010 in Encyclopedia of Polymer Science and Technology. Copyright 2011, John Wiley & Sons, Inc. This material is reproduced with permission of John Wiley & Sons, Inc.]

$C' = C/p$, $A = 4C'/(4 - \alpha)$, and F_n is as already defined.

Equation (27) has three parameters: F_n as before, C equivalent to ν , and the new parameter α . Some evaluations are presented in Figure 6, once again using the styrene data as a template. These illustrate that: (i) CLDT acts to broaden MMDs (a point that will be returned to); and (ii) (27) with $\lambda = 0$ and $\alpha = 0.19$ provides a beautiful description of the experimental data.⁴¹ In contrast to the fitting with (22b), both these values are mechanistically plausible: λ as already explained, while this α is spot on for CLDT of long-chain styrene.¹⁸ One may feel highly encouraged by this success.

2.3.2 Instantaneous Number-Average Degree of Polymerization

Number-average degree of polymerization or DP_n is just the arithmetic mean of the number CLD (see below). For the discrete and continuous forms of the Schulz–Flory distribution, (22a) and (22b) respectively, one obtains

$$DP_n \stackrel{\text{def.}}{=} \sum_{i=1}^{\infty} i n_i = F_n \frac{1}{1 - S} + (1 - F_n) \frac{2}{1 - S} \quad (28a)$$

$$\begin{aligned} DP_n &\stackrel{\text{def.}}{=} \int_0^{\infty} i n_i di = F_n \nu + (1 - F_n) 2\nu \\ &= \nu(2 - F_n) = \nu \left(2 - \frac{2F_w}{1 + F_w} \right) \quad (28b) \end{aligned}$$

One sees in these equations the well-known result that combination ($F_n = 0$) gives double the DP_n of disproportionation ($F_n = 1$). A more widely used form⁹ of (28b) is that originally due to Mayo:⁴²

$$\frac{1}{DP_n} = \frac{k_{tr} c_X}{k_p c_M} + \frac{(1 + \lambda)(0.5 R_i \langle k_t \rangle)^{0.5}}{k_p c_M} \quad (29)$$

This suggests plotting data as $1/DP_n$ versus a varied quantity, for example, c_X or $(c_1)^{0.5}$. Such plots are known as *Mayo plots* and the resulting linear fits are used to obtain rate coefficients from the intercept and/or slope.⁹ An example is presented in Section 6. While (29) is parameter-rife, one should not forget the truth of (28): the value of DP_n actually depends on only two composite parameters. A subtle but important change from (28b) and (29) is that from k_t to $\langle k_t \rangle$: in fact these equations hold also for CLDT,^{5,43} even if the Schulz–Flory distribution is only for CLIT.

A *propos* CLDT, in the event of negligible transfer and the geometric-mean model one has

$$DP_n = \Gamma\left(\frac{2}{2-\alpha}\right) \left[\frac{(2R_i k_t^{1,1})^{0.5}}{k_p c_M} \left(\frac{2}{2-\alpha}\right) \right]^{-2/(2-\alpha)} \times \left(\frac{2}{2-\alpha} \frac{2}{1+\lambda}\right) \quad (30)$$

This may be derived either as the first moment of (27)⁴⁰ or, more simply, by substituting (17) for $\langle k_t \rangle$ into (29).¹⁸

The importance of the equations here is that DP_n is the index of polymer size that is most commonly used in correlations for material properties. So these equations are important not only for modeling of material properties but also in establishing that material properties are intimately connected with kinetics, because it is evident that DP_n is entirely a product of polymerization kinetics.

polydispersity index.⁴⁴ The definition and results for (22a) and (22b), respectively, are

$$D_n \stackrel{\text{def.}}{=} \frac{DP_w}{DP_n} = \frac{1}{2}(1 + F_w)(2 + S - F_w) \quad (31a)$$

$$D_n = \frac{1}{2}(1 + F_w)(3 - F_w) \quad (31b)$$

Here, DP_w denotes weight-average degree of polymerization, while the subscript n is used with dispersity to denote that this particular ratio reflects the variance of the *number* CLD³⁸ (analogous to DP_n denoting the mean of this distribution). In the long-chain limit ($S \rightarrow 1$), (31a) is identical to (31b). The latter equation easily yields the textbook results of $D_n = 1.5$ for combination ($F_w = 0$) and $D_n = 2$ for disproportionation and/or transfer ($F_w = 1$).

For CLDT in the absence of transfer, one obtains from (27) that⁴⁰

$$D_n = \frac{1+\lambda}{2} \left\{ \frac{\Gamma\left(\frac{6-\alpha}{2-\alpha}\right)}{\left[\Gamma\left(\frac{4-\alpha}{2-\alpha}\right)\right]^2} + 1 - \lambda \right\} \quad (32)$$

2.3.3 Instantaneous Dispersity

Dispersity D_n is the IUPAC-recommended name for what is commonly but problematically called

This correctly reduces to (31b) for CLIT ($\alpha = 0$). Some evaluations of (32) are presented in Figure 7. This makes clear that both disproportionation/transfer (i.e., increasing λ) and CLDT (i.e.,

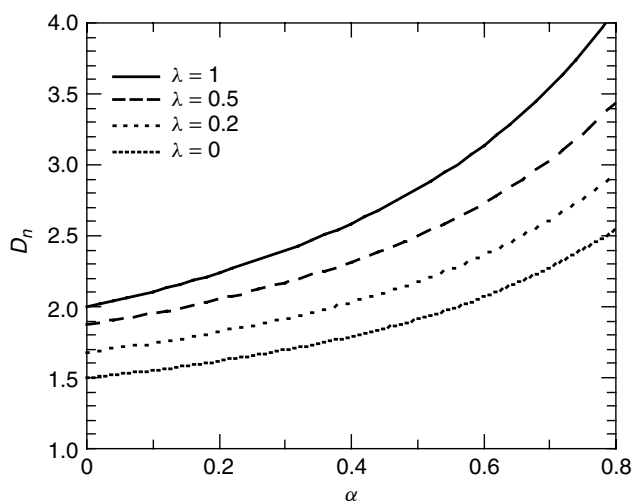


Figure 7 Dispersity D_n as a function of CLDT exponent α for $\lambda = 1$ (100% disproportionation), 0.5, 0.2, and 0 (100% combination) as calculated using (32). [The Kinetics of Radical Polymerization in Encyclopedia of Polymer Science and Technology, November 2010 in Encyclopedia of Polymer Science and Technology. Copyright 2011, John Wiley & Sons, Inc. This material is reproduced with permission of John Wiley & Sons, Inc.]

increasing α) act to increase D_n (i.e., broaden a MMD). Unfortunately, one cannot discriminate between these two causes of broadening from MMD data alone, as is implicit in the results of Figures 4 and 6. Rather, one needs prior information—for example, independent measurement of the disproportionation-to-combination ratio⁸—in order to be unambiguous in MMD modeling.

D_n is the almost universally used parameter for characterizing MMD broadness. This section has made clear how its value is rooted in kinetics. Once again, one sees the importance of kinetics.

2.3.4 Cumulative Quantities

All the equations presented so far have been for *instantaneous* molar masses. While these equations remain useful for *understanding* molar-mass results, their strict quantitative applicability is necessarily limited to polymer made over narrow conversion ranges. This is because any conversion of monomer into polymer results in change of c_M , which means that ν at the very least will alter in value (23b). But this is just the tip of the iceberg: c_1 will decrease with time (Section 2.2.2), while k_t and f probably will change with conversion (Section 2.2.3). This means that *cumulative* molar-mass quantities—that is, ones from polymerization over any significant interval of conversion—should be modeled via numerical integration of (6) and (7). This will yield c_{Di} (7), the concentration of dead polymer of chain length i , which is a form of the number-CLD. From this, one can then obtain all MMD quantities of interest as above. The commercial package PREDICI⁴⁵ provides a hassle-free way of achieving all this.

2.3.5 General Remarks on Molar Masses

A major aim in studying RP kinetics is to obtain values of rate coefficients, which potentially can depend on many variables: temperature (T), pressure (p), conversion, chain length, viscosity, and perhaps more. Frequently, this is attempted using information on molar mass. While the primacy of polymer molar mass is indisputable, one has to understand that it is difficult to extract unambiguous mechanistic information from MMD quantities, and

it is a dangerous exercise to attempt this. This is so for four different reasons, all of which reinforce each other.

Firstly, most experimental MMDs are from a broad range of conversions, meaning that they are the sum of numerous different instantaneous MMDs (Section 2.3.4). It seems impossibly ambitious that one might deconvolute a cumulative MMD into instantaneous MMDs from which authentic kinetic information may, with confidence, be extracted. This is problematic even where a succession of MMDs has been recorded with conversion. Yes, in principle one may then obtain *pseudo-instantaneous* MMDs through subtraction of cumulative MMDs. But the problem here is that this operation requires very high precision in the SEC signal, and this usually only exists (in terms of relative error) around an MMD peak.

This leads into the second general problem: n_i at small i is very influential in determining DP_n , but it is specifically at small i that the SEC signal—being proportional to $n_i i^2$ ((25) and (26))—is necessarily weak. Thus SEC can never yield the highly important quantity of DP_n with high precision. A visual illustration of this problem is provided by Figure 6. The two calculated MMDs in this figure have the same DP_n , but to the naked eye they look different. This is because the pronounced sections of the MMD at high i have relatively small influence on DP_n , but the sections at low i , where SEC signals are too small to be easily distinguished, have high influence.

Then there is the third problem, which is that SEC is still hostage to significant systematic errors, most notably from calibration,⁴⁶ band broadening,⁴⁷ and baseline selection. As has recently been summarized,⁴¹ all these factors can lead to the *apparent* MMD from SEC being quite different to the *true* MMD.

Finally, there is the problem explained in Section 2.3.3: even if one has a perfectly accurate instantaneous MMD, there can be ambiguity surrounding the mechanistic cause of its width (is it due to CLDT or to combination versus disproportionation/transfer?) and even its position (is it termination or transfer?).

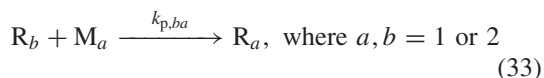
None of this is to deny that molar-mass modeling is of utmost importance and must be carried out. Nor is it to disparage SEC, which has improved to become a very reliable technique and is in no immediate danger of being overtaken by

mass spectrometry (MS),⁴⁸ its only serious competitor, as the preeminent technique for MMD determination of synthetic polymers. However, it is to urge that for genuine mechanistic investigations—as opposed to just arriving at an empirically successful description of MMDs—one should strive as far as possible to determine rate coefficients in separate kinetic experiments, preferably ones that are rate-based. This is especially so for $\langle k_t \rangle$ determination, in particular in regard to its conversion and chain-length dependences.³⁰ Armed with information from such experiments, one may then attack the task of understanding molar-mass information. For this, we strongly recommend modeling the entire MMD, as opposed to just seeking to reproduce an average molar mass and perhaps the dispersity. Given the discussion above, the reasons for this recommendation should be obvious.

2.4 Copolymerization

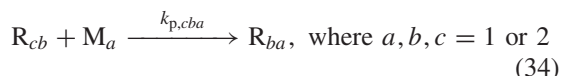
The fundamental equations above hold unchanged for copolymerization. What makes things more involved is that rate coefficients become averages over some composition. This issue is most important for propagation, and so for good reason it has received by far the greatest amount of attention. This is not just because k_p is paramount in determining rate and molar mass, but also because, as will shortly be seen, propagation alone determines *composition*, which is a vitally important copolymer quantity.

The *terminal model* (TM) for (binary) copolymerization propagation is



This says that k_p is influenced both by the monomer and the radical-bearing end unit of a growing chain. Even a non-chemist could hardly deny that matters cannot be any simpler than this. It turns out that the TM often does a sterling job of describing copolymerization data, as will be seen. For where it is insufficient, there are a plethora of more elaborate models to choose from. These have been reviewed elsewhere⁴⁹ and will not be described here. This is because most of these models may now be seen as flights of fancy. Ever since Fukuda *et al.*'s epochal paper of 1985,¹¹ the plausibility of

the *penultimate model* (PM) could not rationally be gainsaid. This model allows radical reactivity also to depend on the second monomer unit from the end of a chain:



Again, most chemists would regard this model as a matter of common sense, because part of the richness of chemistry is that the reactivity of functional groups is influenced by what is two or more bonds away from them. It may well be that there are other complicating factors at work in copolymerization, but these are unlikely to be as significant as that of the penultimate unit on k_p . Further, fact is that it is very rare for the PM, with its eight rate coefficients, not to be able to provide a global description of all data. Therefore, there is essentially no need to go beyond the model of (34).

2.4.1 Instantaneous Copolymer Composition

A very important copolymerization quantity is average whole-chain composition, that is, the fraction F_1 of residues of monomer type 1 in the polymer chains. This is because material properties of copolymers are intimately linked to F_1 . One of the most famous results in polymer science is

$$F_1 = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2f_1 f_2 + r_2 f_2^2} \quad (35)$$

where f_1 is the mole fraction of monomer 1 in the binary monomer mixture. For the TM, the two (*monomer*) reactivity ratios are $r_a = k_{p,aa}/k_{p,ab}$, where $a, b = 1$ or 2 and $b \neq a$. These capture the relative preference of a particular radical for the two different *monomers*. Equation (35) still holds for the PM, but the r_a 's are more complicated, as follows:⁴⁹

$$r_a = r_{ba} \frac{r_{aa} f_a + f_b}{r_{ba} f_a + f_b}, \text{ where } a, b = 1 \text{ or } 2 \quad \text{and } a \neq b \quad (36)$$

$$r_{aa} = \frac{k_{p,aaa}}{k_{p,aab}} \text{ and } r_{ba} = \frac{k_{p,baa}}{k_{p,bab}}, \quad \text{where } a, b = 1 \text{ or } 2 \text{ and } a \neq b \quad (37)$$

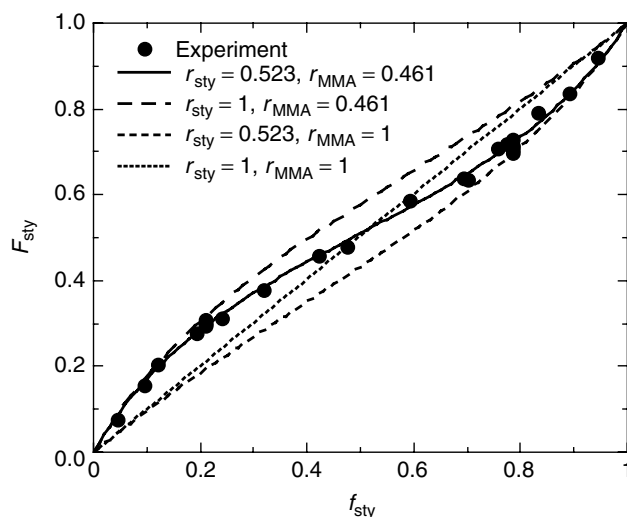


Figure 8 Mole fraction F_{sty} of styrene in copolymer as a function of mole fraction f_{sty} of styrene in monomer feed for styrene/methyl methacrylate bulk, low-conversion copolymerization at 40 °C. Points: experiment;¹¹ lines: evaluations of (35) with (constant) r values as displayed, where the unbroken line is the best (nonlinear least squares) fit to the data.

Thus now composition depends on four reactivity ratios rather than two. In both cases, F_1 depends only on ratios of $k_{p,(c)ba}$ values, not the values individually.

To obtain the r values, (35) should be fitted by nonlinear least-squares to experimental measurements of F_1 as a function of f_1 . An example is presented in Figure 8. It is evident that an exemplary fit is obtained with the TM, with constant values of r_1 and r_2 (cf. (36)). Examples where the PM is necessary for the fitting of composition data are rare but do exist, for example, styrene/acrylonitrile.⁵⁰ In the usual instance, there is no need to invoke (36).

It is instructive to evaluate (35) for some other pairs of r values. Results are also presented in Figure 8. One sees that, in this case, changing each best-fit value of r by a factor of (approximately) 2 does not have a profound effect, while changing them both by this amount actually keeps the composition curve in the vicinity of the data throughout (although admittedly $r_1 = r_2 = 1$ does make the system azeotropic under all conditions, a significant change). It is stressed that these effects vary with the r values. Nevertheless, these calculations give some insight into the difficulty of obtaining r values with high precision.

It is important to be clear that (35) is for *instantaneous* copolymer composition, that is, the copolymer produced at any instant. Thus it should

only be used for data gathered over a small range of conversion. Where there is significant change in conversion, there will be change of f_1 due to monomer consumption being at a different ratio (except in the rare event of $F_1 = f_1$, i.e., *azeotropic* conditions). This means that F_1 will change from instant to instant: so-called *composition drift* occurs. In this event, one should use an integrated composition equation to fit cumulative (average) F_1 data.

2.4.2 Overall Propagation Rate Coefficient

The following equation gives the value of k_p for SSP of two monomers:⁴⁹

$$k_p = \frac{r_1 f_1^2 + 2f_1 f_2 + r_2 f_2^2}{\frac{r_1 f_1}{k_{p,11}} + \frac{r_2 f_2}{k_{p,22}}} \quad (38)$$

A common misconception is that this equation with fixed r cannot adequately fit copolymerization k_p data. In fact, such data can be very well fitted in this way,⁵¹ but the problem is that the r values so obtained are quite different to those from fitting of composition data. As will be seen (Section 4.3.1), there is plentiful evidence that r

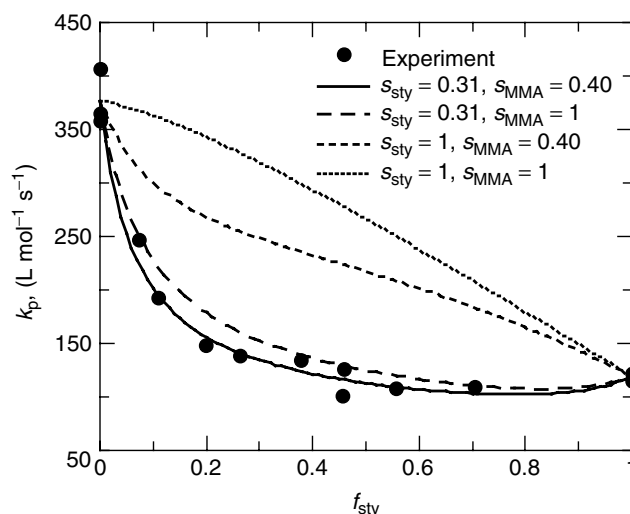


Figure 9 Overall propagation rate coefficient k_p as a function of mole fraction f_{sty} of styrene in monomer feed, for styrene/methyl methacrylate bulk, low-conversion copolymerization at 40 °C. Points: experiment;¹¹ lines: implicit-penultimate-model calculations ((38) and (39)) with s values as displayed and with $r_{\text{sty}} = 0.523$ and $r_{\text{MMA}} = 0.461$ (Figure 8). The unbroken line is the best (nonlinear least squares) fit to the data, while the dotted line ($s_{\text{sty}} = s_{\text{MMA}} = 1$) is the terminal-model prediction for this dataset.

values from composition correspond to the physical truth. When one uses such values in (38), usually an unacceptably inaccurate prediction for $k_p(f_1)$ is obtained, as is illustrated in Figure 9 for the system of Figure 8.

This highly unsatisfactory situation was first fully exposed by Fukuda *et al.*¹¹ and their explanation has stood the test of time: the PM is at work in copolymerization k_p . With this model, (38) still holds, but values in it vary with f_1 , the r_a according to (36), and the $k_{p,aa}$ according to:⁴⁹

$$k_{p,aa} = k_{p,aaa} \frac{r_{aa}f_a + f_b}{r_{aa}f_a + \frac{f_b}{s_a}}, \text{ where } a, b = 1 \text{ or } 2$$

$$\text{and } a \neq b \quad (39)$$

$$s_a = \frac{k_{p,baa}}{k_{p,aaa}}, \text{ where } a, b = 1 \text{ or } 2 \text{ and } a \neq b \quad (40)$$

The s_a 's are called *radical reactivity ratios*, because, whereas it is the monomer that varies in the r ratios, it is the penultimate radical unit that varies in the s ratios. This immediately implies that one should expect different behaviors from these two types of ratio.

The above development immediately raises two important issues. First, how should one deal with

the proliferation of parameters from four (TM) to eight (PM) involved in k_p prediction, an increase that provides too much flexibility in data fitting? Secondly, how to explain that, if the PM is necessary to understand k_p , then why is it not needed for F_1 data? Happily, Fukuda *et al.*¹¹ were immediately able to find a satisfactory explanation that eliminates both these problems. To wit, they reasoned that the absence of any regular need for the PM to describe composition data may be interpreted as likely evidence that $r_{21} \approx r_{11}$ and $r_{12} \approx r_{22}$, in which event the TM for composition is recovered (36). At first sight, this seems to contradict the very premise of the PM, but not when one thinks about it more closely: it seems quite reasonable to have that the penultimate unit affects the absolute value of $k_{p,cba}$ but not so much the *ratio* involved in r_a ; indeed, transition state (TS) theory provides support for this notion.⁵² This being the case, one has the far more manageable situation of introducing only two extra parameters, s_1 and s_2 , for describing k_p data.

By now, the idea that $r_{21} = r_{11}$ and $r_{12} = r_{22}$ has come to be known as the *implicit penultimate model* (IPM),⁵³ meaning that there is a penultimate-unit effect in propagation but it is not explicitly observable in composition, only in (overall) k_p . Most copolymerization datasets (F_1 and k_p) can be flawlessly described by this model, as is illustrated for

styrene/MMA in Figure 9. The procedure is that one fits F_1 with the TM ((35); e.g., Figure 8), and then one uses the so-obtained r values in fitting k_p data with the PM ((38) and (39)) such that only s_1 and/or s_2 may be varied (e.g., Figure 9). Only in rare cases is this procedure—the IPM—not adequate (see Section 4.3.2 for an example).

One must be aware that, just because the IPM works, this does not guarantee that the obtained reactivity ratios values represent the physical truth. A number of workers have explored this theme.^{51,54,55} Particularly worthy of mention is that (i) composition data is only weakly sensitive to deviations of r_{21} from r_{11} and r_{12} from r_{22} , meaning that success with $r_{21} = r_{11}$ and $r_{12} = r_{22}$ does not mean these equalities strictly hold;⁵⁴ (ii) k_p data usually is not sensitive to *both* s_1 and s_2 , but only to one of them.⁵⁵ This is illustrated in Figure 9, where it is shown that variation of s_{MMA} has only a very weak effect on calculated values of k_p . This means that this data does not deliver the value of s_{MMA} with even crude precision.^{5,55}

2.5 Pulsed-Laser Polymerization

The idyll of pulsed-laser polymerization (PLP) is sufficiently closely realized that it can be considered a reality. It is that a laser pulse instantaneously creates a crop of uniformly sized small radicals from photoinitiator, and thereafter there is no new radical generation (until the next pulse). Thus PLP is essentially the antithesis of SSP, because the system is permanently in a nonsteady (or nonstationary) state. There are several other long-known techniques for effecting nonsteady-state polymerization (NSSP),³⁰ but all have been rendered virtually redundant by the advent of PLP in the mid-1980s. This is because PLP may be employed in two particularly potent ways, as now described.

2.5.1 Single-Pulse PLP for Measuring Termination Rate Coefficients

PLP creates a monodisperse crop of radicals of size $i = 1$ at time $t = 0$. These then grow with time. Although there is some broadening of the distribution of sizes due to the stochastic nature

of propagation (leading to a Poisson distribution), to excellent approximation one can regard the population as remaining of single size given by $i = k_p c_M t + 1$.⁵⁶ This assumes that initiation *and* transfer—both leading to generation of small radicals—occur to a negligible extent during this period. For the most part, these are reasonable assumptions. What it leads to is that the termination rate at any instant is that between radicals of identical chain length, and so by measuring this rate one can obtain $k_t^{i,i}$. Further, as time goes on, a complete range of i will be traversed, meaning that in principle one can obtain the entire variation of $k_t^{i,i}$ with i .

This is the so-called single-pulse PLP (SP PLP) method for measuring termination rate coefficients. While this exceptional potential for determining CLDT rate coefficients was grasped some decades ago,⁵⁷ its widespread realization¹⁹ has occurred only in recent times with the coupling of the technique to electron paramagnetic resonance (EPR) spectroscopy (see **Analysis of Radicals by EPR**).⁵⁸ c_R is *directly* measured on a microsecond timescale by quantitative EPR, and the resulting variation is analyzed to obtain $k_t^{i,i}$. Ideally, one could differentiate the experimental data and thence obtain model-free $k_t^{i,i}$ from dc_R/dt ; however, in practice it has been found better to assume a power-law model for $k_t^{i,i}$ (e.g., (18)):

$$k_t^{i,i} = k_t^{1,1} i^{-\alpha} \quad (41)$$

When this is introduced into (13), one obtains for SP PLP⁵⁶

$$\frac{c_{R,0}}{c_R} - 1 = \frac{2c_{R,0}k_t^{1,1}}{k_p c_M (1 - \alpha)} [(k_p c_M t + 1)^{1-\alpha} - 1] \quad (42)$$

where $c_{R,0}$ is the radical concentration created by the laser pulse, which of course is measured as part of the experiment. An example of fitting SP PLP EPR data with (42) to obtain α and $k_t^{1,1}$ is given in Figure 10.⁵⁹ This illustrates the unique potency of the method for investigating CLDT of relatively small radicals, i.e., determining $k_t^{1,1}$ and α for small chains.

There are two important limits of (42). The first is that, for long times⁵⁸

$$\frac{c_{R,0}}{c_R} - 1 = \frac{2c_{R,0}k_t^{1,1}(k_p c_M)^{-\alpha}}{(1 - \alpha)} t^{1-\alpha} \quad (43)$$

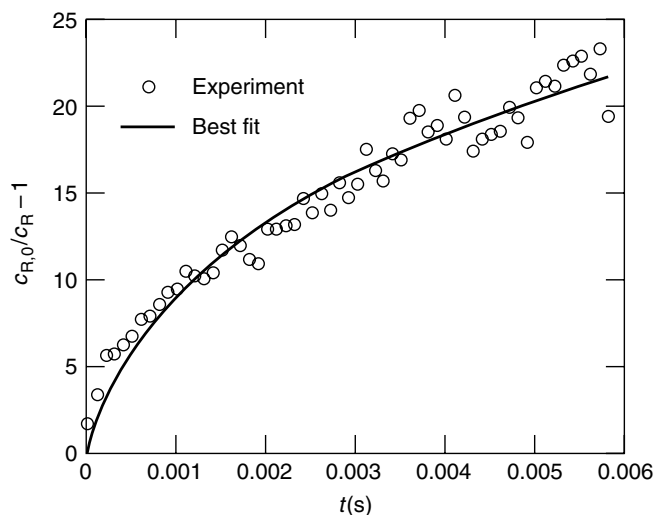


Figure 10 Radical concentration, plotted as $c_{R,0}/c_R - 1$, versus time t for a typical SP PLP EPR experiment. Points: data for 1.5 M methyl acrylate in toluene at -40°C ; line: (42) with best-fit values of $\alpha = 0.82$ and $k_t^{1,1} = 1.8 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.⁵⁹

This suggests plotting data as $\log(c_{R,0}/c_R - 1)$ versus $\log t$, fitting a straight line, and very simply extracting α from the slope.⁵⁸ This approach has been used for studying long-chain termination via SP PLP EPR.¹⁹

The second limit is that of CLIT, that is, $\alpha = 0$:

$$c_R = \frac{c_{R,0}}{2k_t c_{R,0} t + 1} \quad (44)$$

With this expression, (12) is integrable, giving the result

$$\frac{c_M}{c_{M,0}} = (2k_t c_{R,0} t + 1)^{-k_p/(2k_t)} \quad (45)$$

Here, $c_{M,0}$ is the monomer concentration at the time of laser pulsing. Equations (44) and (45) are the basis of the long-standing⁶⁰ SP PLP NIR method for k_t determination: near-infrared (NIR) spectroscopy is used to monitor c_M on a microsecond timescale, and the resulting variation is fitted with (45) to obtain k_p/k_t , from which k_t can be procured if k_p is known. It is a universal feature of NSSP methods that they yield k_p/k_t , whereas SSP methods all yield $k_p/(\langle k_t \rangle)^{0.5}$, for example see (16) and (29).³⁰ As the notation here implies, the k_t yielded by NSSP experiments is more complicated in that it is an average over both time and chain length.

The conversion consequent upon a single laser pulse is usually extremely small, much less than 1%.

Thus SP PLP—whether carried out in conjunction with EPR or NIR—may be used to map out the variation of termination rate parameters with conversion in extremely fine detail, far more so than with any other method:³⁰ one simply has to start an SP PLP experiment and continue to make measurements as conversion slowly increases under the action of the laser. This is another reason why SP PLP has been recommended as the premier method for studying termination kinetics in RP.³⁰

2.5.2 Multiple-Pulse PLP for Measuring Propagation Rate Coefficients

Consider carrying out a PLP in which laser pulses periodically strike at intervals of t_d (standing for “dark time”). This situation will be termed *multiple-pulse PLP* (MP PLP). When a new pulse arrives, the radical CLD will consist of essentially monodisperse populations of sizes $k_p c_M t_d$, $2k_p c_M t_d$, $3k_p c_M t_d$, and so on, from previous pulses: this follows from the principles explained above. As a result of the new pulse, these populations will be suddenly subjected to a vastly increased frequency of termination, because of the creation of a whole host of new radicals. Thus there will be a marked increase in the production of dead chains around sizes $k_p c_M t_d$, $2k_p c_M t_d$, $3k_p c_M t_d$, and so on.

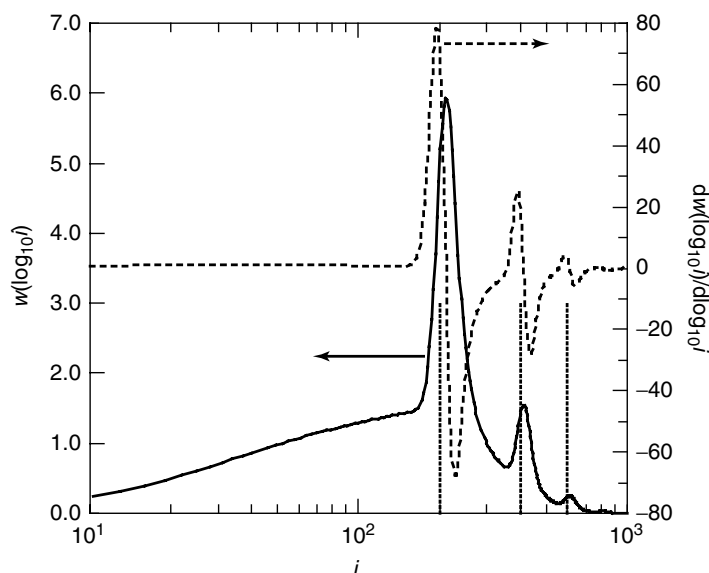


Figure 11 Results from simulation of a multiple-pulse PLP with $k_{pCM} = 2000 \text{ s}^{-1}$, $k_t = 1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, $c_{R,0} = 5 \times 10^{-8} \text{ M}$, $t_d = 0.1 \text{ s}$, $\lambda = 1$, and $k_{trX} = 0$.⁶² Full line: $w(\log_{10} i)$, where w is weight fraction and i is chain length; broken line: $dw(\log_{10} i)/d \log_{10} i$; dotted vertical lines: positions of chain lengths (left to right) $k_p c_M t_d$, $2k_p c_M t_d$, and $3k_p c_M t_d$, showing that these are very close or equal to positions of the maxima in the derivative trace.

Therefore if the dead-chain CLD is determined at the end of the experiment, it will contain identifiable features at these chain lengths, designated i_n . By reading off these values, it is a simple matter to determine k_p , because t_d (the inverse of the laser pulsing frequency) and c_M are easily controlled and known:

$$k_p = \frac{i_n}{n t_d c_M}, \quad n = 1, 2, 3, \dots \quad (46)$$

This was the revolutionary idea published by Olaj *et al.* in 1987.⁶¹

A theoretical validation of this idea is presented in Figure 11, which shows a set of results⁶² from numerical solution of (6) and (7) for the situation of MP PLP. It is evident that the chain length $k_p c_M t_d$ and its integer multiples lie a little to the low-molar-mass side of the CLD peaks rather than exactly at their center. The reason for this was realized right from the beginning:⁶¹ the radical CLD consists of Poisson distributions and termination is not instantaneous. Without either one of these conditions, $k_p c_M t_d$ corresponds to the peak positions. How then to determine k_p ? Workers have remained with Olaj *et al.*'s initial suggestion of using the position of the point of inflection on

the low-molar-mass side of each CLD peak.⁶¹ It is shown in Figure 11 that these features give $k_p c_M t_d$, and hence k_p , accurately. However, one should always remember that this is not an *exact* result, and so it introduces a small but unavoidable degree of systematic error into the values of k_p obtained by this technique. Again, this is evident in Figure 11.

That is the theory: what about reality? A typical set of results is presented in Figure 12.⁶³ It is clear that in essence the theoretical expectations of Figure 11 are observed. The major difference is that SEC column broadening acts to disperse the sharp features of the theoretical CLD. Nevertheless, these features are still clearly visible in the actual CLD, and it has been confirmed that this broadening does not undermine k_p determination.⁶⁴ This study also illustrates how the sharpness and relative intensities of the PLP-induced peaks are a function of the parameters k_t , $c_{R,0}$, and t_d , but that this also does not affect k_p determination.⁶⁴ Standard practice is to use only the first MMD inflection point ($n = 1$ in (46)) for quantitative k_p determination, because the first maximum in experimental derivative traces is far more strongly evident than the higher order maxima, as may be seen in Figure 12. Instead, these are best employed as “consistency

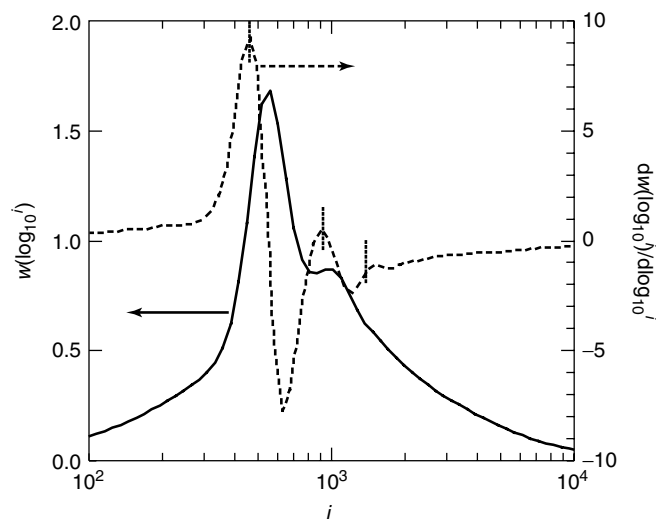


Figure 12 Results from an MP PLP of bulk methyl methacrylate at 40 °C with $t_d = 0.1$ s.⁶³ Full line: $w(\log_{10} i)$, where w is weight fraction and i is chain length; broken line: $dw(\log_{10} i)/d \log_{10} i$; short dotted vertical lines: positions of chain lengths (left to right) 460, 2×460 , and 3×460 , making it clear that the positions of the maxima in the derivative trace are (close to) equal to multiples of $k_p c_M t_d$. [The Kinetics of Radical Polymerization in Encyclopedia of Polymer Science and Technology, November 2010 in Encyclopedia of Polymer Science and Technology. Copyright 2011, John Wiley & Sons, Inc. This material is reproduced with permission of John Wiley & Sons, Inc.]

checks”: their position should be close to the appropriate multiple—see (46)—of the position of the first peak for the obtained value of k_p to be considered robust.⁶⁵ Again, Figure 12 exemplifies the successful meeting of this criterion.

It took only a short time before the MP PLP method was recommended by IUPAC as the method of choice for k_p determination.⁶⁵ Reviews testify to how widely and successfully it has been deployed.^{66,67} The major reasons for this are the intuitive nature of the method and the fact that it is independent of knowledge of essentially all other rate parameters.

3 INITIATION

An excellent survey of the experimental methods and kinetic results about initiator decomposition is given in Moad and Solomon's book.⁶ A variety of methods have been used for detection of the disappearance of initiators and the appearance of products from initiator decomposition. They encompass spectroscopic methods such as UV–vis and IR–NIR spectroscopy. Trapping techniques have been employed and the type and concentration of the so-obtained primary adducts have been

measured. Most recently, electrospray ionization (ESI) mass spectroscopy on oligomeric species has turned out to be a promising method for detection of the type of initiator fragments that start macromolecular growth by addition to a monomer molecule.^{68–71}

The two pieces of kinetic information that are essential knowledge in applying chemical initiators in RP are (Section 2.1) decomposition rate coefficient k_d , which defines decline in initiator concentration with time, and efficiency of initiation f , which indicates the fraction of primary radicals that start chain growth. As initiator decomposition rates are mostly determined in independent experiments by monitoring initiator decay in an inert solvent, it is recommended to employ a solvent as similar as possible to the monomer system of interest, since k_d depends on solvent properties. Of course, f can be measured only in the presence of monomer (without which $f = 0$ by definition). In any event, the solvent in which k_d has been measured should be stated when presenting polymerization data. As an example, for use with ethylene polymerization, k_d values from decomposition experiments of initiators dissolved in compressed *n*-heptane appear to be appropriate.

There are a number of classes of chemical initiators, for example, azo compounds, dialkyl peroxides, hydroperoxides, peroxyesters, diacylperoxides, peroxycarbonates, and peroxydicarbonates (see **Overview of Radical Initiation**). In what follows, we present aspects of using peroxyesters, $R(CO)OOC(CH_3)_2R^*$, as a source of primary reactive species for RP. Of course, the general principles thus revealed should hold also for other classes of initiators, and the presented values of rate parameters give a feel for these with all initiators.

3.1 Decomposition Rate Coefficients

Quantitative IR spectroscopy has turned out to be very useful for measuring the decay of peroxide concentration or, alternatively, the increase in the concentration of products from decomposition. Two discontinuous procedures have been used:

1. At lower reaction temperatures, the peroxide solution is contained in an internal cell, which is filled and assembled in a glove box under an argon atmosphere. The internal cell is positioned into an optical high-pressure cell and pressurized with *n*-heptane acting as the pressure-transmitting medium. The assembly is heated to the reaction temperature and the collection of IR spectra is started. In the case that the decomposition rate becomes too fast and a major fraction of the peroxide is decomposed before reaction conditions of constant T and p are reached, the peroxide solution is directly fed into a pre-heated autoclave. The solution is then quickly pressurized and the collection of IR spectra is started.
2. Kinetic analysis under conditions where decomposition is fast, for example reaction half-lives well below 1 minute, has been performed using a tubular reactor which essentially consists of a high-pressure capillary of 10 m (or even longer) length and 0.5 mm internal diameter.⁷² The IR spectroscopic analysis is performed at reaction pressure, but at lower temperature, in an optical cell that is positioned directly behind the tubular reactor.

A wide variety of peroxyesters with the general structure $R(CO)OOC(CH_3)_2R^*$ —see Figure 13—are commercially available,⁷³ where R and R^* may

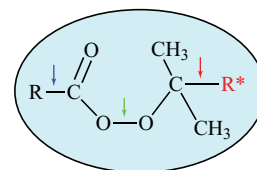


Figure 13 General structure of a peroxyester, with the arrows indicating the positions where bonds may break during initiator decomposition.

be primary, secondary, or tertiary alkyl groups such as methyl, ethyl, *iso*-propyl, and *tert*-butyl. The primary step of thermally induced initiator decomposition consists of breaking the O–O bond. In the case of very fast or even concerted successive bond scission of the primary radical fragments from initiator decomposition, the overall decomposition rate coefficient k_d may be affected. The follow-up reactions chiefly are β -scission reactions, in which the labile bond in a β -position to the radical functionality is broken. An important such β -scission process is decarboxylation of the primary radical $R(CO)O\cdot$. Also, the second radical fragment from peroxyester decomposition, $OC(CH_3)_2R^*\cdot$, may undergo β -scission, forming acetone plus an R^* radical. The β -scission reactions are particularly fast in cases where a stable radical, for example, a *tert*-butyl radical, is produced.

The k_d values of primary peroxyesters—i.e., where R is CH_3 or CH_2R' —are more or less identical at the same temperature and pressure, whereas the type of R moiety matters with secondary and tertiary peroxyesters. This difference between primary peroxyesters on the one hand and secondary and tertiary peroxyesters on the other is understood as being due to close-to-concerted β -scission with secondary and tertiary peroxyesters but slow β -scission with primary peroxyesters. Within the latter group of initiators, the R group of the $R(CO)O$ moiety is too far away from the peroxy linkage to affect the primary decomposition of the O–O linkage of the peroxyester. The opposite is the case with tertiary peroxyesters, where the stable tertiary radical is immediately formed and the specific type of R moiety thus affects decomposition kinetics.

This interpretation is supported by the activation energies measured for the overall first-order decomposition rate coefficients k_{obs} of peroxyesters.^{74,75} In Figure 14, numbers for the activation energy at low pressure $E_A(0 \text{ bar})$ are plotted against the bond

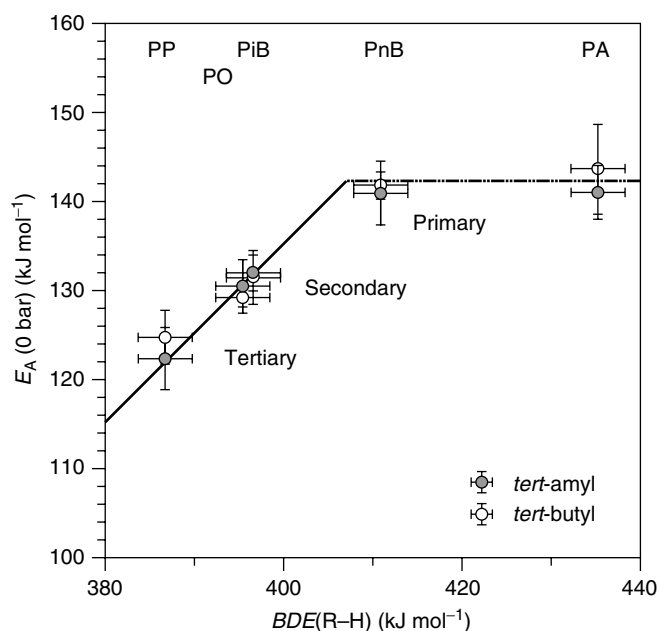


Figure 14 Activation energy $E_A(0 \text{ bar})$ of the decomposition rate coefficient for *tert*-amyl (filled circles; $R^* = \text{ethyl}$) and *tert*-butyl (open circles; $R^* = \text{methyl}$) peroxyesters at low pressure as a function of bond dissociation energy of the associated alkane $BDE(R-H)$. PP: peroxypivalate; PO: peroxy-2-ethylhexanoate; PiB: peroxy-*iso*-butyrate; PnB: peroxy-*n*-butyrate; PA: peroxyacetate. [Reproduced with permission from Ref. 75. © Oldenbourg Verlag, 2003.]

dissociation energy of the R–H bond $BDE(R-H)$, which serves as a measure of the stability of the radical R. For primary peroxyesters, the activation energy is insensitive toward $BDE(R-H)$, whereas for secondary and tertiary peroxyesters the stability of R clearly matters. Further, $E_A(0 \text{ bar})$ of secondary and tertiary peroxyesters is linearly correlated with the associated $BDE(R-H)$, indeed, the correlation has unity slope. As shown, these trends are the same for both *tert*-butyl and *tert*-amyl peroxyesters, that is, they are independent of R^* . This indicates that the correlation essentially reflects the decarboxylation process of the $R(\text{CO})\text{O}$ radical.

Similarly, the pressure dependence of k_{obs} is clearly different for primary peroxyesters on the one hand and for secondary and tertiary peroxyesters on the other.^{74,75} Plotted in Figure 15 are values of $k_{\text{obs}}/k_{\text{obs}}(2000 \text{ bar})$, that is, decomposition rate coefficient relative to the value at 2000 bar. Secondary and tertiary peroxyesters behave similarly in that they exhibit a weak decrease of k_{obs} toward higher pressure, whereas primary peroxyesters show a pronounced decrease. This difference is explained as follows: In the case of primary peroxyesters, the

activation volume is assigned to single-bond scission, which is associated with a pronounced increase in molar volume of the activated state. On the other hand, secondary and tertiary peroxyesters undergo almost concerted bond scission with the immediate production of the linear CO_2 molecule. This gives rise to only a weak increase in molar volume of the activated state, even though two bonds are broken.

Rate coefficients for decomposition of aliphatic *tert*-amyl peroxyesters are given by

$$k_{\text{obs}}(p, T) = A \exp \left(\frac{E_A(0 \text{ bar}) + \Delta V^\ddagger p}{RT} \right) \quad (47)$$

with values of the parameters A , $E_A(0 \text{ bar})$, and $\Delta V^\ddagger$ as listed in Table 1.⁷⁵ Expressions for $k_{\text{obs}}(p, T)$ for *tert*-butyl peroxyesters are also available.⁷⁴

3.2 Initiator Efficiency

The mechanism of the primary peroxyester dissociation event is of relevance for initiator efficiency. In the case of concerted two-bond scission, the primary

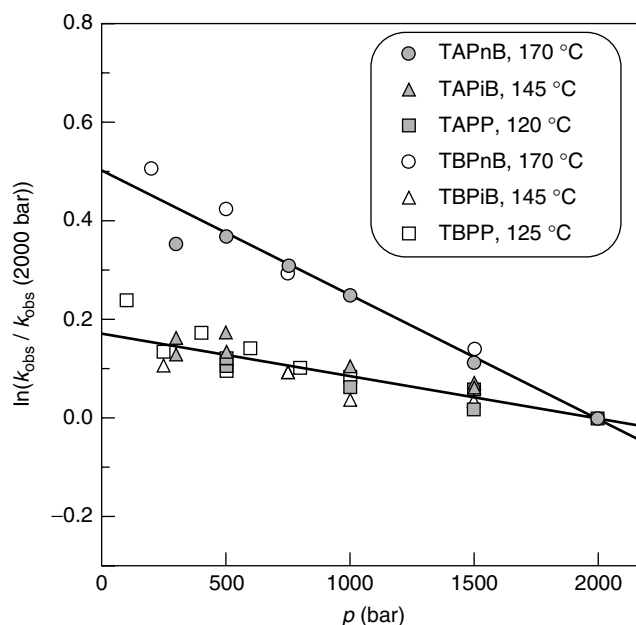


Figure 15 Pressure dependence of observed decomposition rate coefficient relative to value at 2000 bar, $k_{\text{obs}}/k_{\text{obs}}(2000 \text{ bar})$, for *tert*-amyl peroxyesters (TA; filled symbols) and *tert*-butyl peroxyesters (TB; open symbols) at constant temperature (between 120 and 170 °C). PnB: peroxy-*n*-butyrate (circles; primary R^{*}); PiB: peroxy-*iso*-butyrate (triangles; secondary R^{*}); PP: peroxy-pivalate (squares; tertiary R^{*}). [Reproduced with permission from Ref. 75. © Oldenbourg Verlag, 2003.]

Table 1 Values of A , $E_A(0 \text{ bar})$, and $\Delta V^\ddagger$ for use in (47) for estimating initiator decomposition rate coefficients as a function of p and T for *tert*-amyl peroxyesters.⁷⁵

Initiator	$A \text{ (s}^{-1}\text{)}$	$E_A \text{ (0 bar)}$ (kJ mol ⁻¹)	$\Delta V^\ddagger$ (cm ³ mol ⁻¹)
TAPA	1.52×10^{15}	141.2	12.5
TAPnB	1.03×10^{15}	139.6	8.2
TAPiB	7.53×10^{14}	132.9	2.6
TAPEH	7.27×10^{14}	130.5	2.8
TAPP	4.11×10^{14}	122.7	2.4

TAPA, *tert*-amyl peroxyacetate; TAPnB, *tert*-amyl peroxy-*n*-butyrate; TAPiB, *tert*-amyl peroxy-*iso*-butyrate; TAPEH, *tert*-amyl peroxy-2-ethylhexanoate; TAPP, *tert*-amyl peroxy-pivalate.

radical fragments from decomposition may react with each other, by combination or disproportionation, within the solvent cage. These follow-up reactions reduce radical concentration and thus lower the initiator efficiency. In case of single-bond scission, combination of the primary fragments from peroxyester decomposition recovers the initiator, which may dissociate again to produce growing radicals. It is for this reason that the initiator efficiency of

primary peroxyesters is above that of secondary and tertiary peroxyesters.

Despite their lower efficiency, secondary and tertiary peroxyesters are widely used initiators, as they decompose much faster and thus allow radical production at lower temperatures. As monomer conversion is associated with a significant enhancement of temperature—in ethylene high-pressure polymerization amounting to about 11 °C per 1% conversion under adiabatic conditions—it is important to have an initiation strategy that delivers radicals at a practicable rate over a wide temperature range if one is to attain high monomer conversion in technical polymerization processes. In ethylene polymerizations, either mixtures—so-called cocktails—of initiators are applied or a high-temperature initiator is fed at the later stages of the tubular reactor.

The kinetically relevant quantity for modeling initiation in radical polymerization is R_i , which is the rate at which primary initiator-derived radicals add to monomer and thus start chain growth (Section 2.1). R_i is given by (8) for monofunctional peroxides; for bifunctional initiators, this simple expression is multiplied by 2, for trifunctional by 3, and so on. By definition, f is in the range

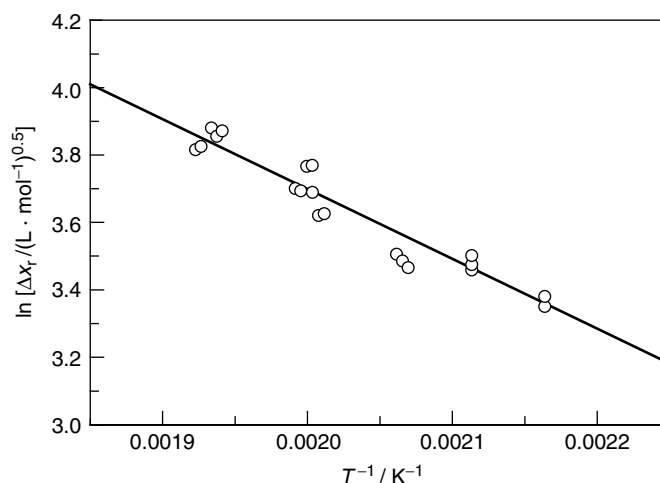


Figure 16 Arrhenius plot of reduced peroxide-induced monomer conversion Δx_r for ethylene polymerization initiated by di-*tert*-butyl peroxide and carried out at 2000 bar in the CSTR of a mini-plant device (see text).⁷⁶

from zero to unity. The fraction $(1 - f)$ refers to radicals that are consumed in side reactions other than recombination back to the initiator molecule.

Because of its enormous technical relevance, initiator efficiency has been studied in quite some detail for ethylene high-pressure polymerizations with initiation by a wide variety of organic peroxyesters.⁷⁶ Determination of f has been carried out via the quantity “reduced peroxide-induced monomer conversion” Δx_r .⁷⁷ Δx_r has been measured under stationary conditions in a continuously stirred tank reactor (CSTR). The quantity Δx_r is related to the rate coefficients of propagation k_p and termination k_t , to CSTR residence time τ , and to initiator efficiency f , via

$$\Delta x_r = \frac{\Delta x}{(c_{I,dec})^{0.5}} = \frac{k_p}{k_t^{0.5}} f^{0.5} \tau^{0.5} \quad (48)$$

$c_{I,dec}$ is the difference between c_I of the mixture prior to entering the CSTR and the actual c_I in the CSTR.

To avoid uncertainties that may result from the imprecise knowledge of k_p and k_t at polymerization conditions, it is recommendable to use (48) for f estimation by comparison with Δx_r measured for a reference initiator of known f under otherwise identical polymerization conditions, i.e., the same k_p , k_t , and τ .⁷⁷ Shown in Figure 16 is an Arrhenius plot of Δx_r for ethylene polymerizations at 2000 bar initiated by DTBP (Section 1.2). For this system,

f_{DTBP} is close to unity.⁷⁷ Therefore this system may be used to determine f of an arbitrary peroxyester: one compares the measured Δx_r values for the initiator under investigation and for DTBP under otherwise identical reaction conditions, and then via the known decomposition rate coefficients of the two initiators (which are involved in determining $c_{I,dec}$) one obtains the efficiency f for the initiator of interest.

The initiator efficiencies of 15 peroxides⁷³ are collated in Table 2.⁷⁶ Both alkyl groups R and R* of the *tert*-alkyl peroxyesters R-(CO)-O-O-C(CH₃)₂-R* (Figure 13) have been varied. The efficiency values of the peroxyesters under investigation are in the range $0.4 < f < 0.9$. The only previous literature values are for TBPEH and TBPP, for which Luft and coworkers^{78,79} found f_{TBPEH} to be above f_{TBPP} for ethylene polymerizations at 1700 bar. This is consistent with the numbers in Table 2 and with results reported by van der Molen *et al.*⁸⁰

To visualize the dependence of initiator efficiency on the type of peroxyester R group, f values of the five *tert*-butyl peroxyesters in Table 2 are plotted in Figure 17. Clearly, the size of f depends on whether the carbon atom in the α position to the carbonyl group is primary, secondary or tertiary. In passing from primary to tertiary peroxyesters, the initiator efficiency clearly decreases, but at the same time is essentially independent of the size of R. As a second piece of information, Figure 17 indicates that

Table 2 Initiator efficiencies f of peroxyesters $R-(CO)-O-O-C(CH_3)_2-R^*$ in high-pressure ethylene polymerization at 2000 bar.⁷⁶

Peroxyester	f
TBPA	0.79 ± 0.06
TBPPent	0.85 ± 0.05
TBPiB	0.66 ± 0.08
TBPEH	0.62 ± 0.03
TBPP	0.37 ± 0.04
TAPA	0.69 ± 0.08
TAPnB	0.73 ± 0.07
TAPiB	0.56 ± 0.08
TAPEH	0.61 ± 0.10
TAPP	0.48 ± 0.06
TMBPA	0.76 ± 0.06
TMBPEH	0.61 ± 0.07
TMBPP	0.50 ± 0.05
TMPPA	0.50 ± 0.05
TMPPP	0.50 ± 0.02

The beginning letters of the abbreviations refer to $C(CH_3)_2-R^*$: TB, *tert*-butyl; TA, *tert*-amyl; TMB, 1,1,3,3-tetramethylbutyl; TMP, tetramethylpropyl. The end letters refer to $R-(CO)-O-O$: PA, peroxyacetate; PnB, peroxy-*n*-butyrate; PPent, peroxy-*n*-pentanoate; PiB, peroxy-*iso*-butyrate; PEH, peroxy-2-ethylhexanoate; PP, peroxy-pivalate.

f does not significantly depend on polymerization temperature. This finding may be understood as a consequence of f being determined by fast in-cage radical–radical processes.

With respect to initiator efficiency, it is of primary importance whether successive β -scission of primary radical species from initiator decomposition occurs within the short time interval, of about 1 ns duration, during which the radicals $R^*C(CH_3)_2O^*$ and $RCOO^*$ remain caged together. The two dominant follow-up reactions are decarboxylation of $RCOO^*$ (giving R^* and CO_2) and “deacetonization” of $R^*-C(CH_3)_2O^*$ (giving acetone and R^* radical). Both of these are β -scission reactions. With primary peroxyesters, for example, *tert*-butyl peroxyacetate, decarboxylation is too slow to occur to a large extent on the nanosecond timescale. On the other hand, the lower energy of tertiary radicals, for example, of *tert*-butyl, makes β -scission processes leading to *tert*-butyl radicals very fast, as with peroxy-pivalates. Any subsequent in-cage loss of radicals results in a lowering of initiator efficiency. This is pronounced in the case that the *tert*-butyl radical arises while highly reactive oxygen-centred radicals are simultaneously present. This situation may occur with the decompositions of rather dissimilar peroxyesters, as is illustrated in Figure 18, which takes tetramethylpropyl peroxyacetate and *tert*-butyl peroxy-pivalate as examples. With both peroxyesters, a *tert*-butyl radical is rapidly formed by deacetonization and decarboxylation, respectively. It then reacts with the other primary radical, which is oxygen-centred, via very fast disproportionation, resulting in lowered f .

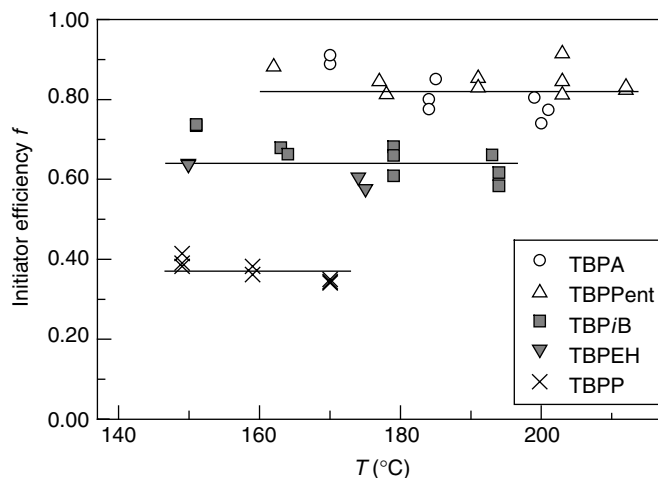


Figure 17 Initiator efficiency f of *tert*-butyl peroxyesters in high-pressure ethylene polymerization at 2000 bar. Abbreviations for initiators are as in Table 2. The upper, middle, and lower lines indicate the arithmetic mean values of f for primary, secondary, and tertiary peroxyesters, respectively. [Reproduced from Ref. 76. © Wiley-VCH Verlag GmbH & Co. KGaA, 2007.]

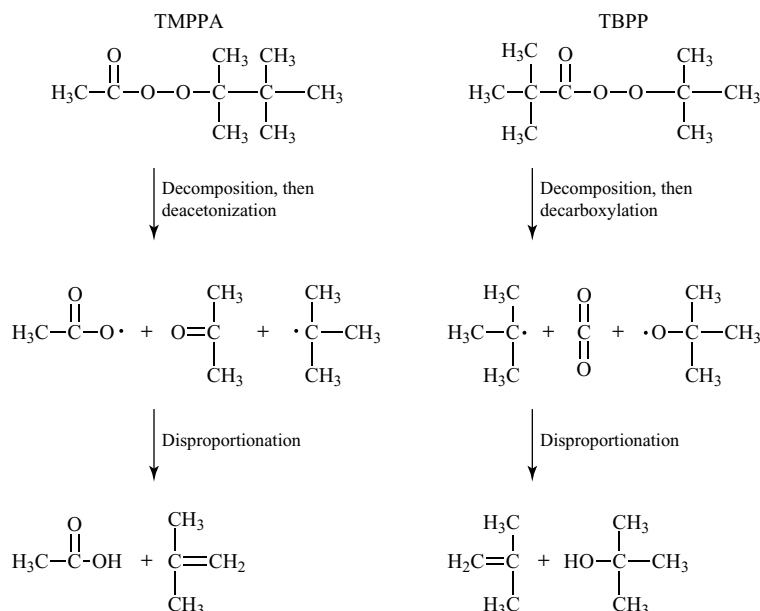


Figure 18 Decomposition scheme for tetramethylpropyl peroxyacetate (TMPPA, left) and *tert*-butyl peroxyvalate (TBPP, right), showing irrecoverable loss of primary radicals, meaning initiator efficiency is low.

Density functional theory (DFT) calculations in conjunction with unimolecular rate theory support the findings for the dependence of β -scission rate coefficient k_β on the type of R-substituent.⁸¹ In passing from the *tert*-butoxy radical to the 1,1,2,2-tetramethylpropyloxy radical, k_β increases by about four orders of magnitude. These results from DFT calculation indicate that deacetonization occurs as an in-cage process with 1,1,2,2-tetramethylpropyloxy radicals, whereas with *tert*-butoxy, *tert*-amyloxy, and 1,1,3,3-tetramethylbutyloxy radicals this reaction most likely takes place out of the cage.

As well as variation from initiator to initiator, f also depends on conversion, as outlined in Section 2.2.3. Unfortunately, this important variation has been measured only very occasionally, most notably by quantitative IR³⁶ and NMR³⁷ spectroscopy, which may be used to monitor the appearance of end groups vis-à-vis side products from the initiator.

3.3 Photoinitiation

It is beyond the scope of this section to describe photoinitiation in any detail. However, a short

comment appears to be appropriate, as a variety of laser-induced techniques have become of pivotal importance for detailed investigations into rate coefficients of radical polymerization (Section 2.5). 2,2-Dimethoxy-2-phenyl acetophenone (DMPA) and benzoin have frequently been used as photoinitiator in PLP experiments. A problem with these initiators is that one fragment is resonance-stabilized—as shown in Figure 19 for DMPA—and thus is not prone to start propagation. Not only does this result in low efficiency (i.e., wasted initiator) but it may lead to different kinetics. For example, in SP PLP experiments to investigate chain-length-dependent termination (Section 2.5.1), the proportionality between radical size and time after applying the laser is affected, resulting in highly unusual $c_M(t)$ traces.⁸²

In view of this situation, α -methyl-4(methylmercapto)- α -morpholinopropiophenone (MMMP) has been used as a more ideal photoinitiator.^{83,84} As shown in Figure 19, neither of the primary radicals from its photochemical decomposition is resonance-stabilized, and therefore they both rapidly add to monomer.

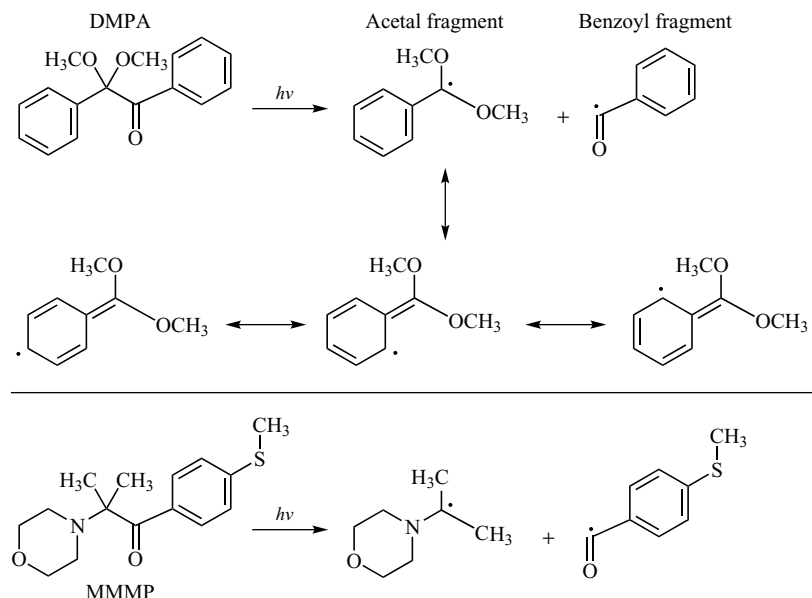


Figure 19 Photoinduced decomposition of 2,2-dimethoxy-2-phenyl acetophenone (DMPA; top portion of scheme) and α -methyl-4(methylmercapto)- α -morpholinopropiophenone (MMMP; bottom). As shown, the acetal fragment from DMPA is resonance stabilized. Therefore it adds to monomer relatively slowly.

4 PROPAGATION

The addition of monomer to a radical species is considered to be a chemically controlled process, which is controlled by electronic, steric, and polar effects. The primary addition step, in which an initiator-derived radical species adds to a monomer molecule, differs from subsequent addition reactions in which monomer adds to monomer-specific radicals giving rise to radical chain extension by one monomer unit. With the exception of the early such addition steps of monomer to a monomer-specific radical, no chain-length dependence is expected to occur with propagation reactions.¹⁵ Propagation appears to be rather simple in that a radical species adds to monomer producing the same type of radical. Nevertheless, attempts to estimate accurate propagation rate coefficients from quantum chemical *ab initio* methods have not been overly successful so far, even if such calculations do detect the major trends. As a consequence, precise propagation rate coefficients must still be experimentally determined. Measurements are particularly important for propagation in polar solvents, as the environment of the reacting species is not easily implemented into *ab initio* calculations. Another difficulty is

associated with the occurrence of different types of radicals, for example, of secondary and tertiary radicals in the case of acrylate polymerization, the concentrations of which are not readily accessible from quantum chemical calculations. In view of all this, this section will focus on what has been learned about propagation from experimental data.

4.1 Measurement of Propagation Rate Coefficients

All the understanding of k_p that is presented here stems from measurement of values via the MP PLP technique of Section 2.5.2, which is also referred to as the PLP SEC method, because molar-mass analysis of the polymeric product from multiple pulsing has overwhelmingly been carried out by SEC (notwithstanding the existence of several successful studies using MS instead). It is impossible to overstate how much this technique has advanced the entire field of RP kinetics. Prior to its advent, the principal method of determining k_p was by combining a $k_p/\langle k_t \rangle$ measurement from NSSP with a $k_p/\langle k_t \rangle^{0.5}$ measurement from SSP (Section 2.5.1). Not only was this experimentally

laborious (NSSP methods are not easy³⁰), but CLDT makes it impossible to have that $\langle k_t \rangle$ is the same in these two different types of experiment.¹⁶ Simulations have shown that this leads to large errors in both k_p and $\langle k_t \rangle$,⁸⁵ explaining why prior to MP PLP there was so much scatter in the literature data for k_p . There do exist other solutions to this difficulty, for example use of an emulsion polymerization technique⁸⁶ or an EPR technique⁸⁷ for measuring k_p . However, the former may only be used for an extremely limited number of monomers, while the latter may be subject to both random and systematic error.⁶⁵ Further, neither is as easy or as intuitive as the MP PLP technique. Thus to all intents and purposes, one may say that the latter should always be used to measure k_p .

4.2 Understanding Propagation Rate Coefficients

The MP PLP technique has been applied to the study of k_p for a wide variety of monomers.^{66,67} Many of these values have been critically evaluated by the IUPAC Subcommittee on Modeling of Polymerization Kinetics and Processes.⁸⁸ So far, this IUPAC subcommittee has collated reliable k_p for styrene,⁶⁵ MMA,⁸⁹ other alkyl methacrylates,⁹⁰ methacrylates with cyclic ester groups,⁹¹ *n*-butyl acrylate (BA),⁹² and methacrylic acid (MAA) in aqueous solution.⁹³ The reader is referred to these works for the resulting Arrhenius expressions. The data demonstrate a pronounced family-type behavior for methacrylates and acrylates, with the activation energy of k_p being more or less identical within each family. Therefore the variations in k_p from monomer to monomer within each family are essentially due to changes in the pre-exponential factor of the Arrhenius equation.

Because of chemical control, k_p is considered to be independent of the degree of monomer conversion, unless conversions are reached where the system becomes glassy, at which point k_p switches to being diffusion-controlled, and therefore starts varying with viscosity.³⁵ Moreover, k_p in solution should not be strongly affected by the monomer content. To clarify whether this latter assumption is valid, it seemed worthwhile to investigate systems with strong intermolecular interactions, for example, hydrogen-bonded monomers, such as acrylic acid,⁹⁴

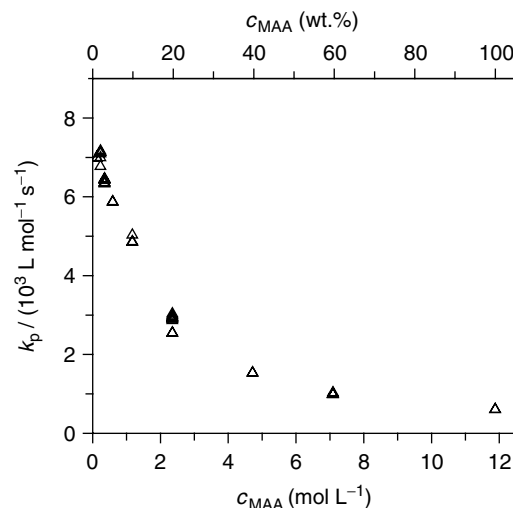


Figure 20 Variation of the propagation rate coefficient k_p of methacrylic acid with MAA concentration c_{MAA} in aqueous solution at 25 °C.⁹⁵

MAA,^{93,95} *N*-vinyl pyrrolidone,⁹⁶ and *N*-vinyl formamide⁹⁷ in aqueous solution.

In what follows, the aspects of k_p variation in aqueous solution are illustrated taking MAA as an example. The MAA system is of particular interest for studies of solvent effects on k_p , as PLP SEC experiments may be carried out over the entire concentration range from 1% up to bulk MAA. An enormous reduction in k_p upon increasing MAA concentration occurs, as is illustrated by the k_p versus c_{MAA} plot in Figure 20.

The significant lowering of k_p with MAA content is essentially, if not entirely, due to a decrease of the Arrhenius pre-exponential factor $A(k_p)$, whereas the activation energy $E_A(k_p)$ is more or less insensitive toward c_{MAA} .⁹⁵ This pronounced change is a genuine kinetic effect, which may be adequately understood in terms of transition state (TS) theory. As Heuts *et al.* pointed out,⁹⁸ the size of $A(k_p)$ is largely governed by the degree to which the internal rotations of the TS for propagation are hindered. This fundamental kinetic effect is associated with the fact that three transitional degrees of freedom are replaced by internal rotational or hindered vibrational degrees of freedom upon formation of the TS structure from a radical and a monomer molecule. In the event of severe hindrance of these internal motions, the associated

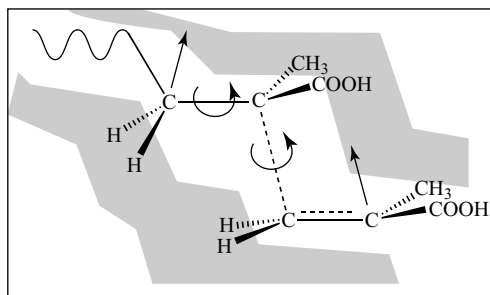


Figure 21 Illustration of the transition state (TS) structure for propagation in methacrylic acid polymerization. The gray areas indicate the surrounding molecular environment. In bulk polymerization, these areas consist entirely of MAA molecules. In aqueous solution, they are made up of water and MAA. The arrows indicate internal rotational motions associated with the formation of the TS structure from a radical (top left) and a monomer molecule (bottom right). Clearly, these motions are affected by the gray areas.

entropy penalty results in a significant lowering of the pre-exponential factor, and hence of k_p .

Illustrated in Figure 21 is the TS structure for MAA propagation. It has been drawn according to the figure given by Heuts *et al.* for ethylene homopolymerization.⁹⁸ The upper left part shows the terminal unit of an MAA macroradical. Given in the lower right part of Figure 21 is the MAA molecule that adds to the macroradical. The dashed line represents the bond that is formed in the TS structure. The arrows indicate the three degrees of hindered internal rotational-type motion associated with TS formation. The hindrance of internal rotational mobility may result from intramolecular effects, for example, ones induced by substituents on the backbone, and/or from intermolecular effects, for example, polar or hydrogen-bonding interactions. Intermolecular effects play a dominant role in the case of MAA propagation because of the strong hydrogen bonds between carboxylic acid moieties. Intramolecular effects should not be responsible for the major changes in hindrance to internal rotation upon varying the MAA content, as these interactions do not affect the substitution at the polymeric backbone.

Upon passing from polymerization in dilute aqueous solution to MAA bulk polymerization, the essential change in molecular environment consists in the gradual replacement of water molecules by MAA molecules. Toward higher MAA content, the particularly strong hydrogen-bonded interactions

between carboxylic acid groups become dominant. The formation of intermolecular cyclic dimeric COOH structures induces a larger friction than that associated with the interaction of the TS structure with water molecules. That the intermolecular interactions influence k_p may also be demonstrated by adding sodium hydroxide to the solution of non-ionized MAA. In aqueous solution at 5 wt.% MAA, k_p is lowered by about one order of magnitude in passing from the non-ionized to the fully ionized monomer.⁹⁹ Of course, increasing the degree of ionization acts to enhance the intermolecular interactions.

That $A(k_p)$ is correlated with the hindrance to chain mobility of the transition structure may also be seen from a comparison of the $A(k_p)$ values for MAA, MMA, and methyl acrylate (MA) bulk homopolymerizations. These $A(k_p)$ values read: $0.38 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for MAA,⁹⁵ $2.67 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ MMA,⁸⁹ and $16.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ MA.⁶⁶ With respect to $A(k_p)$ of MMA, the pre-exponential of MAA is lower by about one order of magnitude because of the hindrance provided by the strong hydrogen bonds. The $A(k_p)$ value of MA, on the other hand, is significantly higher than with MMA due to the favorable effect on internal rotational mobility that results from replacing the methyl group at every second carbon atom of the backbone with a hydrogen atom.¹⁰⁰

The studies of k_p of MAA in aqueous solution are of general importance in making clear that, contrary to the general expectation, the propagation rate coefficient may be strongly solvent-dependent. The explanation behind the large effect is a genuine kinetic one, which indicates that such effects may occur with all systems, although of course to widely differing extents. The strong solvent effect on k_p seen in aqueous solution of MAA is due to the significant difference of intermolecular interactions of the TS structure with an environment essentially consisting of water molecules and an environment consisting of MAA molecules. Thus clearly different degrees of friction to internal rotation occur in the two environments, giving rise to largely different pre-exponentials $A(k_p)$. That k_p has been considered for a long time to be insensitive to solvent content is due to the fact that mostly solvents have been investigated that, with respect to polarity, are similar to the monomer. With monomer and solvent having (almost) the same polarity, kinetic theory predicts at most small differences

between bulk and solution $A(k_p)$. It should also be mentioned that the advent of PLP SEC has enabled k_p data to be collected systematically and accurately, elements that previously were often lacking from studies, leading to the obscuring of solvent effects.

It needs to be kept in mind that bulk polymerization may be considered as a solution polymerization with monomer acting as the solvent. An immediate consequence of this latter insight is that k_p should not depend on the degree of conversion in bulk polymerizations, as the molecular environment of the TS structure remains the same throughout the polymerization to higher conversion: the radical site is embedded somewhere within a monomer-swollen macroradical coil and will not see other polymer, with the exception of oligomeric material or situations where the coils are interpenetrating. However, this insensitivity of k_p to monomer conversion must not hold in solution polymerizations. This has been demonstrated for MAA polymerizations in aqueous solution,¹⁰¹ where k_p was observed to increase toward higher degrees of monomer conversion. This effect may also be adequately understood in terms of the genuine kinetic argument about control of $A(k_p)$ through the friction experienced by the TS structure. During MAA solution polymerization, MAA molecules in the vicinity of the TS structure, for example, within the coiled macroradical, are replaced by water molecules, thus lowering the friction to internal rotation and enhancing $A(k_p)$, and

hence increasing k_p . This change occurs at constant overall density of COOH moieties, as the polymeric MAA segments produced during reaction do not affect the molecular environment at the radical site, which is essentially given by the ratio of monomeric MAA to water.

The insight into the effect of inter- and intramolecular interactions on $A(k_p)$ and thus on k_p helps us to understand several other seemingly unusual types of k_p behavior, for example, the variation with alkyl ester size of (meth)acrylate k_p . This is shown in Figure 22, which presents data for bulk polymerization⁶⁶ and toluene-solution polymerization¹⁰² of acrylates. Ester size increases from left to right, with MA and dodecyl acrylate (DA) being the smallest and largest family members, respectively. Whereas bulk k_p is enhanced toward larger ester size, the toluene-solution values exhibit some lowering of k_p . The trend seen with acrylate bulk k_p is also observed within the methacrylate family.^{66,90}

These effects may be rationalized on the basis of the new insight into the impact of intermolecular interactions on $A(k_p)$. The increase in bulk k_p upon passing from MA to DA is understood as a result of enhanced shielding of polar groups of the TS structure by longer nonpolar alkyl groups. As a consequence, the dipolar interactions become weaker in passing from MA to DA. This weakening is accompanied by reduced friction to internal rotations and thus an increase in k_p . Within the

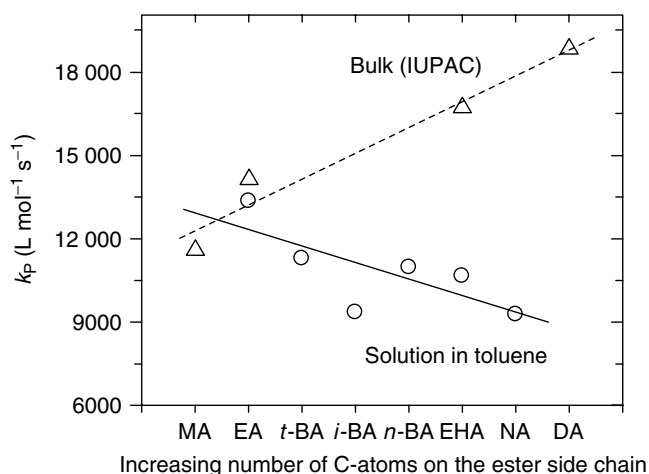


Figure 22 Comparison of propagation rate coefficients k_p for a series of alkyl acrylates in bulk (triangles) and in toluene solution¹⁰² (circles; 1.5 to 4.7 M) at 20 °C. The acronyms refer to acrylates with methyl (MA), ethyl (EA), *tert*-butyl (*t*-BA), *iso*-butyl (*i*-BA), *n*-butyl (*n*-BA), 2-ethylhexyl (EHA), nonyl (NA), and dodecyl (DA) side groups. [Reproduced from Ref. 100. © Wiley-VCH Verlag GmbH & Co. KGaA, 2009.]

solution experiments, the molecular environment varies to a much weaker extent, as toluene acts as the solvent with all the acrylates under investigation. Thus no major change in friction toward rotational mobility of the TS is expected to occur. The weak decrease in k_p that is seen for the toluene-solution experiments toward larger size of the alkyl group is possibly due to some minor enhancement of the shielding of the radical site.

Assigning changes in k_p to effects on internal rotational mobility of the TS structure may also explain the solvent dependence of k_p of MMA and *iso*-bornyl methacrylate.¹⁰³ As compared with bulk k_p , the k_p value in solution increases in solvents with molar volume exceeding that of the pure monomer and vice versa. Larger solvent molecules allow for enhanced rotational mobility than do smaller solvent molecules, which better fill the voids between molecules.¹⁰⁰

Another important point is that the idea of hindered TS rotations as an explanation for k_p behavior was first put forward in relation to the chain-length dependence of propagation at small chain lengths.⁹⁸ So this is another k_p phenomenon that is also explainable within the present framework.¹⁵

Finally, it goes without saying that $E_A(k_p)$ is tremendously important in determining the value of k_p . The discussion here has focused on *trends* in k_p

for cases where E_A is the same. Such family-type behavior—groups of monomers for which $E_A(k_p)$ is essentially the same—is turning out to be remarkably widespread.

4.3 Propagation in Copolymerization

The discussion above has considered only *homopropagation* data. As explained in Section 2.4, these are also involved in *copolymerization*. Additionally, *reactivity ratios* are central. Since the principles presented above are perfectly general, they should also hold for such copolymerization reactivity ratios. Indeed, in what follows it will be seen that these show some peculiarities that are easily understood via the above entropy arguments concerning $A(k_p)$.

4.3.1 Monomer Reactivity Ratios

These are the r 's of (37). Extensive compilations of such values are available.¹⁰⁴ As explained in Section 2.4.1, these values are most commonly obtained by fitting of copolymer composition data. An example has already been seen in Figure 8. A further example is presented in Figure 23. It shows

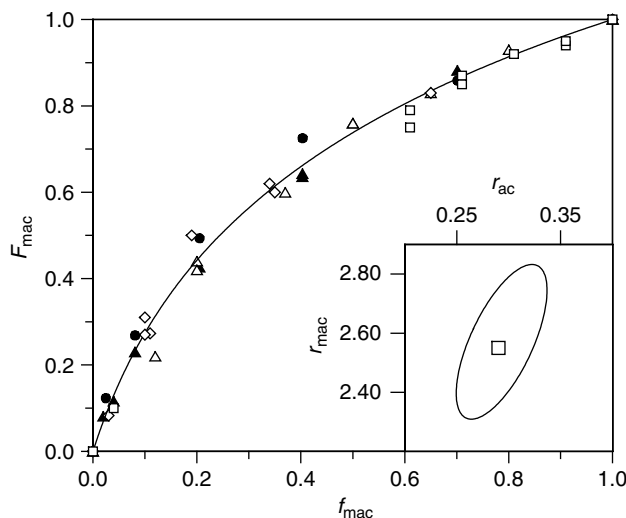


Figure 23 Mole fraction F_{mac} of methacrylate in copolymer as a function of mole fraction f_{mac} of methacrylate in monomer feed for several acrylate (“ac”)/methacrylate bulk systems at 1000 bar: DA/DMA (40 °C, squares), MA/DMA (40 °C, diamonds), DA/MMA (23 °C, full triangles; 40 °C, open triangles), and MA/MMA (23 °C, full circles). Line: best fit of (35). Inset: 95% confidence interval for the best-fit reactivity ratios r_{ac} and r_{mac} . [Reproduced from Ref. 106. © Wiley-VCH Verlag GmbH & Co. KGaA, 2007.]

the composition data that have been taken at temperatures from 23 to 40 °C for four different alkyl acrylate/alkyl methacrylate pairs,^{105,106} these being a small acrylate, MA, with either a small methacrylate (methyl, MMA) or a large methacrylate (dodecyl, DMA), and a large acrylate, DA, with either MMA or DMA. It is clear that the compositions of the four copolymerization systems, namely, MA/MMA, MA/DMA, DA/MMA, and DA/DMA, may be adequately represented by a single pair of acrylate and methacrylate reactivity ratios r_{ac} and r_{mac} . This is one of several important points about reactivity ratios that are brought to light by this figure and which will now be outlined.

1. The r values for a particular monomer pair may generally be used over a range of temperatures. Coote *et al.* showed that styrene/MMA data for 20–60 °C may all be fitted by the one pair of r values.¹⁰⁷ Hutchinson *et al.* have established this even more extensively, as follows: styrene/*n*-butyl methacrylate 50–150 °C,¹⁰⁸ styrene/glycidyl methacrylate 50–140 °C,¹⁰⁹ and styrene/2-hydroxyethyl methacrylate 50–120 °C.¹¹⁰ So it would appear that to good approximation one may regard monomer reactivity ratios as being independent of temperature. This may come as a surprise, as r values are ratios of k_p values, and homopolymerization k_p values are known to vary significantly with temperature.

This result may be understood as follows: Consider styrene/MMA. For bulk styrene, $E_A(k_p) = 32.5 \text{ kJ mol}^{-1}$,⁶⁵ for bulk MMA, $E_A(k_p) = 22.4 \text{ kJ mol}^{-1}$.⁸⁹ So for a cross-propagation reaction in this system—involving one type of radical, the other type of monomer—one may expect that $E_A(k_p)$ is *approximately* halfway between these two values. Referring to how reactivity ratios are defined, this means that $E_A(r_{sty}) \approx 5 \text{ kJ mol}^{-1}$ and $E_A(r_{MMA}) \approx -5 \text{ kJ mol}^{-1}$. As is shown in Figure 24, an E_A of this size results in a rate parameter (the temperature-variation of which is entirely captured by k/A , the quantity presented) having only a relatively small variation over 0–100 °C, which may be considered a large temperature range for composition measurements. Often, the difference in homopropagation E_A will be smaller than in the example here, leading to even smaller $|E_A(r)|$. Given this, it is

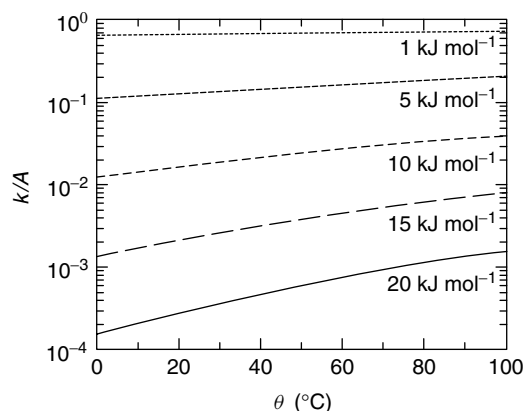


Figure 24 Variation of $k/A = \exp(-E_A/[RT])$, where k is rate coefficient and A pre-exponential factor, for different values of activation energy, E_A , over the temperature range $0 \leq \theta/^\circ\text{C} \leq 100$.

clear why data may be fitted with r values that are independent of temperature: even though $E_A(r) \neq 0$, the actual $E_A(r)$ values are too small for r to change measurably over most practical temperature ranges. Another factor in explaining the apparent lack of variation of r values with temperature is that composition data is relatively insensitive to changes in r , as illustrated in Figure 8.

Lest there be any any confusion, it needs to be stressed that values of r do vary with temperature, and we are not suggesting otherwise. For example, the activation energy for the ethylene reactivity ratio $E_A(r_E)$ has been measured in copolymerization with acrylates,¹¹¹ methacrylates,¹¹² and (meth)acrylic acid,¹¹³ and was found to be remarkably constant—approximately 12 kJ mol^{-1} —from system to system.¹¹³ What enabled these values (and those of the comonomers) to be determined is that they are relatively large and a considerable temperature range was possible, because ethylene is polymerized at high temperature. However, for most systems $E_A(r)$ is smaller and/or the temperature variation is not as great, meaning that data can often be adequately described with temperature-independent values of r .

2. Buback *et al.* examined the rate coefficient data from the literature for small-molecule analogs of acrylate and methacrylate radicals adding to MA and MMA. They showed that this data

leads to $r_{ac} = 0.38$ and $r_{mac} = 3.23$.¹⁰⁵ All things considered, these values are remarkably close to the best-fit macroradical values of Figure 23. Similar close agreement between r from model and corresponding polymer systems has also been observed by other workers. Thus one may be confident that r values from fitting composition data do actually correspond to the physical truth for copolymerization propagation rate coefficients.

3. A third important finding from Figure 23 is that both reactivity ratios r_{ac} and r_{mac} are insensitive to the type of monomer that is added to a particular chain end: for example, r_{MA} appears to be the same in both MA/MMA and MA/DMA copolymerization. Hutchinson *et al.* found the same for styrene/*n*-alkyl methacrylate systems;¹¹⁰ that is, the one set of r values could be used to describe all such data. To understand this remarkable phenomenon, consider the case of r_{MA} in Figure 23. Its constancy means that $k_{pMA,MMA} \approx k_{pMA,DMA}$. Inspection of Figure 21 indicates why this should indeed be the case. The region of the TS structure that controls the extent of hindrance to internal rotation encompasses the radical chain end (probably including the penultimate segment) and the $CH_2=C$ part of the monomer. The specific alkyl ester group is probably too far off this kinetically relevant area to significantly affect $k_{pMA,mac}$, where “mac” refers to an arbitrary alkyl methacrylate. The same type of argument should explain the similarity of the r_{mac} values, and indeed it should hold wherever comonomer is only varied within a monomer family.
4. Finally, as is invariably the case with composition data, the results of Figure 23 may be perfectly adequately fitted with just r_1 and r_2 , which suggests that $r_{11} = r_{21}$ and $r_{22} = r_{12}$ to good approximation (i.e., the “IPM” of Section 2.4.2). The reason why this simplification mostly holds is probably that $r_{11} = k_{p111}/k_{p112}$ and $r_{21} = k_{p211}/k_{p212}$, for example, are ratios of propagation rate coefficients that apply to radicals with identical terminal and penultimate units. The ratioing procedure seems to eliminate the impact of the penultimate unit on the rate coefficients.⁵² The same argument may be used to explain why r_{22} is close to r_{12} .

In summary, a pair of r_a values: is generally adequate to describe composition data without needing to invoke penultimate unit effects (point 4 above); to good approximation will hold independent of temperature (point 1); and also to good approximation will hold for other monomer pairs where monomer variation is within the same family only (point 3). Given the undoubted complexity of copolymerization k_p values, these are remarkable and highly useful simplifications. Further, these findings are surprising given the decades of effort that have gone into devising complex schemes for estimating r_a values that are implied to be highly variable.

4.3.2 Radical Reactivity Ratios

These are the s 's of (40). As explained in Section 2.4.2, their values are obtained by fitting of copolymer k_p data. The best available compilation of these values is that of a recent work.¹¹⁴ An aim of this work was to objectively assess the proposal that¹¹⁵

$$s_1 s_2 = r_1 r_2 \quad (49)$$

Fukuda *et al.* derived this relationship solely on *enthalpic (energetic)* grounds.¹¹⁵

Equation (49) has infused much of the work on copolymerization k_p over the last two decades. Quite often this equation seems to hold;^{49,116} however, it has never been clear whether this is for genuine mechanistic reasons or is simply a consequence of large joint-confidence intervals for s_1 and s_2 .⁵⁵ As has recently been summarized,⁵ gradually the evidence against (49) has mounted, culminating in the meta-analysis of Ref. 114. Points were found to be scattered almost randomly on the plot of $s_1 s_2$ versus $r_1 r_2$ from this work, leading the authors to conclude “[$s_1 s_2 = r_1 r_2$] is obeyed in some rare cases only ... This means, rather unfortunately, that this theorem is of little help in reducing the number of parameters.”¹¹⁴

In hindsight it is not surprising that (49) is unlikely to be the physical truth. Because r values involve variation of the *monomer*, it is clear that they must entail enthalpic considerations. However, s values involve variation of only the penultimate unit of the radical. Not only does it seem obvious

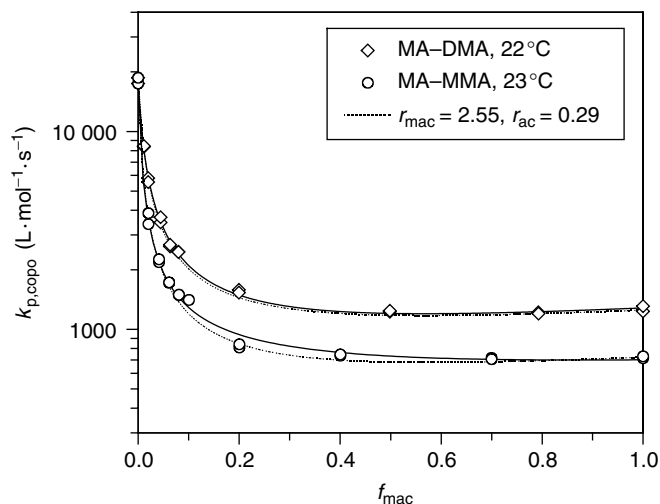


Figure 25 Propagation rate coefficient $k_{p,copo}$ as a function of the methacrylate mole fraction f_{mac} of MA/MMA and MA/DMA copolymerizations at 1000 bar. The dotted lines are the respective TM predictions with $r_{mac} = 2.55$ and $r_{ac} = 0.29$, while the full lines are IPM best fits. [Reproduced from Ref. 106. © Wiley-VCH Verlag GmbH & Co. KGaA, 2007.]

that such substitution should result in *steric* effects, but it also seems likely that a penultimate unit should have only a small effect on the energy of the associated radical, because the two entities are several bonds apart.⁵²

Where does this leave understanding of s values? In what follows we summarize the findings of the recent acrylate/methacrylate study that has already been mentioned.¹⁰⁶

The almost identical composition behavior of the four acrylate/methacrylate systems (Figure 23) may suggest that also the propagation rate coefficients behave similarly. Experimental values of copolymerization k_p for MA/MMA and MA/DMA are plotted in Figure 25.¹⁰⁶ The full lines represent best fits with the IPM (Section 2.4.2), whereas the dotted lines are calculated from the TM with $r_{ac} = 0.29$ and $r_{mac} = 2.55$, these being the values from composition analysis (Figure 23). The remarkable observation from Figure 25 is that the TM affords an impressive prediction of measured k_p for both MA-containing copolymerization systems. Particularly surprising is the excellent quality of the fit in the case that alkyl ester sizes are dissimilar, i.e., with the MA/DMA system, where the TM is capable of simultaneously representing copolymer composition and copolymer propagation behavior with the same pair of reactivity ratio numbers.

The behavior of MA/DMA raised interest in checking whether the same simple behavior occurs with the complementary system, namely, DA/MMA. That this is definitely not the case is immediately clear from the k_p data presented in Figure 26.¹⁰⁶ The TM with $r_{ac} = 0.29$ and $r_{mac} = 2.55$ completely fails to reproduce the experimental data. It should, however, be noted that the IPM also does no satisfactory job. A better representation of k_p for DA/MMA is achieved by fitting the data to the TM expression for k_p . This results in a different pair of reactivity ratios: $r_{DA} = 0.30$, $r_{MMA} = 0.64$. These are obviously no satisfactory values, as they predict there is an azeotropic composition ($F_{mac} = f_{mac}$) for this system; however, Figure 23 shows this definitely is not the case (cf. Figure 8). Moreover, using two sets of reactivity ratios, one for composition and one for propagation kinetics, is obviously no satisfactory situation. The disagreement of the pairs of reactivity ratio data clearly indicates the need for applying a PM.

To keep the number of adjustable parameters low, a simplified IPM model may be used that adopts the reactivity ratio data from composition analysis and assumes the product of the two radical reactivity ratios to be unity, that is, $s_{ac}s_{mac} = 1$. This relationship may be justified using TS theory and assuming that only entropic effects

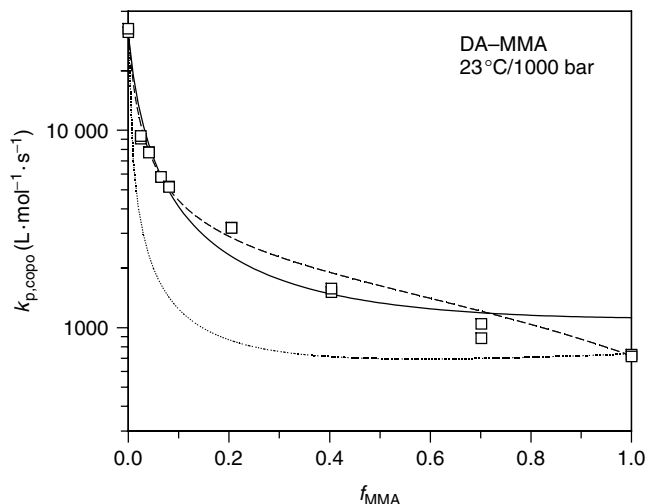


Figure 26 Propagation rate coefficient $k_{p, \text{copo}}$ for the DA/MMA system at 23 °C and 1000 bar plotted as a function of methacrylate mole fraction f_{mac} of the monomer mixture. The dotted line is the TM prediction with $r_{\text{mac}} = 2.55$ and $r_{\text{ac}} = 0.29$; the full line is from IPM fitting; and the dashed line is from TM fitting of $k_{p, \text{copo}}$ alone, which results in the reactivity ratios $r_{\text{mac}} = 0.64$ and $r_{\text{ac}} = 0.30$. [Reproduced from Ref. 106. © Wiley-VCH Verlag GmbH & Co. KGaA, 2007.]

are significant in determining s values.^{52,100,106} It leaves s_{ac} as the single parameter to be varied in fitting copolymerization k_p data. For MA/DMA, this yields $s_{\text{MA}} = 0.99$ and $s_{\text{DMA}} = 1.01$,¹⁰⁶ which reflects the almost perfect TM behavior (Figure 25). Similar is the case for MA/MMA. For DA/DMA, the k_p data is well described but the s values deviate significantly from unity: $s_{\text{DA}} = 0.34$ and $s_{\text{DMA}} = 2.97$.¹⁰⁶ For DA/MMA, the deviations are even greater— $s_{\text{DA}} = 0.09$ and $s_{\text{MMA}} = 11.32$ ¹⁰⁶—and the fit is lacking, as is implicit in Figure 26. This suggests that for DA/MMA even the PM may be insufficient and pen-penultimate segments should be included into the modeling. In all of these examples, $r_1 r_2 \approx s_1 s_2 = 1$, even though one may be sceptical of the grounds for (49). It is therefore significant that $s_1 s_2 = 1$ has recently been shown to work well for several styrene/methacrylate systems where $r_1 r_2$ is considerably less than 1.⁵

As well as the value of the product $s_1 s_2$, there is also the issue of the meaning of the individual s_a values. Here, the argument of hindrance to internal mobility has again been invoked for acrylate/methacrylate systems.^{100,106} It is especially relevant in considering MA/DMA and DA/MMA, where the enormous differences in propagation behavior are not easily understood. Two contributions to hindrance of rotational mobility may be

distinguished: (i) an intermolecular mobility term, *interMT*, associated with shielding of dipolar intermolecular interactions by alkyl ester groups; and (ii) an intramolecular mobility term, *intraMT*, associated with the type of penultimate unit. Replacing a methacrylate penultimate segment by an acrylate segment has a favorable intramolecular effect on chain-end mobility and vice versa. The *intraMT* and *interMT* contributions have been shown to explain at a qualitative level all the s_{ac} and s_{mac} values presented above.^{100,106} Therefore this model shows promise for wider understanding of copolymerization k_p .

Indeed, the insight that hindrance to internal rotational motion controls $A(k_p)$ has been shown in this section to help understand many aspects of homopropagation and copolymerization behavior that previously were not clear.

5 TERMINATION

5.1 Measurement of Termination Rate Coefficients

There are numerous methods for determining $\langle k_t \rangle$, far too many to cover here. Instead, the interested reader is referred to a comprehensive review on

this topic.³⁰ This number is considerably reduced when restricted to methods that shed light on CLDT, as is essential for mechanistic investigation of termination. Again, this topic has recently been thoroughly reviewed.¹⁸ What emerges from these two reviews is that SP PLP EPR, as outlined in Section 2.5.1, is the most powerful technique for determining $k_t^{i,i}$. The understanding of CLDT that is presented here stems largely from measurements made this way.

Mention should also be made of a simple technique for probing CLDT of long chains. Combining (17) and (30) results in^{24,40}

$$\langle k_t \rangle = k_t^{1,1} G(DP_n)^{-\alpha}, \text{ where} \\ G = \left[\Gamma \left(\frac{2}{2-\alpha} \right) \right]^{\alpha-2} \left(\frac{2}{2-\alpha} \frac{2}{1+\lambda} \right)^{\alpha} \quad (50)$$

Thus a plot of $\log \langle k_t \rangle$ versus $\log DP_n$ has slope $-\alpha$ and intercept $\log(Gk_t^{1,1})$. Under normal circumstances, $G \approx 1$, meaning that the intercept directly yields an approximate value of $k_t^{1,1}$. In this way, a series of experiments in which the rate of initiation, for example, is varied in order to vary the measured quantities of $\langle k_t \rangle$ and DP_n may be used to obtain α and $k_t^{1,1}$.¹⁸

5.2 Chain-Length Dependence at Low Conversion

The issue of CLDT has occupied minds for over 50 years.^{21,22} It is not a simple matter. Almost all experimental studies have concentrated on low-conversion conditions. Ultimately, the campaign has been successful, with essentially all of the significant advances having been made over the last 25 years. Recently, the topic was comprehensively reviewed.¹⁸ This section presents a brief summary of the essential findings and lines of thought.

Figure 27 shows $\langle k_t \rangle$ data for both bulk styrene¹¹⁷ and bulk MMA¹¹⁸ at low conversion. Clearly, there is a variation of $\langle k_t \rangle$ such that, as average chain size becomes smaller, termination becomes more rapid. This is consistent with intuition regarding CLDT. Quantitatively, these results are to be interpreted in the light of (50). From the slopes of the linear fits to the data, one obtains $\alpha \approx 0.16$, while from the intercepts it follows that $k_t^{1,1} \approx 10^8 \text{ M}^{-1} \text{ s}^{-1}$. Both

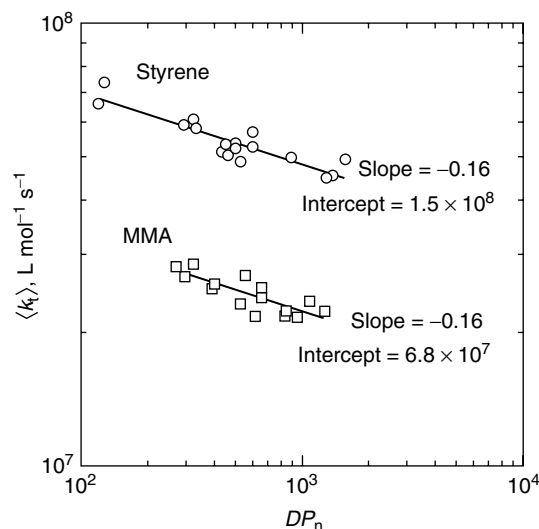


Figure 27 Termination rate coefficient $\langle k_t \rangle$ as a function of number-average degree of polymerization DP_n as measured using MP PLP at 25 °C for bulk styrene¹¹⁷ (circles) and bulk methyl methacrylate¹¹⁸ (squares). Lines: linear best fits to each dataset, with slope and intercept as displayed.

these values are typical of what has been found wherever *careful* studies of this nature have been carried out.¹⁸

Considering first the exponent for variation of $k_t^{i,i}$ with chain length, $\alpha \approx 0.16$ is exactly in agreement with what theory¹¹⁹ predicts for the case of segmental rearrangements upon coil overlap being the rate-determining step for termination. In other words, the middle step in Figure 28 sets the tone. It is stressed that this is established *only* for (relatively) long chains *only* in dilute solution conditions.

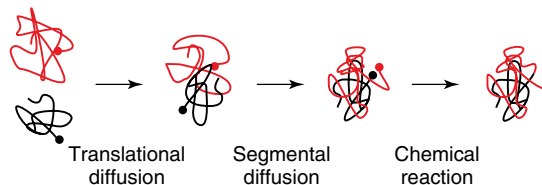


Figure 28 Depiction of the three mechanistic steps involved in the termination process. [Reprinted from Progress in Polymer Science, Vol. 34, C. Barner-Kowollik and G. T. Russell, Chain-length-dependent termination in radical polymerization: Subtle revolution in tackling a long-standing challenge, 1211–1259, Copyright (2009), with permission from Elsevier.]

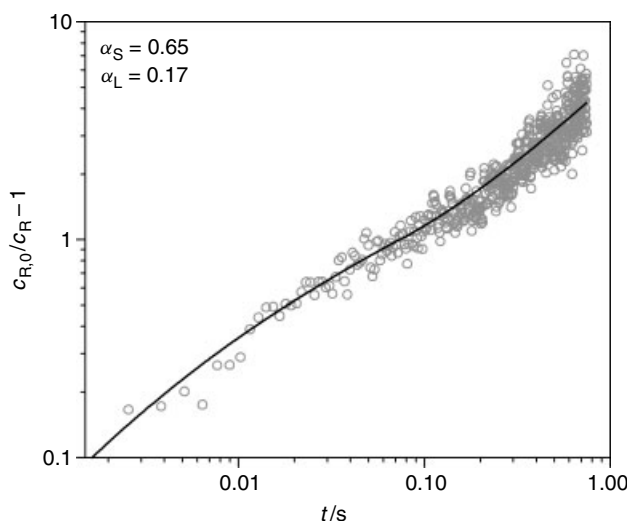


Figure 29 Log-log plot of radical concentration in the form of $c_{R,0}/c_R - 1$ versus time t from an SP PLP EPR experiment with dodecyl methacrylate at 0 °C and low conversion. Points: experiment; line: integrated rate law for composite model⁵⁶ with $k_t^{1,1} = 1.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $\alpha_S = 0.65$, $\alpha_L = 0.17$, and $i_c = 50$. [Reproduced from Ref. 120. © American Chemical Society, 2006.]

Turning now to the values of $k_t^{1,1}$ implied by Figure 27, two serious problems emerge:²⁴ (i) The distinction in Figure 28 between translational diffusion and segmental diffusion is one that does not exist for oligomers at the very least. In other words, for short chains it does not make sense to speak of diffusion upon overlap as being a separate and different diffusion step in the termination process. Thus there is no reason why $\alpha \approx 0.16$ should hold for all chain lengths right down to $i = 1$ and, indeed, the derivation of $\alpha = 0.16$ is clearly one predicated on macroradicals being long chains.¹¹⁹ Hence there is no reason to have confidence in extrapolating the linear fits of Figure 27 down to the size of monomeric radicals. (ii) In fact, the measured values of small-molecule termination rate coefficients show that $k_t^{1,1} \approx 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for monomers such as styrene and MMA.¹⁷ This is an order of magnitude higher than the intercepts of the fits of Figure 27. The only real way of explaining this is that CLDT must be considerably stronger (i.e., higher α) for short chains.

In view of the above situation, Smith *et al.* proposed what they termed the *composite model* for termination:²⁴

$$\begin{aligned} k_t^{i,i} &= k_t^{1,1} i^{-\alpha_S}, \quad i \leq i_c \\ k_t^{i,i} &= k_t^{1,1} (i_c)^{-\alpha_S + \alpha_L} i^{-\alpha_L}, \quad i > i_c \end{aligned} \quad (51)$$

The key feature of this model is that, at chain length i_c , there is a crossover from short-chain termination behavior with power-law exponent α_S , to long-chain behavior characterized by α_L . Note from the second line of (51) that an *apparent* $k_t^{1,1}$ of value $k_t^{1,1} (i_c)^{-\alpha_S + \alpha_L}$ will be returned by long-chain experiments. Since $\alpha_S > \alpha_L$, this explains why the intercepts of the linear fits of Figure 27 (i.e., the apparent values of $k_t^{1,1}$) are less than expected. By a happy coincidence, the SP PLP EPR method, with its unprecedented ability to probe the CLDT of short radicals, emerged⁵⁸ just after (51) was proposed. It was immediately found that SP PLP EPR data could only be explained by α being significantly different for short and long chains.⁵⁸ This is exemplified in Figure 29.¹²⁰

In a nice case of experiment–theory synergy, theory²⁴ was first of all needed to explain the unexpected⁵⁸ SP PLP EPR results, while since then the sheer volume of such results has served to reinforce the theory, for by now there have been many SP PLP EPR studies,¹⁹ all finding composite-model behavior along the lines of Figure 29. A pair of CLDT methods based on reversible addition–fragmentation (chain-)transfer (RAFT) polymerization¹²¹ (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and**

Applications) have also found such behavior across a variety of monomers.¹⁸ This behavior is as follows:¹⁸ (i) $\alpha_L \approx 0.2$, in agreement with long-chain studies (e.g., that of Figure 27) and theory;¹¹⁹ (ii) α_S is considerably greater than α_L , being in the range 0.5–0.65 for styrene and methacrylates. These values are remarkably consistent with oligomer diffusion data,^{122,123} suggesting that the rate of short-chain termination is simply controlled by center-of-mass diffusion (Figure 28); (iii) i_c ranges from 100 for MMA down to about 20 for some acrylates. All this is exactly as envisaged when the composite model was proposed.²⁴ For tables of values, the reader is referred to Ref. 18.

A feature of the already mentioned small-molecule termination rate coefficients from model systems is that they are in good agreement with the Smoluchowski equation.¹⁷ Applied to the monomeric radicals of RP systems, this equation reads

$$k_t^{1,1} = \frac{1}{4} 2\pi(D^1 + D^1)\sigma \quad (52)$$

Here, D^1 is monomer diffusion coefficient, σ is the radical–radical separation at which the chemical reaction of termination occurs (Figure 28), and the fraction accounts for spin multiplicity. From the Stokes–Einstein equation, one has $D^1 \sim (r_1\eta)^{-1}$, where η is viscosity and r_1 is the hydrodynamic radius of monomer. Therefore, one predicts that $k_t^{1,1}r_1\eta$ should be relatively constant as monomer, solvent, and temperature are varied, and that $E_a(k_t^{1,1}) \approx E_a(\eta^{-1})$. Barth *et al.* have shown that these predictions are obeyed by all SP PLP EPR data thus far gathered.^{19,59} It appears that $k_t^{1,1}$ often is as simple as (52).

All in all, it may be said that the current situation in regard to low-conversion termination is enormously pleasing and amounts to a remarkable success story from a troubled background.

5.3 Conversion Dependence of Termination Rate Coefficients

Dilute solution conditions prevail only for the first few percent conversion of a bulk polymerization. Therefore, one needs to know far more about termination than has been revealed in Section 5.2.

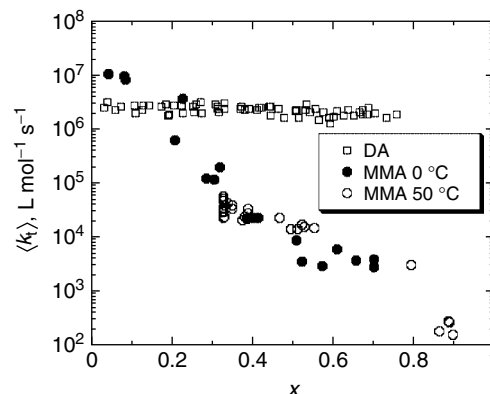


Figure 30 Variation of overall termination rate coefficient $\langle k_t \rangle$ with fractional conversion x of monomer into polymer for bulk polymerization of methyl methacrylate at ambient pressure and 0 °C¹²⁴ (filled circles; reprocessed values¹⁶) and 50 °C¹²⁵ (empty circles), and for DA at 1000 bar and 40 °C¹²⁶ (squares; reprocessed values⁶⁶).

Specifically, one is interested in the *entire* variation of $\langle k_t \rangle$ with conversion, a topic introduced in Section 2.2.3. This is especially important for the modeling of commercial processes. Figure 30 presents data for bulk MMA^{124,125} and bulk DA¹²⁶.

Considering first the MMA data, one sees that there is enormous variation of $\langle k_t \rangle$ across the span of conversion, with $\langle k_t \rangle$ dropping by over five orders of magnitude. Further, the decrease is irregular rather than constant. In particular, initially $\langle k_t \rangle$ is relatively constant—the so-called plateau region—before it undergoes a steep decrease starting around 20% conversion. This gives rise to the “gel effect” of Figure 3, as discussed in Section 2.2.3. Starting around 40–50% conversion, there appears to be a period of relatively gentle decline in $\langle k_t \rangle$. This has been interpreted as being due to so-called reaction-diffusion control of termination:¹²⁷ the translational diffusion of macroradicals is so slow, due to the high concentration of polymer which gives rise to very high viscosity and extensive chain entanglements, that the fastest mode of motion of a radical chain end is that effected by addition to monomer.¹²⁸ In this situation, termination ceases to be chain-length dependent, and the rate coefficient is given by the remarkably simple equation¹²⁷

$$k_t = C_{RD}(1-x)k_p \quad (53)$$

The reaction–diffusion proportionality constant C_{RD} is a function of $c_{M,0}$, σ (52), and a parameter characterizing the random-coil dimensions of the polymer. At very high conversions, $\langle k_t \rangle$ becomes so small (Figure 30) that one would certainly expect (53) to be valid.³⁵

Given the multifaceted and extreme variation of $\langle k_t \rangle$ with x that is displayed by MMA, the complete lack of variation in the DA data of Figure 30 comes as a surprise: the plateau region seems to extend over the entire range of conversion, and there is no hint of reaction diffusion ((53) predicts a fivefold decrease in k_t in going from 0 to 80% conversion). Of course, from a strictly modeling point of view, the extremely simple behavior of DA makes life very easy: one can just take $\langle k_t \rangle(x)$ to be a constant. However, from another point of view, this result makes life difficult: how is it that increasing polymer concentration gives rise to such a spectacular autoacceleration of rate in the case of MMA, but to no change in $\langle k_t \rangle$ for DA? After all, bulk viscosity also increases by many orders of magnitude in going from DA to poly(DA), so why is there no gel effect in this system? This makes the very important point that the variation of k_t with x is not always sensitive to changes in macroviscosity; it is especially important to be aware that this is the case during the initial plateau region, as Figure 30 makes clear.

The two examples of Figure 30 may be considered as extremes: most monomers have $\langle k_t \rangle(x)$ that varies more than DA's but less than bulk MMA's. Given the successes outlined in Section 5.2, one may be optimistic that as CLDT methods—so far largely only applied to dilute solution conditions—are turned to the entire range of conversion, the mysteries of Figure 30 will clear up. Manifestly, the composite model is very successful for the initial plateau region (which can be quite extended, e.g., the DA data of Figure 30); however, it remains to be seen how (51) fares beyond these conditions, when, for example, termination may come under reaction-diffusion control, meaning that the composite model loses relevance as envisaged (although employing $\alpha_S = \alpha_L = 0$ will render it still mathematically correct). Beyond low conversions, one can also anticipate that the MMD of dead polymer will exert an influence on termination rate coefficients, because translational diffusion coefficients are known to depend on the size and architecture (e.g., degree of crosslinking) of the matrix polymer

through which movement occurs. So the formulation of a truly microscopic description of termination, along the lines of that presented in Section 5.2, is still some way from realization for the full range of conversion.

Given this situation, it is appropriate to introduce the model of Buback for variation of k_t with x :¹²⁹

$$k_t = \frac{1}{(k_{tSD})^{-1} + \eta_r/k_{tTD,0}} + \frac{C_{RD}(1-x)}{(k_{pC})^{-1} + \eta_r/k_{pD,0}}$$

where $\eta_r = \exp(C_\eta x)$ (54)

Although this model does not incorporate CLDT explicitly (hence discarding the brackets around k_t), it does so to some extent in that it is based on many of the concepts outlined above. To start with, there is the recognition of segmental diffusion (k_{tSD} ; Figure 28), translational diffusion (k_{tTD} ; Figure 28), and reaction diffusion steps, all contributing to k_t .¹²⁹ There is inclusion of viscosity effects, whereby variation of η_r , which is the viscosity relative to that at zero conversion, results in change of k_{tTD} from its zero-conversion value $k_{tTD,0}$. This also results in variation of k_{pD} , the diffusion-controlled value of k_p . This is important in glassy systems, in which k_p is lower than its chemically controlled value k_{pC} (all k_p values discussed to date have been of the latter nature).

Equation (54) has proven very useful for modeling and for reaching a qualitative understanding of the different $k_t(x)$ variations that are observed from system to system (e.g., Figure 30): these stem from the interplay of termination mechanisms being different.^{66,129} An example of using equation (54) for these purposes is presented in Figure 31. Firstly, the 0 °C MMA data of Figure 30 is fitted with (54). Not only does this give a relatively simple mathematical description of a highly nuanced variation, but it also clearly reveals four mechanistic regions, as originally postulated by Soh and Sunderberg.¹³⁰ These are, and are marked, as follows: (i) the initial plateau region, in which $k_t \approx k_{tSD}$, that is, segmental diffusion is rate determining; (ii) the gel effect starting and taking off due to a switchover to translational diffusion being the rate-determining termination step; (iii) k_{tTD} becoming so low that reaction-diffusion takes over as being rate determining; (iv) still the case that $k_t = k_{tRD}$, but the switchover to diffusion-controlled propagation means that k_t once again decreases strongly

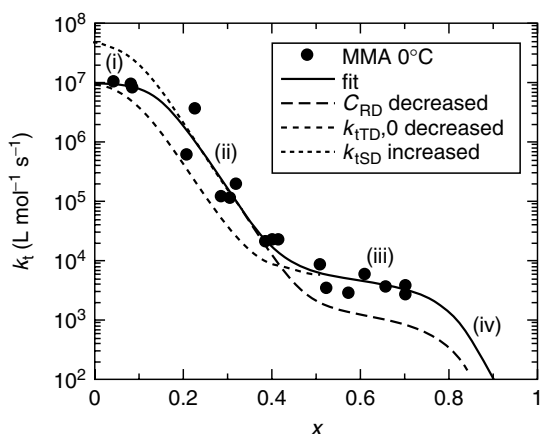


Figure 31 Variation of termination rate coefficient k_t with fractional conversion x of monomer into polymer. Points: bulk polymerization of methyl methacrylate at 0 °C (from Figure 30). Lines: evaluations of (54): unbroken: fit to points, obtained with $k_{tSD} = 1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, $k_{tD,0} = 5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, $C_\eta = 27$, $C_{RD} = 80$, $k_{pC} = 142 \text{ M}^{-1} \text{ s}^{-1}$,⁸⁹ and $k_{pD,0} = 5 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$; large dashes: as for fit except $C_{RD} = 20$; small dashes: as for fit except $k_{tD,0} = 1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$; and dots: as for fit except $k_{tSD} = 5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$. The regions marked (i)–(iv) are described in the text.

with x , as in region (ii). Such behavior is evident in the 50 °C MMA data of Figure 30 for $x > 0.8$.

Figure 31 also presents evaluations of (54) with alternative parameter values. As is shown, broadly speaking it is the case that C_{RD} influences regions (iii) and (iv), k_{tSD} region (i), and $k_{tD,0}$ region (ii). This gives an idea of the utility of the equation and how parameter values need to be tweaked in order for different situations to be described. For example, the DA data of Figure 30 obviously indicate that parameter values are such that $k_t = k_{tSD}$ over a tremendously extended range of conversion.

5.4 Termination in Copolymerization

Being diffusion-controlled, termination is different from propagation, which is chemically controlled (except in the uncommon event of a system being glassy). For this reason, termination in copolymerization should be described differently from propagation, because terminal and penultimate unit effects on radical reactivity are concepts tied to the notion of chemical control. It is therefore a surprise that in fact the treatment

of copolymerization termination has proceeded in exactly this direction, with the most recent work finding that the following equation is well suited for describing data:^{126,131,132}

$$(k_t)^{0.5} = p_{11}(k_{t,1111})^{0.5} + p_{21}(k_{t,2121})^{0.5} + p_{12}(k_{t,1212})^{0.5} + p_{22}(k_{t,2222})^{0.5} \quad (55)$$

In this equation, $k_{t,badc}$ is the rate coefficient for termination of chain-end *ba* with chain-end *dc*, while p_{ba} is the fraction of radicals of type R_{ba} (34), and may be calculated via parameters from fitting of F_1 and k_p data.

Equation (55) has recently been critiqued as part of a review covering termination in copolymerization.⁵ The nub of the matter is that, if k_t depends only on the last two units of a copolymer chain, then it seems impossible to explain that termination is chain-length-dependent, that is, it depends on the entire length of a chain. This is not to dispute that simple whole-chain models of termination in copolymerization—as have been reviewed⁴⁹—often function inadequately in describing the variation of copolymerization k_t with f_1 .^{49,116,131} However, it is to suggest that something fundamental is still lacking from our understanding of termination in copolymerization.

In view of this situation, attention is drawn to the following empirical model:¹³³

$$\log k_t = f_1 \log k_{t,1} + f_2 \log k_{t,2} + f_3 \log k_{t,3} \quad (56)$$

As stated here, this equation is for a three-component system, where $k_{t,i}$ refers to homotermination rate coefficient of monomer *i* and f_i to its mole fraction. It is obvious how to adapt (56) for any number of monomers being present. This equation has been found to provide a good description of the plateau-region (i.e., low conversion) data from acrylate terpolymerization,¹³³ methacrylate terpolymerization,¹³³ and acrylate/methacrylate copolymerization.¹²⁶ In the decade since these studies, the relationship between solution viscosity and $k_t^{1,1}$ at low conversion has been established (Section 5.2). This is of interest in that viscosity of a liquid mixture is given by a relationship of the form of (56). This may explain the successes of this equation, which, it should be mentioned, has the considerable virtue of not containing any adjustable parameters (whereas (55)

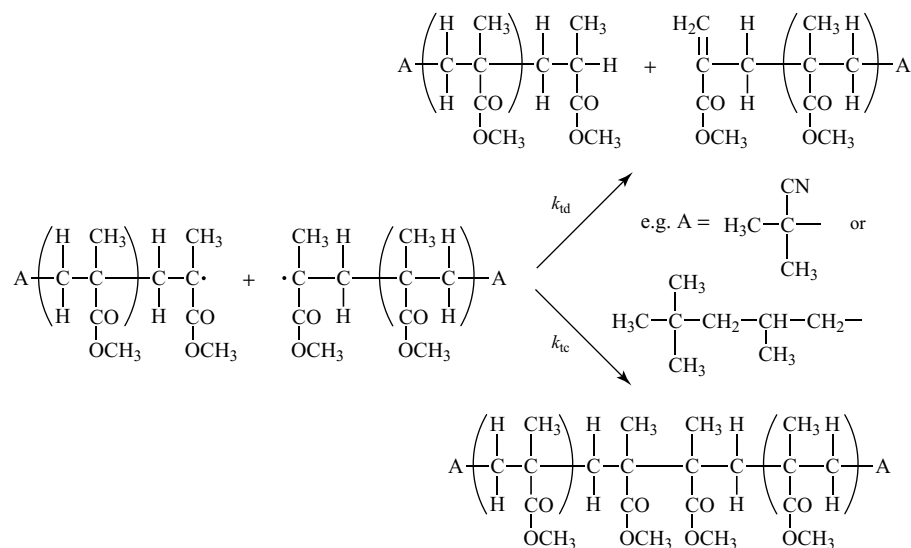


Figure 32 The competing termination reactions of disproportionation (rate coefficient k_{id}) and combination (rate coefficient k_{ic}) in radical polymerization of methyl methacrylate. The end groups resulting from the popular initiators 2,2'-azoisobutyronitrile (AIBN;¹³⁴ upper example of A) and bis(3,5,5-trimethylhexanoyl) peroxide (BTMHP;⁸ lower) are also shown.

has two, namely, $k_{t,2121}$ and $k_{t,1212}$). Nevertheless, one should be aware that (56) will not always work; for example, quite clearly it does not describe Ma *et al.*'s styrene/diethyl fumarate data.¹³¹

5.5 Disproportionation-to-Combination Ratio

The fraction λ (11) of termination by disproportionation is not inconsequential: in the event of dead-chain formation being predominantly by termination, it causes DP_n to vary by a factor of 2 (Section 2.3.2), it has a major effect on MMD broadness (Section 2.3.3), and it results in the number of initiator-derived end groups on the polymer being as different as 1 or 2, as shown in Figure 32. All of these effects may be important in terms of material properties, while the third may be of significance for polymer modification chemistry. Given this, the situation portrayed in Figure 33 is shocking: despite over 50 years to tackle the issue, there is no agreement on the value of λ for MMA. This state of affairs reflects the historical difficulty of measuring λ , which means that for other monomers the situation is just as vague in this regard.

Fortunately, the emergence of large-molecule MS promises to remedy this calamitous state. Figure 32

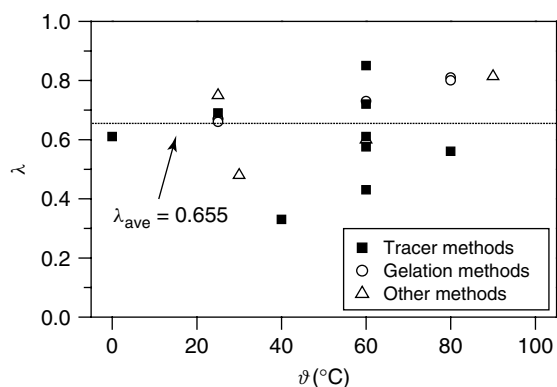


Figure 33 Literature values of the fraction λ of termination by disproportionation as a function of temperature for radical polymerization of methyl methacrylate. The values were obtained by different techniques as indicated. λ_{ave} , the average of all these values of λ , is also shown. [Reprinted with permission from Ref. 8. Copyright 2009 American Chemical Society.]

makes clear that, as long as the mass of the initiating radical is different from the mass of monomer (and multiples thereof), disproportionation and combination give rise to polymer molecules of different molar mass. Thus MS can distinguish species formed by each termination mode, as is clear from Figure 34. Since MS signal intensity reflects the

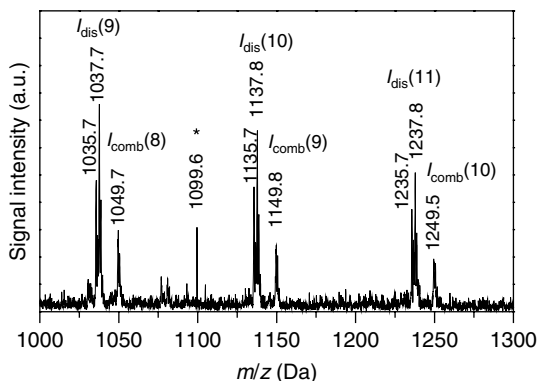


Figure 34 Portion of the ESI-MS spectrum of poly(methyl methacrylate) obtained from polymerization in benzene solution at 85 °C with BTMHP (Figure 32) as initiator. The molar mass of each of the prominent peaks is given. All of these peaks are combination products (“comb”), disproportionation products (“dis”), or internal standard (*), as indicated. The numbers in brackets are the number of methyl methacrylate residues. For example, the signals labeled $I_{\text{comb}}(8)$ are from oligomer made up of eight MMA units and 2,4,4-trimethylpentyl at each end (Figure 32). [Reprinted with permission from Ref. 8. Copyright 2009 American Chemical Society.]

amount of a species, it should be possible to obtain λ (or, equivalently, $k_{\text{td}}/k_{\text{tc}}$) from an analysis of these intensities.

Since disproportionation produces two polymer molecules whereas combination produces only one (Figure 32), it is the case that $k_{\text{td}}/k_{\text{tc}} = (n_{\text{d}}/2)/n_{\text{c}}$, where the n refer to the *overall* numbers of chains from the respective modes of termination. In originally proposing the above method for λ determination and using it with AIBN (Figure 32), Zammit *et al.*¹³⁴ assumed that this relationship holds also with $n_{i,\text{d}}$ and $n_{i,\text{c}}$, the numbers of chains for *individual* chain lengths i (Figure 34). In fact this is not the case. Starting with (22a) and using other results in Section 2.3.1, it is straightforward to show that⁸

$$\frac{\frac{1}{2}n_{i,\text{d}}}{n_{i,\text{c}}} = \frac{\nu}{(i-1)(\frac{1}{\lambda}-1)} = \frac{\nu(k_{\text{td}}/k_{\text{tc}})}{(i-1)} \quad (57)$$

In other words, there is a natural variation of $n_{i,\text{d}}/n_{i,\text{c}}$, as obtained from MS intensities, with both i and kinetic chain length ν (23b). Using (57), MS data from employing bis(3,5,5-trimethylhexanoyl) peroxide (BTMHP) (Figure 32) as initiator was recently shown to *self-consistently* give the value

$\lambda = 0.63$ for MMA at 85 °C.⁸ Probably not coincidentally, this is almost exactly the same as the average of all the literature values in Figure 33, as shown.

Now that a reliable method for the determination of λ seems to have been developed, it can be hoped that it will be applied to a wide variety of systems. Until that has been done, one really only has the results of small-molecule studies on which to go.^{6,17} The rule of thumb from such investigations is that combination ($\lambda = 0$) will predominate for 2° macroradicals (e.g., styrene and acrylate systems), while disproportionation ($\lambda = 1$) can be significant for 3° macroradicals (e.g., methacrylate systems, as is evident from Figure 34). The physical basis for this rule is that the more energetically favorable reaction, namely, combination, will occur unless there is considerable steric hindrance to the two free electrons becoming proximate enough for a C–C bond to form. Considering Figure 32, it should not be surprising that with MMA there is such hindrance. Even so, the value $\lambda = 0.63$ shows that more combination occurs with MMA than is commonly believed. This emphasizes that the presented rule of thumb is just a starting guideline, not an inviolable principle.

6 SMALL-MOLECULE CHAIN TRANSFER

Values of k_{trX} most commonly are determined using (29). An example of a so-called Mayo plot is given in Figure 35, which shows values of $1/DP_n$ from bulk polymerizations of MMA with different concentrations of the chain-transfer agent (CTA) dodecyl mercaptan (DDM; Section 1.2).⁴³ According to (29), the slope of a plot of $1/DP_n$ versus $c_{\text{DDM}}/c_{\text{MMA}}$ is equal to k_{trX}/k_p . These values are presented in Figure 35. It is evident that $k_{\text{trX}} \approx k_p$ for this system at 40–60 °C, which tells that an MMA macroradical has approximately equal reactivity with DDM and MMA. This is typical for conventional CTAs.

To give some idea of the variation that is possible with k_{trX} values, the above value for DDM with MMA may be compared with two extremes: (1) So-called catalytic chain-transfer agents are certain transition-metal complexes, most notably low-spin Co^{II} complexes such as cobaloximes, that are extremely efficient and are not consumed by the

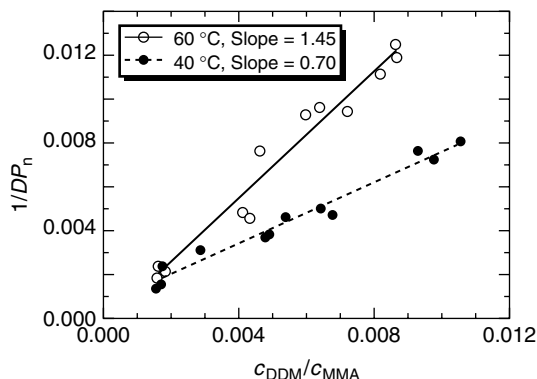


Figure 35 Reciprocal number-average degree of polymerization $1/DP_n$ from low-conversion bulk polymerization of methyl methacrylate (MMA) as a function of concentration c_{DDM} of dodecyl mercaptan at two different temperatures, as indicated. Points: experimental values;⁴³ lines: linear best fits, with slopes as displayed. [The Kinetics of Radical Polymerization in Encyclopedia of Polymer Science and Technology, November 2010 in Encyclopedia of Polymer Science and Technology. Copyright 2011, John Wiley & Sons, Inc. This material is reproduced with permission of John Wiley & Sons, Inc.]

transfer process.¹³⁵ For such species with MMA, it has been determined by the Mayo procedure that $k_{\text{trX}}/k_p \approx 10^4$ at 60 °C.¹³⁵ (2) At the other end of the spectrum, it has been found that $k_{\text{trX}}/k_p \approx 10^{-5}$ for chain transfer to monomer in MMA at 60 °C.¹³⁶ Again, this value was determined using (29). So with these examples one sees variation of k_{trX} by nine orders of magnitude for MMA macroradicals undergoing transfer to different small molecules at 60 °C. Of course, in practice these variations are counterbalanced by concentration variations: the high value of c_M in bulk systems negates the small value of k_{trM} to make transfer to monomer a competitive reaction in many circumstances, while chain transfer to catalytic CTA is kept in check by using only ppm quantities.¹³⁵ The message here is one that was implicitly delivered right at the beginning with (9): it is the *frequency* of transfer $k_{\text{trX}}c_X$ that is important.

It is also interesting to compare the activation energies for these transfer processes. For catalytic CTAs, Heuts *et al.* report that there is hardly any temperature dependence of k_{trX}/k_p , with E_A if anything being slightly negative.¹³⁵ For transfer to MMA monomer, $E_A(k_{\text{trX}}/k_p) = 23 \text{ kJ mol}^{-1}$.¹³⁶ Exactly the same value has been found for transfer

to monomer in styrene.¹³⁷ For DDM with MMA, the situation is unclear. The two values of Figure 35 suggest $E_A(k_{\text{trX}}/k_p) \approx 30 \text{ kJ mol}^{-1}$. On the other hand, Hutchinson *et al.* found essentially no variation of k_{trX}/k_p across 20–80 °C for the same system.¹³⁸ Considering all the data at their disposal, Heuts *et al.* concluded that “the activation energy for k_{trX} exceeds the activation energy for k_p by about 10 kJ mol^{-1} .”⁴³ Given the absolute values of k_{trX}/k_p mentioned above, it is not unreasonable that $E_A(k_{\text{trX}}/k_p)$ for the DDM/MMA system should be in between those of the two “extreme” systems.

A highly interesting result from the study of Hutchinson *et al.* is that k_{trX}/k_p is the same for DDM with MMA, ethyl methacrylate, and *n*-butyl methacrylate, but is 20 times higher with styrene. As is commented, this suggests that “a single set of experiments can be done to characterize the chain-transfer ability of an agent with an entire monomer family.”¹³⁸ Again, this is not unreasonable: for each reaction, the reactant is the same (cf. homopropagation, where the small molecule is different in each case), while the only thing that changes about the radical is the length of the pendant alkyl group, which of course is away from the radical site.

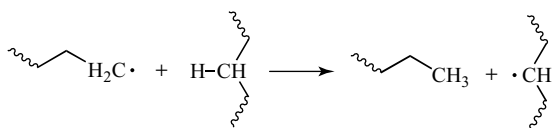
It should be evident from (29) and Figure 35 that the experiments to determine k_{trX}/k_p are undemanding and the data analysis is straightforward. It should also be evident that k_{trX}/k_p values are tremendously important, for transfer often determines MMD; indeed, the purpose of using a CTA is usually to afford control of DP_n . It, therefore, is completely perplexing that *systematic* studies into the variation of k_{trX}/k_p are few and far between (as opposed to one-off measurements, which are numerous¹⁰⁴). For example, the premier data on the variation with temperature of styrene transfer-to-monomer rate coefficients are still considered to be those from 1955, when SEC did not exist, and DP_n values were determined by viscometry!¹³⁷ Given this negligent situation, there is not a lot more that can be reported as known about the mechanism of chain transfer to small molecules. This is an area that is crying out for orderly study. There even exists already a theoretical framework for investigation, in the form of predictions of trends on the basis of TS theory.¹³⁹ It simply remains to start testing and refining these ideas.

7 OTHER INFLUENTIAL REACTIONS

A principal contention of this work is that, if one properly understands the foundations of RP kinetics (Section 2) that follow from the fundamental suite of reactions of Section 1.2, then enormous progress can be made in explaining RP kinetic phenomena. A good example of this is the variation of k_p of hydrogen-bonded monomers with water content (Section 4.2 and Figure 20). This results in large changes in rate, which previously were explained in terms of complexation phenomena and/or the occurrence of additional reactions. However, with the advent of PLP SEC, it has become clear that these variations in rate are largely driven simply by a solvent effect on k_p rather than by any exotic phenomenon.⁹⁵ This notwithstanding, there are situations where the diversity of RP kinetics is due to extra reactions being important. This section presents the two leading examples of such reactions.

7.1 Chain Transfer to Polymer

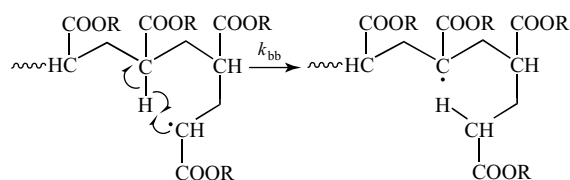
Chain transfer to polymer (CTP) is the reaction whereby a radical abstracts the hydrogen from a C–H bond on a polymer molecule, thereby transferring the radical activity to the carbon from whence the hydrogen came:



This has long been known to be the signature reaction of ethylene systems, resulting in the short-chain branches (SCBs) and long-chain branches (LCBs) that give LDPE its defining characteristics. In the case of ethylene, CTP involves conversion of a primary radical into a lower-energy secondary radical, as shown above. However, the activation energy for breaking a C–H bond to form a secondary radical is relatively high, meaning that the high-pressure and high-temperature conditions of LDPE synthesis are required to achieve significant rates of CTP. In acrylates, on the other hand, the CTP reaction involves conversion of a secondary radical into a tertiary radical (see below). So there is still an energetic driving force. However, it is

easier to break a C–H bond to form a tertiary radical than it is to form a secondary radical. Thus CTP should occur under milder conditions with acrylates, even though in principle it is the same reaction as with ethylene. Indeed, it has emerged over the last decade¹⁴⁰ that CTP takes place with acrylates at *ordinary* temperatures and pressures, and that it is responsible for many unusual kinetic phenomena in these systems.

This development started with the use of ¹³C NMR to show that the polymer from RP of BA contains quaternary carbons to such a level that approximately 1% of BA units are branch points.¹⁴¹ A few years later, it was established that the predominant form of CTP in these systems is *intramolecular* (leading to SCBs) rather than *intermolecular* (which results in LCBs).¹⁴² In other words, there is a 1,5-hydrogen shift reaction:



This reaction is commonly known as backbiting (rate coefficient k_{bb}). It occurs because the C–H bond is rendered labile by the nearby carbonyl bond, because the TS—a six-membered ring, as intimated above—is energetically favorable, and because the same also holds for the product, a tertiary radical, as already mentioned. These factors are not specific to BA, and so backbiting may be expected to occur with all acrylates.

The above reaction influences RP kinetics because the product radical, which is tertiary in nature, adds to monomer at least two orders of magnitude slower than the reactant radical, which is secondary in nature.^{140,143} Thus the situation is similar to degradative chain transfer (Section 1.2) in that the transfer process yields a relatively stable radical that therefore *retards* the polymerization. That this population of “mid-chain radicals” (MCRs) is significant has been definitively established by quantitative EPR spectroscopy.^{144,145} This work shows that for acrylate homopolymerization at room temperature and above, one must distinguish the two populations of radicals. A *steady-state*

analysis leads to¹⁴⁶

$$k_p = \frac{k_{p\text{SPR}}}{1 + \frac{k_{bb}}{k_{p\text{MCR}}c_M}} \quad (58)$$

Here, SPR stands for secondary propagating radical, that is, the reactant radical in the reaction immediately above. Amongst other things, (58) reveals that, as c_M decreases, overall k_p decreases. The physical reason for this is that slowly propagating MCRs are longer-lived because of the lower monomer concentration. A consequence of this is that overall k_p varies with solvent level in such a way that polymerization rate has order with respect to monomer that is unusually higher than 1 (cf. (16a)), with values of 1.6–1.8 being typical.^{5,140,147} In other words, the additional component is due to k_p varying with c_M . A comprehensive kinetic treatment of the effect of backbiting on steady-state rate has been given and can be recommended.¹⁴⁷

Backbiting also serves to explain unusual PLP-SEC behavior of acrylates. One of the “consistency checks” of this method is that k_p should be independent of the laser pulse repetition rate under normal circumstances.⁶⁵ As is shown in the typical results of Figure 36,¹⁴⁸ acrylates are abnormal. For many years this situation was not understood, and so it was not clear what (if any) k_p value should be recommended for wider use from such results.

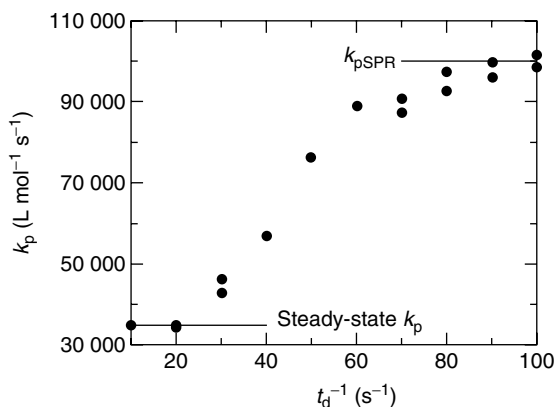


Figure 36 Variation of propagation rate coefficient k_p with laser pulse repetition rate t_d^{-1} (where t_d is the time between pulses) from multiple-pulse PLP of 1.35 M acrylic acid in water at 6 °C. Points: experiment;¹⁴⁸ horizontal lines: limiting values of k_p at high t_d^{-1} (upper) and low t_d^{-1} (lower).

Now this situation has been resolved, as follows.¹⁴⁶ The data display a transition from a high value of k_p at high pulse frequency (i.e., small t_d) to a lower value of k_p at low pulse frequency (i.e., long t_d). The high value may be identified as $k_{p\text{SPR}}$: there is so little time between pulses, which produce SPRs, that the entire radical population will be of this nature. When t_d is long, on the other hand, a steady state between SPR creation (by MCR propagation) and loss (by backbiting) will be established and will prevail for most of the time. This means that k_p is given by (58), and so one may easily determine $k_{bb}/k_{p\text{MCR}}$ from the lower limiting value of k_p . For example, the data of Figure 36 deliver $k_{bb}/k_{p\text{MCR}} = 2.4 \text{ M}$.¹⁴⁸ It has subsequently been shown that, as would be intuitively expected, one may in fact obtain k_{bb} and $k_{p\text{MCR}}$ individually from the entire variation of k_p with t_d .¹⁴⁹ Thus so-called frequency-tuned PLP SEC should be regarded as an important tool in the elucidation of acrylate kinetics.

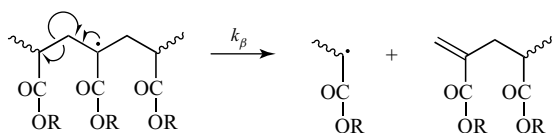
1,5-H-shift reactions can also occur with primary (initiating) radicals, and therefore can be important in explaining initiation kinetics.¹⁵⁰ In general, CTP has a tendency to occur where there is a methyl, methylene, or methine group α to a carbonyl group, for example, vinyl acetate (although this is not definitively established), itaconates, and acrylates, respectively (note the absence of such a group in methacrylate systems). In each case, the adjacent carbonyl bond activates a C–H bond for radical attack. This is an important motif in RP chemistry, as is the 1,5-H-shift reaction, with the two sometimes coinciding, as above for acrylates. Another important motif is β -scission, as now discussed.

7.2 β -Scission

It has already been seen in Section 3 that β -scission is an important reaction in initiation. It is also the basis of RAFT polymerization (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).¹⁵¹ *Depropagation*, the reverse reaction of propagation, is another example of β -scission in RP, becoming important at high temperatures and giving rise to the phenomenon of “ceiling temperature”: the temperature above which

it is not possible to form high polymer. This section will outline how awareness has recently grown of the importance of β -scission in acrylate systems.

Just over a decade ago, it was shown by ^1H NMR that high-temperature polymerization of various acrylates produces macromonomers in high yield.¹⁵² The reaction at work is



As shown, this is a β -scission reaction, and it relies on the prior occurrence of CTP in order to generate an MCR. Because this reaction converts an MCR back into a SPR (as shown), it reduces the retardative effect of backbiting. As this statement makes clear, β -scission competes with propagation as a pathway for MCRs to take.

Barner-Kowollik *et al.* have been intensively studying β -scission in acrylates. They have pointed out that this reaction actually gives rise to a complicated scheme,¹⁵³ because of the reversible nature of β -scission, the fact that β -scission can occur on either side of the radical position in the MCR (i.e., also to the right rather than to the left of the radical above), and the fact that the macromonomer product may have either a chain-starting species (e.g., from initiator) or H as terminus at the saturated end. Nevertheless, the end result can be remarkably simple. Namely, there is the equivalent of the limit of dominant dead-chain formation by transfer to small molecule: in its lifetime a radical undergoes many cycles of (acrylate SPR) addition, CTP, and β -scission, each time producing an H-ended macromonomer. Thus this species is the dominant product, which is why Junkers *et al.* described this chemistry as that of a “macromonomer production machine”.¹⁵³ Therefore it has been used to build up a “macromonomer library”¹⁵⁴ for acrylates, with structures all the time being verified by MS.^{153,154}

8 CONCLUSION

The classical (chain-length-independent) and terminal-model kinetics of Section 2 predate 1985, but otherwise almost all the work presented in this

article has taken place in the last 25 years. One may therefore be astounded at the progress that has been made in RP kinetics over this period: from a position of understanding almost nothing, now a vast amount is understood. The irony is that many outsiders, and even quite a few insiders, have little appreciation that these exciting and important developments have been occurring. As has been demonstrated here, the key to all this progress has been the development of the proper *machinery*. By this word is meant both robust, inquisitory experimental methods such as MP PLP and SP PLP EPR, and practicable kinetic equations for the treatment of subtle but influential phenomena such as chain-length-dependent termination, penultimate-unit effects in copolymerization, and backbiting. The wielders of these tools can expect to keep the progress rolling on as they tackle the many fundamental issues in RP kinetics that remain to be addressed.

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Radical Polymerization in Industry

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1 INTRODUCTION

The goal of this article is to provide a brief overview of radical polymerization (RP) in industry. It will highlight the role of this technique in the context of polymer industry and review its mechanistic and process aspects from the point of view of industrial polymerization. Then, recent progress in industrial applications of controlled RP will be shown. Of course, treatment of such a multifaceted discipline as industrial RP (IRP) is possible only in very limited depth. Therefore, only the most salient features of IRP will be discussed and references for further reading will be given. In accord with the IUPAC recommendation,¹ the term *radical polymerization* will be used instead of *free radical polymerization*.

Life as we know it would not be possible without synthetic polymers, which are commonly called *plastics*. The term *plastics* should not be confused with the technical adjective *plastic*, describing permanent deformation of materials that were strained beyond a certain point. Thus, plastics in this article incorporate all synthetic polymers and macromolecular materials, not only those undergoing plastic (thermoplasts) or elastic (elastomers) deformation but also highly cross-linked and hard thermosetting polymers. Diverse semisynthetic macromolecular materials such as vulcanized rubber, celluloid, or galalith were discovered and already used in the nineteenth century. However, the spread of polymers to every aspect of modern life was possible only after the fundamentals of polymer science

were laid down during 1920–1930.^{2,3} An account of the history of polymers has been given by Morawetz.⁴

The industrial production of several plastics such as bakelite, polystyrene (PS), low density polyethylene (LDPE), or poly(vinyl chloride) (PVC) already started before World War II. However, only the progress in science and technology and the economic growth of the postwar period allowed the worldwide production of polymers to grow at around 9% per year, from 1.5 million tons (mt) in 1950 to about 230 mt in 2009. Of these 230 mt, 55 mt was produced in Europe⁵ (Figure 1). In terms of volume (m³), the production of polymers exceeds that of iron and steel.

Globally, the long-term growth of plastics is expected to be at around 4% and hence higher than the gross domestic product (GDP) growth. The average worldwide consumption⁵ of plastics is significantly below that of the industrialized regions (Figure 2), thus leaving room for future growth.

Up to 2015 and beyond, the fastest growth is expected in Asia. One of the important stimulators of the future demand for polymers is the growing concern about climate change. In fact, more than 14% of all greenhouse gases worldwide are generated by the transportation sector. Reducing the weight of cars through the replacement of metals by plastic can cut a vehicle's weight by up to 30%, resulting in a significant reduction in fuel consumption. The proportion of plastics in a typical Western European car is about 15% today (160 kg), compared with 6% in 1970. By 2020,

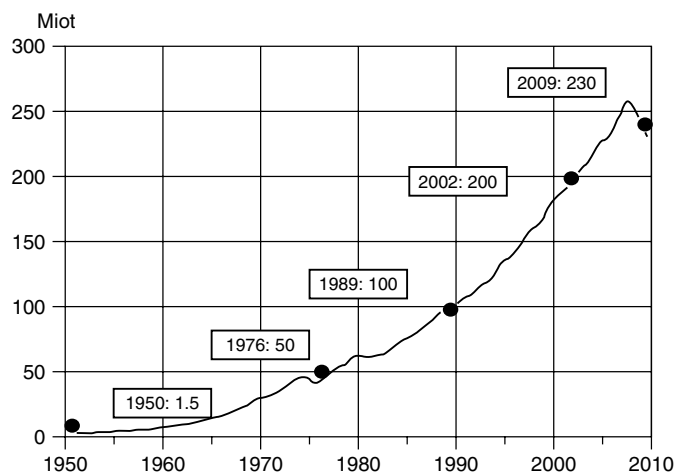


Figure 1 Worldwide production of polymers 1950–2009.

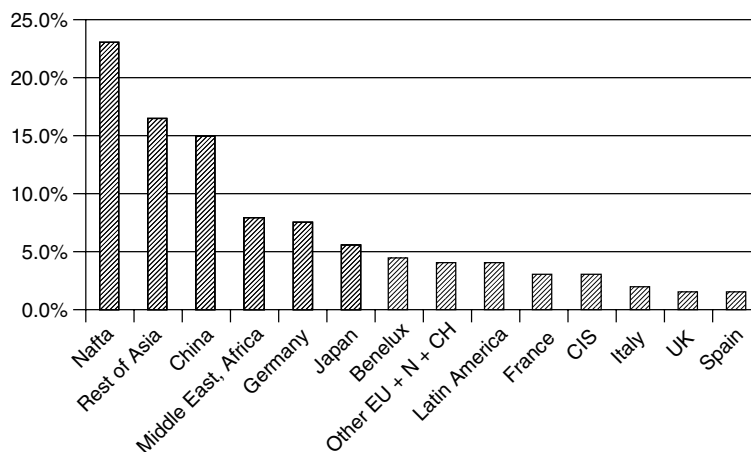


Figure 2 World production of polymers 2009, regional split.

plastics could account for more than 25% of a car's weight.⁶

Countless polymers are known in the literature, but the number industrially manufactured polymers is relatively small. For example in 2009, nine types of polymers accounted for 77% (176 mt)⁶ of the 230 mt⁵ of polymers produced worldwide (Figure 3). The five most important plastics are thermoplastic polymers, namely polypropylene (PP), high density polyethylene (HDPE), linear low density polyethylene (LLDPE), LDPE, and PVC, of which 143 mt were produced.

The rest are smaller volume polymers such as polyesters, with poly(ethylene terephthalate) (PET) as the most important example, PS as well

as engineering plastics, and high-performance polymers. The latter exhibit superior mechanical and thermal properties under a wide range of conditions. As their name suggests, these are used in the manufacture of parts or in applications requiring extraordinary performance rather than for construction, containers, or packaging, which is the domain of commodity polymers. Some examples of engineering plastics and high-performance polymers are acrylonitrile–butadiene–styrene (ABS) copolymers, polycarbonates (PCs), polyamides (PAs), polyurethanes (PURs), polysulfones (PSUs), polyetherketones (PEKs), polyetheretherketone (PEEKs), polyoxymethylene (POM), polyimides (PIs), polyphenylenesulfide (PPS), polyphenylene

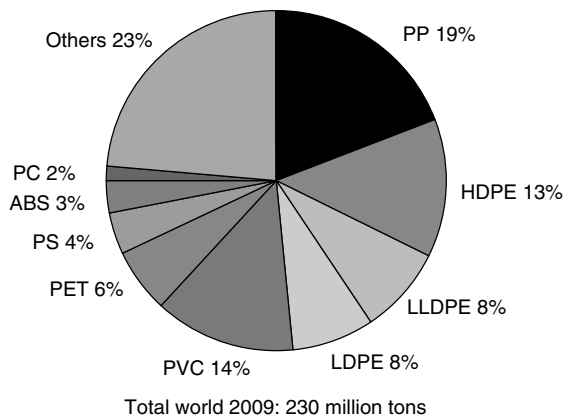


Figure 3 World's largest volume polymers.

oxide (PPO), or fluoropolymers (e.g., Teflon, polytetrafluoroethylene (PTFE), to name just the most relevant. Additionally, there is the important group of thermosetting polymers^{7–9} including epoxides, phenol-formaldehyde, urea, and melamine polymers, as well alkyds and unsaturated polyester resins. Last but not least, must be mentioned the silicone-based¹⁰ polymers. A special case is the family of dispersion^{11,12} polymers that have in common the same state of aggregation but are diverse from the point of view of their chemical composition. Latest data on production volumes of individual polymers and their regional split have been published.¹³

The classes of polymers differ significantly not only in their production volume but also in their selling price,^{14,15} which is 0.5–2.5€ kg^{−1} for commodity polymers, 10–12€ kg^{−1} for PTFE or PSU, and about 60€ kg^{−1} for PEEK. Prices of high-tech polymeric specialties, for example, those for the electronic industry, are even much higher. As the same polymer is often commercialized by different companies under different names, a plurality of trade names¹⁶ exists.

A number of good monographs^{17–21} and reference works^{22–24} provide detailed information on industrial polymers and their applications. Domininghaus *et al.*¹⁴ provides a compilation of physical and technical data that are important for a professional selection of an optimal polymeric material for a given application.

Synthetic polymers are prepared from low molecular weight building blocks called *monomers*

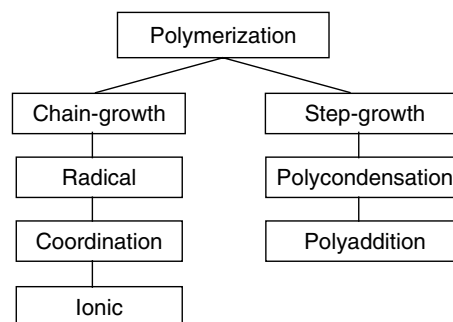


Figure 4 Mechanistic classification of polymerization processes.

by a process known as *polymerization*. Existing macromolecules can be further modified by polymer analogous reactions. Polymerizations can be divided from a mechanistic point of view² into several classes. RP belongs to the class of chain-growth polymerizations (Figure 4).

Polymers produced by RP represent roughly 40–45% of all industrial polymers, which ranks this method among the most important industrial polymerization techniques. Polymers prepared by nonradical processes are not discussed in this article. Abundant literature is available on ionic,^{25–29} step-growth,^{9,29–31} coordination,^{29,32–36} and group-transfer polymerization³⁷ methods.

Nevertheless, it should be noted that there are other industrially important polymer technologies and applications that are based on radical processes. Thus, millions of tons of unsaturated polyester resins^{9,31,38} are cured (cross-linked) with radical initiators, predominantly peroxides. The drying of alkyd resins^{39,40} also proceeds via the radical mechanism. Photopolymerization of coatings, printing inks, adhesives, and micro-electronic components is a multibillion dollar business and still rapidly growing. Radically induced cross-linking^{41,42} of polymers, controlled degradation^{43–45} of the molecular weight of polypropylene, and modification of polyolefins by grafting^{41,46–48} of polar monomers are other examples. Finally, radicals are very often involved in the thermally and photochemically induced degradation^{49,50} of polymers (e.g., in autoxidation) as well as in the mode of action of the necessary stabilizers^{51,52} used to prevent or retard this deterioration.

2 GENERAL AND MECHANISTIC ASPECTS OF INDUSTRIAL RADICAL POLYMERIZATION

The dominant position of RP in industry originates from several unique characteristics that differentiate it from other polymerization methods. Thus, in contrast to ionic or coordination polymerization, RP is tolerant of protic solvents and trace impurities such as oxygen or monomer stabilizers. Consequently, it can be conducted in polar solvents such as alcohols or, more importantly, water with monomers that are not rigorously dried or purified. Furthermore, a large number of low-priced monomers are available. Thus, from an economical point of view, RP is the technique of choice. For example, the cost to polymerize styrene by anionic polymerization is about 50% higher⁵³ than for RP.

2.1 Monomers

Many molecules containing unsaturated homo or heteronuclear double bonds, dienes, trienes, strained cycloaliphatics, *exo*-methylene-substituted cyclic compounds, or vinylcyclopropanes are amenable^{2,54} to RP. However, the major industrial monomers are compounds **1** (Scheme 1) containing C=C double bond(s) where X is primarily X=H, (CH₃) and Y=H, Cl, COOH, COOR, CONH₂, CN, OCOCH₃, C₆H₅, -CH=CH₂), which serve as precursors of the corresponding polymers **2**. Besides the basic monomers that are produced on a very large scale, there exists a variety of specialty monomers that are used to make homopolymers or copolymers with specific properties. Examples are the styrene derivatives 1,4-divinylbenzene, *p*-vinylbenzyl chloride, and *p*-acetoxystyrene, 4-vinyl pyridine, *N*-vinyl pyrrolidone, various esters and amides of acrylic and methacrylic acid (e.g.,

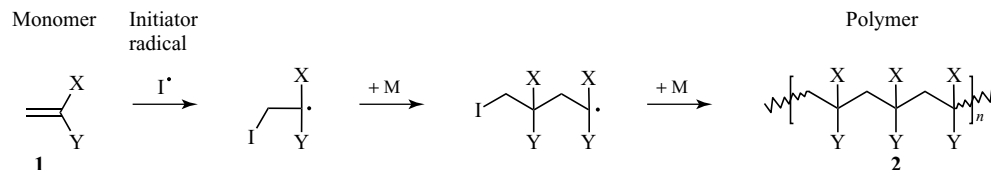
n-butyl acrylate, 2-hydroxyethyl (meth)acrylate, 2-dimethylaminoethyl (meth)acrylate, glycidyl methacrylate, *N*-isopropyl acrylamide), and a variety of (meth)acrylates of polyhydric alcohols (e.g., ethylene glycol, trimethylolpropane, or pentaerythritol). The latter, by virtue of their high functionality, are used as cross-linkers. The synthesis, properties, and applications of specialty monomers are summarized in the book⁵⁵ by Havelka and McCormick. A compilation of commercially available specialty monomers for formulations cured by photopolymerization is provided by Webster *et al.*⁵⁶

The most important monomers along with the applicable polymerization processes and typical uses of the polymers are shown in Table 1.

Technological and economic information on the industrial synthesis of monomers can be found in the monograph of Arpe.⁵⁷ The current raw material base for monomers consists almost exclusively of crude oil and natural gas and will remain so also in the near future. It should be mentioned⁵⁸ that only ~4–8% of crude oil is used for polymer production, the rest serving predominantly as a source of energy. However, in view of the limited availability and increasing price of oil and gas, a shift⁵⁹ to monomers and polymers from renewable⁶⁰ resources, a renaissance of coal, as well as increasing importance of chemical recycling⁵⁸ of polymeric materials is foreseeable.

2.2 Mechanism of Radical Polymerization

The mechanism of RP is now well understood even though some problems such as control of the stereochemistry of the propagation step or sequence control⁶¹ are still not solved. On the other hand, powerful techniques of controlled RP have been developed in the last 20 years and the first commercial applications are appearing. A comprehensive treatment of the chemical and



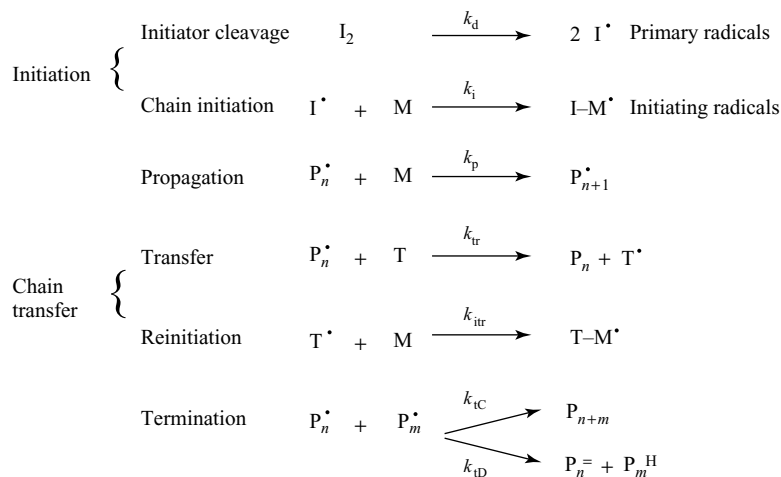
Scheme 1 Radical polymerization of a C=C monomer.

Table 1 Major monomers for industrial RP.

Monomer	Polymerization technique						
	G	B	S	E	L	P	Use
Acrylic acid, acrylamide					+		V
Acrylic esters				+	(+)		A,V
Acrylonitrile						+	F
Methyl methacrylate		+	+	+	+		T
Ethene		+	+	(+)	(+)	(+)	F,T
Styrene		+	+	(+)	(+)		T
<i>p</i> -Methyl styrene			+	+			T
<i>N</i> -Vinyl pyrrolidone		+			+		V
Vinyl acetate		(+)	(+)	+	(+)		A,C
Vinyl chloride	+	(+)	(+)	+	(+)		T
Vinyl fluoride		+					C,T
Vinylidene fluoride			+	+			C,T
Trifluorochloro-, tetrafluoroethene			+				T
Butadiene, chloroprene			(+)	+	+		A,C,E,T

Source: Table adapted from Ref. 2. © Wiley-VCH Verlag GmbH & Co. KGaA, 2005.

Polymerization in the gas-phase (G), in bulk (B), in suspension (S), in emulsion (E), in solution (L), by precipitation (P). Main use as adhesive (A), coating (C), elastomer (E), fiber (F), thermoplastic (T), or various (V). + Mainly, (+) less often.



I_2 is initiator, M is monomer, $\text{P}_n^\bullet$ is a radical of chain length n ,
T is a chain transfer species, P_n is a polymer

Scheme 2 Key mechanistic steps of radical polymerization.

mechanistic aspects of RP is provided by the outstanding monographs⁵⁴ of Moad and Solomon, Matyjaszewski and Davis⁶², and others^{63,64} (see also **Kinetics of Polymerizations**). The mechanism of RP consists of several steps as depicted in Scheme 2.

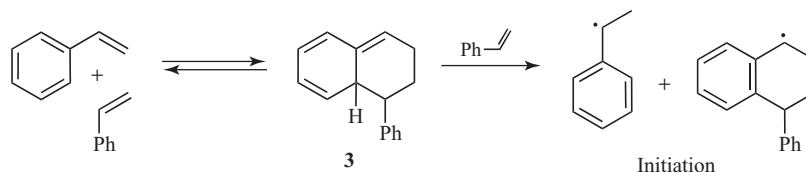
The numerical values for important parameters of RP are given in Table 2.

As the detailed discussion of this generally accepted mechanism is available elsewhere, only those points of industrial importance will be briefly highlighted.

Table 2 General range of values for key parameters of radical polymerization.

$k_d = 10^{-4} - 10^{-6} \text{ s}^{-1}$	$k_i \approx k_p = 10^2 - 10^4 \text{ M}^{-1} \text{ s}^{-1}$	$k_{tc} \approx k_{td} = 10^6 - 10^8 \text{ M}^{-1} \text{ s}^{-1}$
$[I] = 10^{-2} - 10^{-4} \text{ M}$	$[M] = 10^{-1} - 10 \text{ M}$	$[R^*_n] = 10^{-7} - 10^{-9} \text{ M}$

Source: Data from Ref. 65, p. 274.

**Scheme 3** Mayo mechanism of styrene thermal autopolymerization.

2.3 Initiators and Initiation

Initiation of RP begins with the generation of primary radicals (Scheme 2) from the initiator or initiating system. Addition of the primary radicals to the monomer then affords the initiating radicals. The dissociation of the initiator is generally much slower ($k_d \sim 10^{-5} \text{ s}^{-1}$) than the addition of primary radicals to monomer molecules ($k_i \approx 10^4 \text{ M}^{-1} \text{ s}^{-1}$). A comprehensive discussion of all aspects of the different classes of initiators or initiating systems and the various kind of primary radicals (C, O, S, Si, or P-centered) is provided in the monograph⁵⁴ of Moad and Solomon. A survey of radical initiators including decomposition kinetics and half-life times can be found in the handbook⁶⁶ of Denisov and coworkers and to a smaller extent in the *Polymer Handbook*.⁶⁷ Similar information on commercially available initiators is accessible on the websites of the major producers such as AkzoNobel, Arkema, and Wako Chemicals. Braun recounts the origins and development of RP from a historical point of view.⁶⁸ The most important initiators and initiating techniques for industry are discussed briefly below (see also **Overview of Radical Initiation**).

2.3.1 Thermal Autoinitiation

Styrene and its derivatives are the most prominent examples of monomers that generate initiating radicals by a purely thermal reaction without participation of other reagents. For example, at 180 °C, 80% conversion of pure styrene monomer to polymer occurs in 40 minutes. The most accepted mechanism⁶⁹ of styrene autoinitiation involving formation of a Diels–Alder adduct **3** (Scheme 3)

was proposed by Mayo. Thermal self-initiation of styrene is used industrially to prepare extremely pure PS devoid of any initiator and derived functional groups. Thermal autoinitiation of other monomers (acrylates or methacrylates⁷⁰) is much slower and without any practical importance.

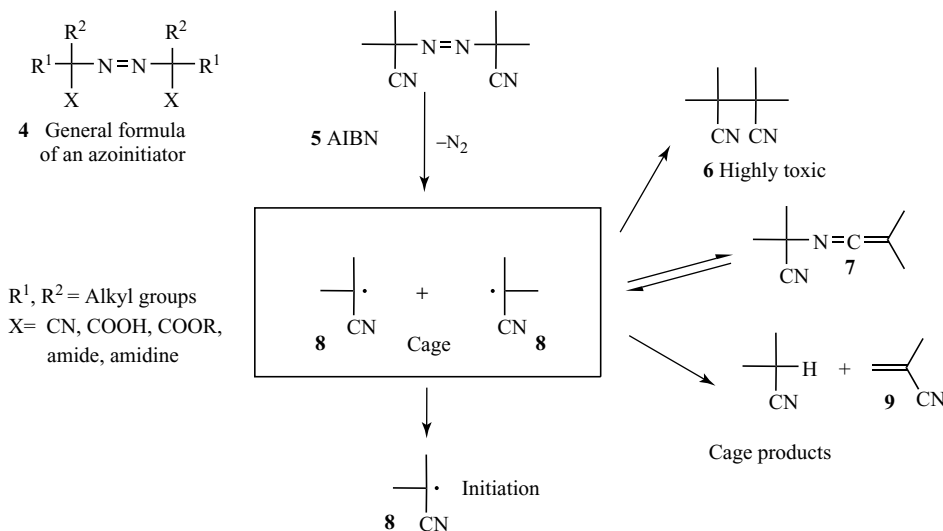
2.3.2 Azoinitiators

Industrially important azoinitiators are symmetrical dialkyldiazenes **4** (Scheme 4) bearing tertiary R groups with substituents (X) which serve to stabilize the incipient radical, thus lowering the decomposition temperature. The most important member of this class is azo-isobutyronitrile **5** (AIBN).

The thermal decomposition of azoinitiators generates two C-centered radicals and nitrogen. The mechanism of the thermal and photochemical decomposition of dialkyldiazenes has been reviewed by Engel.⁷¹ Unfortunately, the yield of initiating radicals is practically never quantitative. In fact, depending on the viscosity of the surrounding media and size of the primary radicals, the latter can undergo an irreversible cage termination reaction leading to inactive products. Hence, only those primary radicals that escape from the solvent/monomer cage participate in chain initiation. This cage effect negatively influences the initiator efficiency (f) which is defined by (1) for an initiator generating n (usually 2) primary radicals and typically⁷² lies in the range of 0.5–0.7 (or 50–70%).

$$f = \frac{\text{Rate of initiation}}{n \times \text{Rate of initiator decay}} \quad (1)$$

The cage termination products may be problematic. For example, the dinitrile **6** formed from AIBN



Scheme 4 Azoinitiators and their decomposition mechanism.

is a highly toxic compound,^{73,74} which prevents the use of AIBN for making polymers that would come into contact with foodstuff. The C–N dimer **7** can redissociate⁷⁵ into the radicals **8**, thus complicating the polymerization kinetics. Furthermore, the methacrylonitrile **9** is readily copolymerized with the monomer and can influence⁷⁶ the polymer properties.

The thermal decomposition of azoinitiators follows first-order kinetics (2), and the temperature dependence of k_d obeys Arrhenius law (3). A very important characteristic of a polymerization initiator is its half-life ($t_{1/2}$) (4), which is the time required to reduce the original initiator concentration by 50%. It can be easily calculated using (2–4) and the tabulated Arrhenius parameters A and E_a .

$$-\frac{d[I]}{dt} = k_d[I] \quad (2)$$

$$k_d = Ae^{-\frac{E_a}{RT}} \quad (3)$$

$$t_{1/2} = \ln \frac{2}{k_d} = \frac{0.693}{k_d} \quad (4)$$

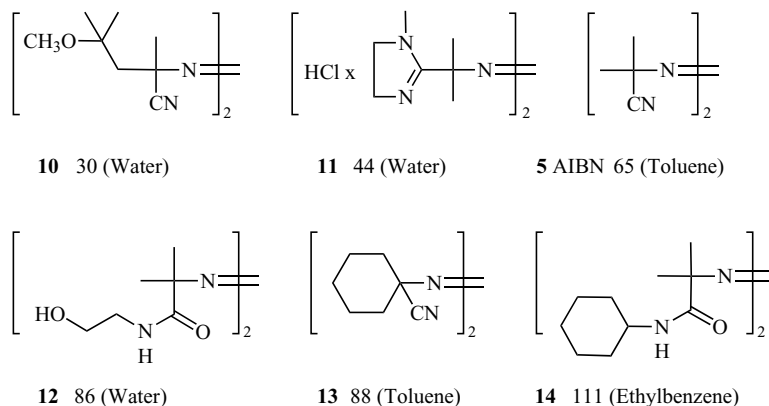
where k_d is the rate constant of initiator decomposition (s^{-1}); $[I]$ is the initiator concentration (M); A is the Arrhenius frequency factor (s^{-1}); E_a is the activation energy for the initiator decomposition (J mol^{-1}); R is $8.3142 \text{ J mol}^{-1} \text{ K}^{-1}$; T is the temperature in K; and $t_{1/2}$ is the half-life time (s^{-1}).

Activation energies of thermal homolysis of azoinitiators lie in the range of $100\text{--}170 \text{ kJ mol}^{-1}$ and thus decomposition rates are very sensitive to temperature. For example, $t_{1/2}$ of AIBN decreases from 10 hours at 65°C to 20 minutes at 90°C and to ~ 45 seconds at 110°C . In terms of volume, AIBN is the most important azoinitiator. There are several other initiators on the market with different cleavage temperatures, solubility in water or organic solvents, or functional groups (X) other than CN. The latter allow introduction of the functionality into the polymeric chain. Examples⁷⁷ are compounds **10–14** shown in Scheme 5.

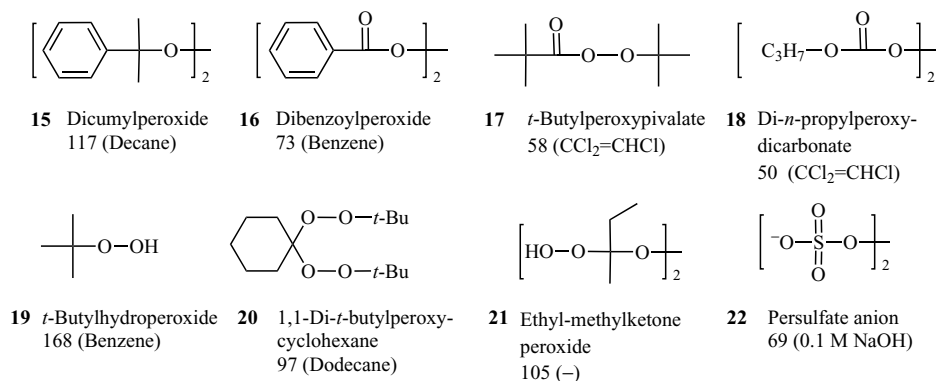
In general, advantage of azoinitiators over the widely used peroxides is their lower tendency to undergo chain transfer reactions. This leads to better defined polymers containing fewer oxygenated impurities, which enhances their thermal or photochemical stability.

2.3.3 Peroxides

Peroxides $\text{R}^1\text{--O--O--R}^2$ are the most important industrial radical initiators, exceeding the production volume of azoinitiators by orders of magnitude. About 45% of the 207 000 tons of peroxides that were utilized⁷⁸ in 2007 by the worldwide plastics industry was used to initiate RPs. The rest found application in radically induced cross-linking



Scheme 5 Examples of commercial azoinitiators with indicated temperatures ($^{\circ}\text{C}$) for a half-life of 10 hours.



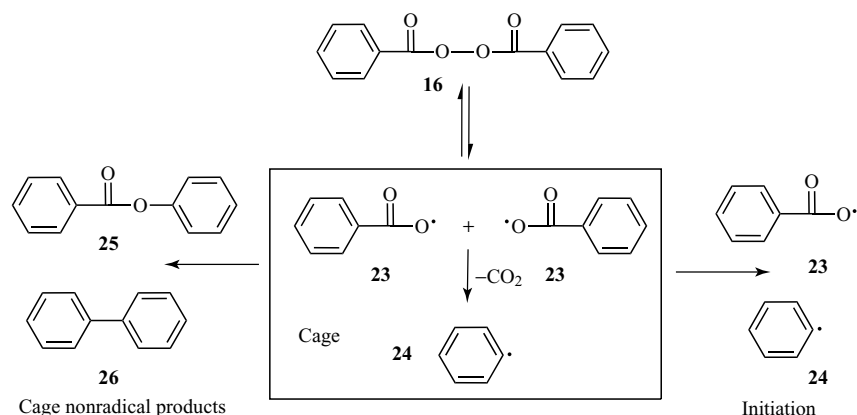
Scheme 6 Examples of commercial peroxide initiators with indicated temperatures ($^{\circ}\text{C}$) for a half-life of 10 hours.

of unsaturated polyester resins and polyethylene, in controlled reduction of molecular weight of polypropylene, and as synergists for flame retardants. A detailed analysis of the markets, applications, and future trends for organic peroxides can be found in the market study⁷⁸ of Townsend Polymer Services. The most important commercial peroxide initiators are dialkylperoxides, diacylperoxides, hydroperoxides, peroxyesters, peroxydicarbonates, peroxyketals, ketone peroxides, and inorganic peroxides. Several dozens of derivatives with varying half-life, solubility, and volatility are available on the market. Typical examples are the compounds **15–22** shown in Scheme 6.

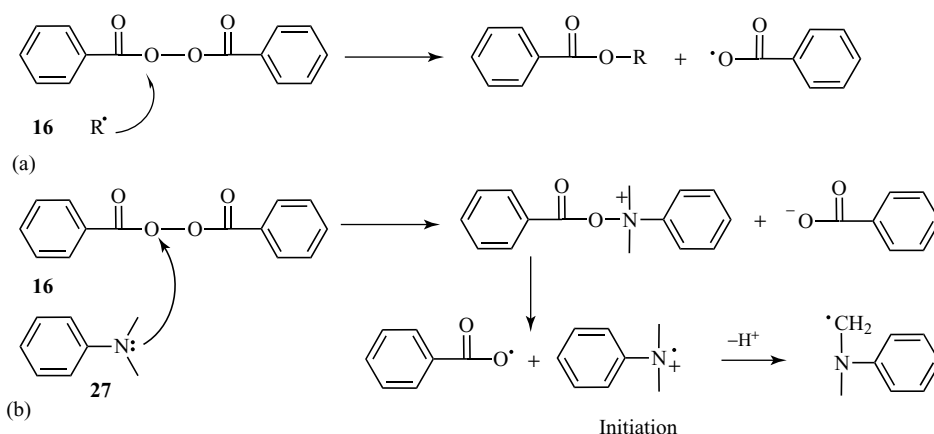
The chemistry of peroxides was recently reviewed.⁷⁹ Generation of radicals from peroxides occurs via homolysis of the weak $-\text{O}-\text{O}-$ bond. The bond dissociation energies^{66,80} of most peroxides lie between 127 (dibenzoyl peroxide) and 211 kJ

mol^{-1} (H_2O_2). The nature of the primary radicals depends⁵⁴ on the structure of the starting peroxide and the type of cage reactions. For example, thermolysis of dibenzoylperoxide **16** gives rise to the relatively long-lived benzoyloxy radicals **23**. As **23** can also decarboxylate to give phenyl radicals **24**, both these radicals are involved in chain initiation. The competitive irreversible coupling of **23** and **24** yields the cage products **25** and **26** (Scheme 7).

Analogously, hydroperoxides generate alkoxy and hydroxyl radicals, and dialkylperoxides are sources of alkoxy radicals. Aliphatic diacylperoxides yield predominantly alkyl radicals because of the very fast in-cage decarboxylation of primary aliphatic acyloxy radicals. However, the simple homolysis of the $-\text{O}-\text{O}-$ bond of peroxides is not the sole decomposition mechanism. In fact, the radical chemistry of peroxides is more complex than that of azoinitiators. Diacyl peroxides are susceptible

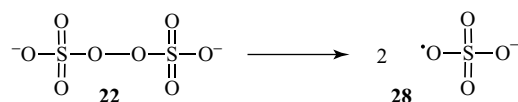


Scheme 7 Thermal decomposition of dibenzoyl peroxide.



Scheme 8 Induced decomposition of dibenzoyl peroxide with (a) radicals and (b) aromatic amines.

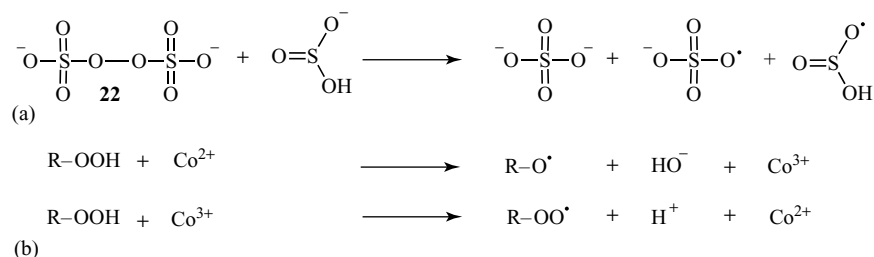
to radical-induced decomposition resulting from homolytic attack of a radical on one of the oxygens of the $-O-O-$ bond (Scheme 8). The consequence is chain transfer from the growing chain to the initiator with the concomitant incorporation of a benzoyloxy group into the polymer in a form of a *secondary* ester. Such end groups may negatively influence the thermal (PS⁷⁶) or hydrolytic (PVC⁸¹) stability of the polymer. Of practical importance is the decomposition of dibenzoyl peroxide **16** induced⁸² by aromatic amines (Scheme 8). As this reaction takes place already at room temperature or even below, addition of an amine synergist (often called *accelerator*) to a polymerizable composition containing **16** allows the polymerization to occur at room temperature or even around 0 °C. Two-component initiating systems consisting of **16** and *N,N*-dimethylaniline **27** (or similar derivatives) are widely used for



Scheme 9 Radical generation from a persulfate.

the room-temperature curing^{9,31,83} of unsaturated polyesters.

The water soluble sodium, potassium or ammonium salts of peroxydisulfuric acid (persulfates) are important initiators for aqueous and emulsion (EP) polymerizations. The mechanism of radical generation from the persulfate dianion **22** depends on pH. Homolytic cleavage affording the sulfate radical anion **28** dominates in neutral media (Scheme 9) whereas heterolytic cleavage occurs in acidic solution.



Scheme 10 Redox reaction between (a) persulfate and hydrogen sulfite, (b) hydroperoxide and Co ions.

Furthermore, redox reactions occur between persulfates **22** and reducing agents such as 2-mercaptoethanol, thiourea, sulfites,⁸⁴ amines, dithionites, or thiosulfates. Such initiating systems are frequently employed in aqueous EPs. In addition to the amine–dibenzoylperoxide system, the redox reaction of hydroperoxides with ions of various transition metals (mostly Co or Mn) is commonly used for the room-temperature curing of unsaturated polyesters. Typically, two-component initiating systems consisting of a hydroperoxide (e.g., cumyl hydroperoxide or ethylmethylketone peroxide **21**) and a Co- or Mn-based accelerator (e.g., cobalt octoate or manganese naphthenate) are used for this purpose (Scheme 10).

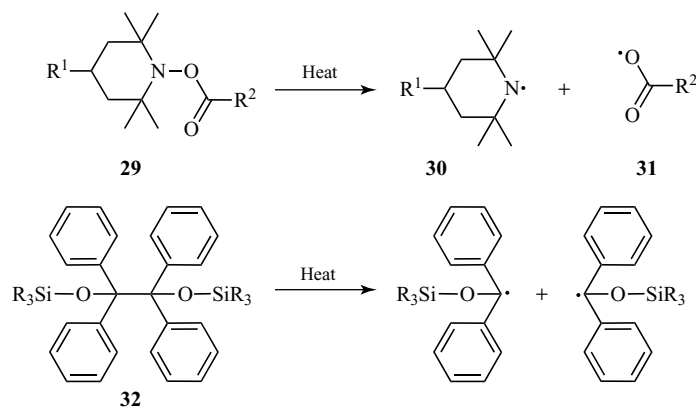
Redox-initiated polymerizations were reviewed⁸⁵ by Misra and Bajpai. A comprehensive discussion of the initiating mechanism of the different peroxide families is available in the monograph⁵⁴ of Moad and Solomon.

Organic peroxides, as well as azoinitiators, are unstable compounds and decompose exothermally at relatively low temperatures. They must be handled

and stored properly and most require some form of temperature control. Guidelines for the safe handling of these initiators were recently reviewed⁸⁶ and are available on the web pages⁸⁷ of their manufacturers.

2.3.4 Miscellaneous Radical Initiators

Peroxides are the most important industrial initiators for RP followed by azoinitiators. Much smaller volumes of specialty initiators are also used. One example is 2,3-dimethyl-2,3-diphenyl butane, known as Perkadox[®] 30 (AkzoNobel), used in styrene polymerization. This C–C dimer thermally dissociates into cumyl radicals ($t_{1/2} = 1$ hour at 259 °C in PhCl). Novel initiators⁸⁸ with improved handling and storage stability as compared to peroxides or azo-compounds are highly desirable and are slowly appearing on the market. Examples are sterically hindered *N*-acyloxyamines⁸⁹ **29** and silylated benzopinacol⁹⁰ derivatives **32** (Scheme 11). The proposed mechanism of action of the *N*-acyloxyamine radical initiators **29** involves⁹¹



Scheme 11 *N*-Acyloxyamine and silylated benzopinacol initiators.

homolysis of the N–OC bond to generate *N*-aminyl radicals **30** and acyloxy radicals **31**. This contrasts with the NO–C bond homolysis of alkoxyamine initiators for controlled RP.

Initiators for controlled RP are discussed in respective sections.

2.3.5 Photoinitiators

Photoinitiators^{92–95} are compounds that generate primary radicals upon irradiation with light of a suitable wavelength (generally UV).

They are niche products used to initiate polymerization (curing) of radically polymerizable/cross-linkable coatings (e.g., on furniture, flooring, metal, plastics, automotive parts, paper, optical fibers), printing inks, and adhesives, or in the production of microelectronic devices. They are not used, however, in the production of bulk, large-volume polymers. Radiation curing in a broader sense⁹⁶ also encompasses curing initiated by electron beam⁹⁷ (EB) or cationic⁹² photoinitiators, but these topics are not treated here.

A UV-curable formulation⁹⁷ for a coating, ink, or adhesive consists of a mixture of (i) 30–50% specialty monomers or oligomers,⁵⁶ which impart most of the basic properties to the final cured or cross-linked material; (ii) 10–40% reactive diluents or monomers, which permit the adjustment of formulation viscosity and crosslink the oligomer; (iii) 1–20% additives and pigments; and (iv) 0.5–8% photoinitiators which provide the initiating radicals. Functionally terminated low to medium molecular weight polymerizable oligomers are the backbone of UV-curable coatings and determine properties of the cured coating: for example, hardness, chemical resistance, and flexibility. Commonly used oligomers include acrylates of polyhydric alcohols, oligomeric diols, and polyols having epoxy-, urethane-, polyester-, or siloxane backbones. Of less importance are the unsaturated polyesters or thiol–ene systems. Oligomers based on methacrylates are sometimes used in combination with acrylates in order to improve thermal resistance and mechanical hardness of the finished coating.

UV-light-triggered radiation curing provides several advantages over thermal curing, which include (i) very rapid cure occurring within seconds,

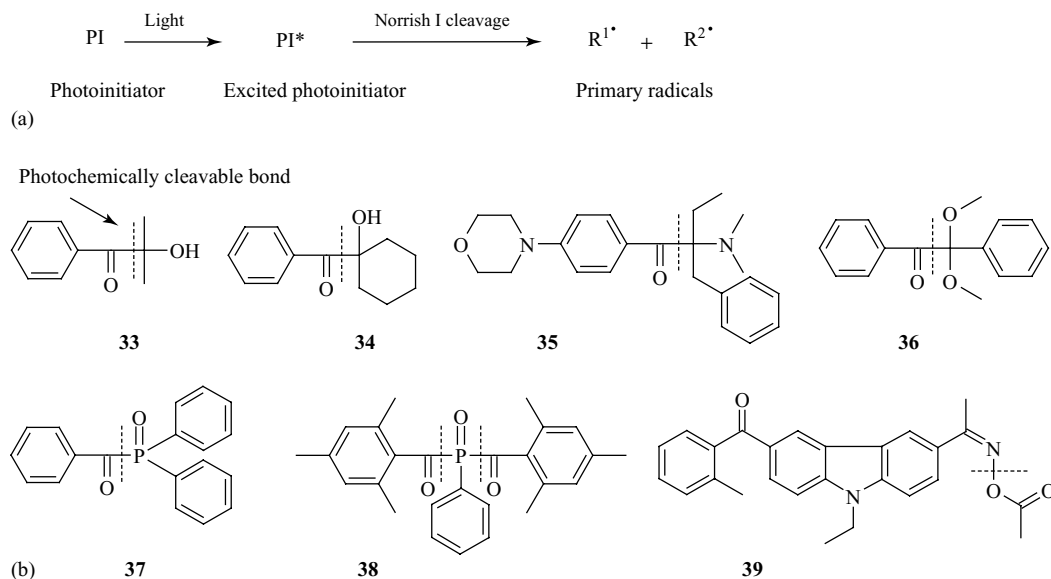
(ii) ambient temperature curing which permits the coating of heat-sensitive substrates such as wood and plastics, (iii) more efficient, compact operations, (iv) zero or low solvent levels, and (v) good film properties and performance. Among the drawbacks of UV curing is the high sensitivity toward oxygen inhibition, the impossibility to cure thick pigmented layers, and the difficulty to cure three-dimensional objects (shadow zones). Details on equipment for UV and EB curing (lamps, electron guns, machinery) can be found in the monograph⁹⁸ of Mehmert and coworkers. A comprehensive overview of photopolymerization in polymer science and technology is provided in the four-volume compendium^{99–102} of Fouassier and Rabek, and Marrion reviews¹⁰³ the chemistry and physics of coatings.

The market study by SRI Consulting¹⁰⁴ provides a detailed analysis of the global market for radiation-curable products. In 2007, the market volume was estimated at 390 000 metric tons with an average growth of 4–5% per year.

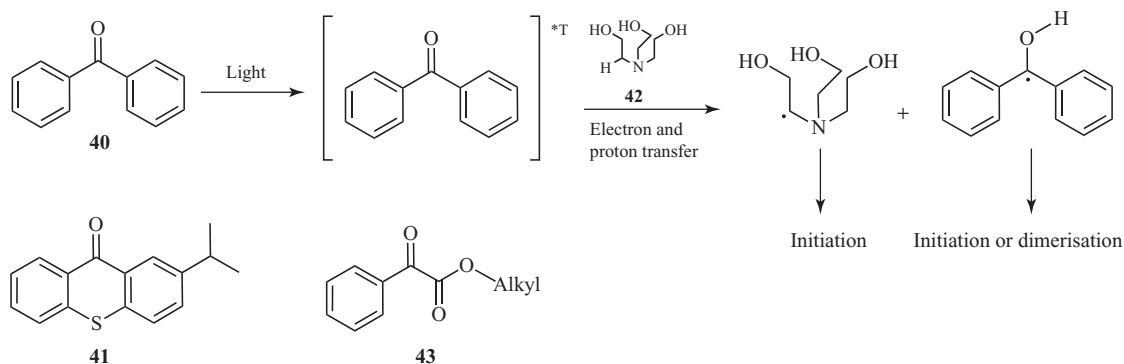
Radical photoinitiators^{92–95} are generally divided into two classes. Compounds undergoing homolytic bond cleavage (Norrish I cleavage) upon irradiation are termed *type I photoinitiators*. Typical examples are α -hydroxyketones **33–34**, α -aminoketones **35**, benzil dialkylketals **36**, acylphosphine oxides **37**, and bisacylphosphine oxides **38** (see Scheme 12). The oxime esters (e.g., **39**) photoinitiators^{95,105,106} were developed for highly specialized applications in electronics such as photocuring of color filter resists and the black matrix resin of liquid crystal displays.

Type II photoinitiators, on the other hand, interact in their excited state with a second molecule (coinitiator) to generate radicals in a bimolecular reaction (Scheme 13). Derivatives of benzophenone **40** and thioxanthone, for example **41**, are the most important type II photoinitiators. Amines such as *N*-methyldiethanolamine, triethanolamine **42**, and esters of 4-dimethylamino benzoic acid are typical examples of coinitiators. The resin matrix itself can also act as a coinitorator if it possesses easily extractable hydrogen atoms. Alkyl phenylglyoxylates **43** are also considered¹⁰⁷ as type II photoinitiators. A compilation of commercially available photoinitiators and a discussion of their chemistry and applications is provided in the book by Dietliker.⁹³

One of the biggest challenges⁹⁵ for the future growth of the UV market is the development of



Scheme 12 (a) Type I photoinitiators and (b) some of their representative examples.



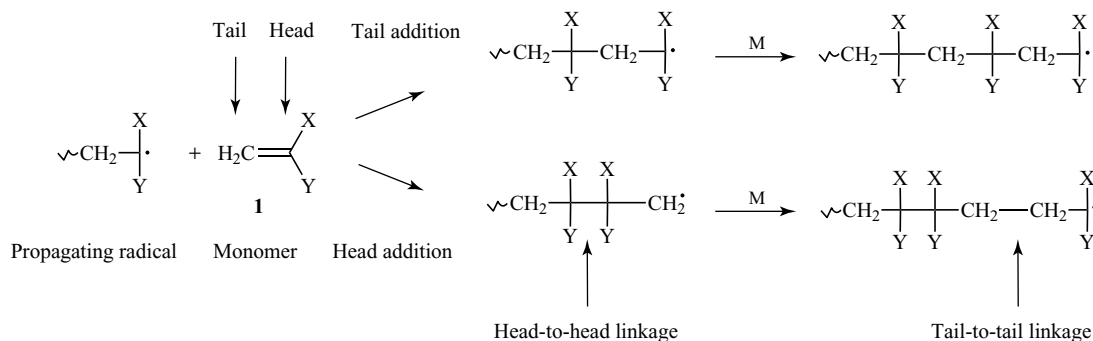
Scheme 13 Type II photoinitiators.

nonextractable, odorless, and low-migration photoinitiators. Such products will be applicable in coatings destined for indirect food contact. So far, few UV-curable systems are present in this market because the photoinitiator or its fragments can migrate into foodstuffs.

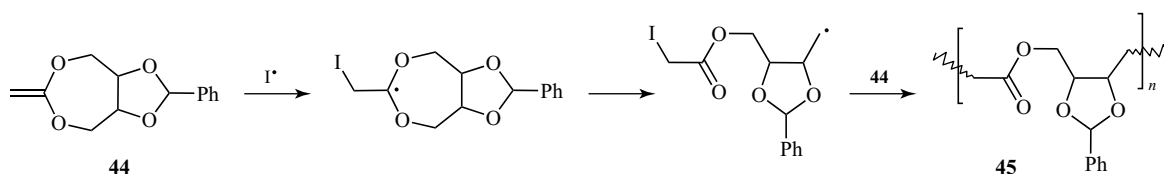
2.4 Propagation

Propagation is the repeated addition of the growing macroradical to monomer. The rate constants of propagation are typically in the range of $k_p \sim 10^2\text{--}10^4 \text{ M}^{-1} \text{ s}^{-1}$. The magnitude of k_p

depends slightly on the degree of polymerization X_n of the macroradical, at least for the first (~ 10) propagations steps. The mechanistic aspects of the propagation step of RP are well understood^{54,62,63} and need not to be discussed here. However, one should note that the simplified picture of a 100% regiospecific head-to-tail addition (Scheme 1) which is shown in many introductory texts on polymerization is not completely correct. In fact, head-to-head addition is observed in polymerizations of most monomers. For example, it occurs to the extent of 11% in the polymerization of allyl esters¹⁰⁸ (Scheme 14).



Scheme 14 Regiosequence isomerism—head versus tail addition.



Scheme 15 Ring-opening polymerization of a cyclic monomer.

Of course, even more variations are observed with diene (1,3-butadiene, isoprene, chloroprene) monomers. It should be noted in this context that even the addition of primary radicals (Scheme 2) to monomers **1** is not always regioselective. For example, in the reaction of benzoyloxy radicals **23** with styrene^{109,110} tail addition (80%), head addition (6%), and addition (in end effect substitution) to the styrene benzene ring (14%) can be observed. Deliberate synthesis of head-to-head polymers and their properties were reviewed¹¹¹ by Vogl and coworkers.

Propagating organic radicals are more or less planar (sp^2 hybridized) and, consequently, the polymers formed by RP are generally atactic. Detailed treatments of the stereochemical aspects of the propagation step in RP are available.^{54,62}

In general, polymers produced by RP have higher densities than the starting vinylic monomers. As a consequence, polymerization is accompanied by volume contraction (up to 20% depending on monomer), which can be a significant problem in adhesive, coating, mold-filling (dental fillings), and other applications where volume change (shrinkage) is undesirable. However, only very low shrinkage or even a net increase in volume is observed with special cyclic monomers^{2,54,112} undergoing radical ring-opening polymerization

(ROP). Each propagation step of ROP results in ring-opening. For example, the ROP of the bicyclic 2-methylene-1,3-dioxepane **44** (Scheme 15) occurs with a small (0.5%) volume expansion. This expansion is probably due to the conversion of the more dense structure of the crystalline monomer **44** into the less dense structure of the amorphous polymer **45**.¹¹³

At low conversion, the overall rate of polymerization R_p is kinetically first order in monomer and half order with respect to initiator (5), for definition of f see (1).

$$R_p = -\frac{d[M]}{dt} = k_p \left(f \frac{k_d}{k_t} \right)^{1/2} [M][I]^{1/2} \quad (5)$$

The kinetic chain length ν (6) is defined as the average number of monomer molecules polymerized by each initiating radical. It can be expressed as the rate of chain propagation divided by the sum of the rates of all of the chain termination processes. In the case of termination by disproportionation, it equals the number average degree of polymerization $\bar{X}_n$.

$$\nu = \frac{k_p[M]}{2(fk_d k_t[I])^{1/2}} \quad (6)$$

Equations (5) and (6) show that increasing the concentration of the initiator will indeed increase

the rate of polymerization, although not linearly, but will inevitably result in a polymer of shorter chain length.

The propagation step is potentially a reversible process. Polymerization can occur spontaneously only when the associated free-energy change ΔG_p is negative. ΔG_p is expressed in (7) where ΔH_p represents the enthalpy and ΔS_p represents the entropy change upon propagation.

$$\Delta G_p = \Delta H_p - T\Delta S_p \quad (7)$$

Each monomer can be characterized by a ceiling temperature T_c at which, for a given monomer concentration, the polymerization rate becomes zero.

Common monomers such as ethene, vinyl acetate, and acrylates have very high T_c 's ($>400^\circ\text{C}$) and depropagation does not occur under viable polymerization conditions. Styrene has a significantly lower ceiling temperature and depropagation must be taken into account above 250°C . The addition of a substituent to the α position of a vinylic monomer greatly reduces T_c . α -Methylstyrene can, for example, be polymerized only at room temperature or below.

2.5 Copolymerizations

Copolymerization of two or more monomers by RP is commonly used in industry to tune the properties of commercial polymers. For example, addition of the polar monomer acrylonitrile to styrene affords a copolymer with much improved oil and grease resistance. Many industrial polymers are prepared from two, three, or even more monomers. In addition to varying chain length and stereochemistry, copolymers differ in their composition (the relative amounts of each monomer incorporated into the copolymer), sequence distribution (the way in which these monomer are arranged within the chain), and architecture (linear or graft or branched) (Figure 5).

Different monomers lead to different radicals, and the relative rates of propagation depend on the steric and electronic properties of both monomer and radical. Therefore, at any given time the ratio at which the monomers are incorporated into the polymer is not equal to their ratio in the monomer mixture. Hence, both the composition

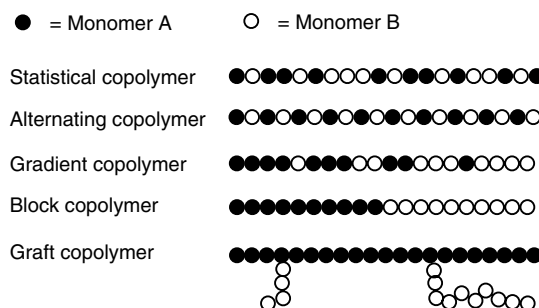
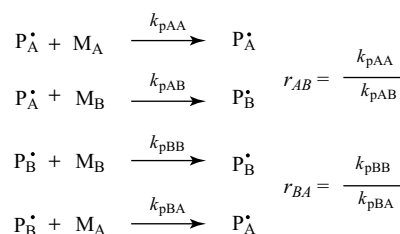


Figure 5 Different types of copolymers.



Scheme 16 Copolymerization of two monomers M_A and M_B .

of the monomer feed and copolymer will change with conversion and, consequently, batch copolymers will in most cases not have homogeneous composition at the molecular level.

Several kinetic models of radical copolymerization have been developed (e.g., terminal, penultimate, complex dissociation, and so on) and details can be found in the monographs of Matyjaszewski and Davis⁶² or Moad and Solomon.⁵⁴ Here, only the simplest, the so-called terminal model¹¹⁴ of radical copolymerization, will be briefly discussed. This model describes the copolymer composition for the majority of systems reasonably well but is less suitable for copolymerization kinetics, for which the penultimate model is more appropriate.

The terminal model assumes that the reactivity of the polymer radical depends only on the nature of its terminal monomer unit: that is, the penultimate unit on the macroradical does not affect its reactivity. Accordingly, the kinetics of copolymerization of two monomers M_A and M_B is determined by the relative rates of four propagation reactions characterized by four propagation rate constants k_{pAA} , k_{pAB} , k_{pBB} , and k_{pBA} (Scheme 16).

The composition of a copolymer formed at a given instant from a specific monomer mixture is

Table 3 Selected terminal model reactivity ratios.

Monomer M _A	Monomer M _B	<i>r</i> _{AB}	<i>r</i> _{BA}
Methyl methacrylate	Ethyl methacrylate	1.0	1.0
Styrene	Acrylonitrile	0.4	0.05
Styrene	Maleic anhydride	0.02	0.01
Vinyl chloride	Vinyl acetate	2.0	0.3
Vinyl acetate	Styrene	0.05	50.0

Source: Data from Ref. 67.

described by the Mayo–Lewis equation¹¹⁴ (8):

$$\frac{F_A}{F_B} = \frac{f_A}{f_B} \left(\frac{r_{AB}f_A + f_B}{f_A + r_{BA}f_B} \right) \quad (8)$$

where $F_A = (1 - F_B)$ and $f_A = (1 - f_B)$ are the instantaneous mole fractions of monomer M_A in the polymer and in the monomer mixture, respectively, and $r_{AB} = k_{pAA}/k_{pAB}$ and $r_{BA} = k_{pBB}/k_{pBA}$ are the monomer reactivity ratios.

Using this equation, it is possible to predict the copolymer composition for a given monomer mixture from just two parameters, namely, the reactivity ratios (sometimes also called *copolymerization parameters*) r_{AB} and r_{BA} , which are available for many monomers.⁶⁷ However, the published data often spans a considerable range. Additionally, several empirical methods⁵⁴ for the prediction of reactivity ratios are available, the most widely used being the *Q*–*e* scheme^{115,116} of Alfrey and Price. A few values of the reactivity ratios are given in Table 3 for illustration.

As seen from Table 3, the values of r_{AB} and r_{BA} are generally different. The special case where $r_{AB} = r_{BA} = 1$ occurs with monomers that are very similar, such as the homologous esters of acrylic or methacrylic acids. For this case, the product is a random copolymer and the monomers are incorporated into the copolymer according to their proportions in the monomer mixture. In cases where $r_{AB} < 1$ and $r_{BA} < 1$, a tendency toward alternation is observed because cross-propagation is favored over homo-propagation. When r_{AB} and r_{BA} approach zero, an alternating copolymer is obtained. A well-known example is the styrene–maleic anhydride copolymer. The situation where r_{AB} and r_{BA} are both greater than 1 is rare, and copolymers with larger blocks consisting of M_A and M_B are the result. In cases where $r_{AB} < 1$ and $r_{BA} < 1$ (or $r_{AB} > 1$ and $r_{BA} > 1$), there always exists exactly one so-called *azeotropic composition* of the monomer mixture at

which the composition of the formed copolymer is the same as that of the monomer mixture. The azeotropic composition is given by (9).

$$\frac{[M_A]_{\text{Azeotrop}}}{[M_B]_{\text{Azeotrop}}} = \frac{1 - r_{AB}}{1 - r_{BA}} \quad (9)$$

Its existence is of significant industrial importance. In fact, a copolymer without compositional heterogeneity can be prepared by conducting simple batch copolymerization if the ratio of both monomers fulfills (9). Analogous composition equations^{117,118} for (rare) azeotropic composition of three or four monomers have also been developed.

Finally, when $r_{AB} > 1$ and $r_{BA} < 1$ (or $r_{AB} < 1$ and $r_{BA} > 1$), one monomer will always be preferentially incorporated into the copolymer. These copolymerizations have no azeotropic composition. Of course, kinetic treatment of ternary⁵⁴ (three monomers) or even quaternary (four monomers) copolymerization is significantly more complicated. For example, nine distinct propagation reactions and six reactivity ratios must be considered in the terminal model for three monomers.

2.6 Chain Transfer and Chain Transfer Agents

A chain transfer reaction is the interaction of the propagation radical with a nonradical species (T) to produce a dead polymer chain and a new radical (T*) capable of initiating a new propagating chain (refer Scheme 2). Details on the theory can be found in the article¹¹⁹ by Chieftain and Gizzard or that by Corner.¹²⁰ In principle, chain transfer can occur with any species present in the polymerizing system (initiator, solvent, monomer, polymer, adventitious impurity, or deliberately added chain transfer agent) and it always causes a reduction in $\bar{X}_n$, the number-average degree of polymerization.

Table 4 Transfer constants (k_{tr}/k_p) at 50 °C.

	Styrene	Methyl acrylate	Methyl methacrylate	Vinyl acetate
Benzene	2×10^{-6}	2×10^{-5}	4×10^{-6}	1×10^{-4}
Toluene	1×10^{-5}	1×10^{-4}	2×10^{-5}	2×10^{-3}
Ethyl acetate	5×10^{-4}	6×10^{-5}	1×10^{-5}	2×10^{-4}
CCl ₄	1×10^{-2}	2×10^{-4}	2×10^{-4}	0.8
1-Butanthiol	20	1.5	0.6	50

Source: Data from Ref. 67.

Furthermore, chain transfer to the polymer results in branching or potentially cross-linking. For example, intramolecular chain transfer (backbiting) leading to branching is observed during the RP of ethylene.¹²¹ Quantitatively, the efficiency of chain transfer to a given species is characterized by its transfer constant $C_{tr} = k_{tr}/k_p$. For efficient chain transfer to occur, the rate constant of reinitiation (k_{tr}) by T^* must be equal to or greater than that for propagation (k_p) (refer Scheme 2). The magnitude of the transfer constant depends on the structure of both the transfer agent and the radical. Since the propagation and transfer reactions show similar temperature dependence, chain transfer constants change only slightly with temperature. The transfer constants for variety of monomers and transfer agents can be found in the literature.⁶⁷ Most organic compounds have low transfer rates, and transfer is important only when they are present in high concentration, that is, as solvent. Table 4 illustrates the C_{tr} values for a few typical solvents and chain transfer agents at 50 °C.

Deliberately added chain transfer agents (T) with large C_{tr} are often used in industrial polymerizations to control (limit or reduce) the molecular weight and molecular weight distribution of polymers. The influence of chain transfer on $\bar{X}_n$ can be described by the Mayo equation¹²² (10):

$$\frac{1}{\bar{X}_n} = \frac{1}{\bar{X}_{n0}} + C_{trT} \frac{[T]}{[M]} \quad (10)$$

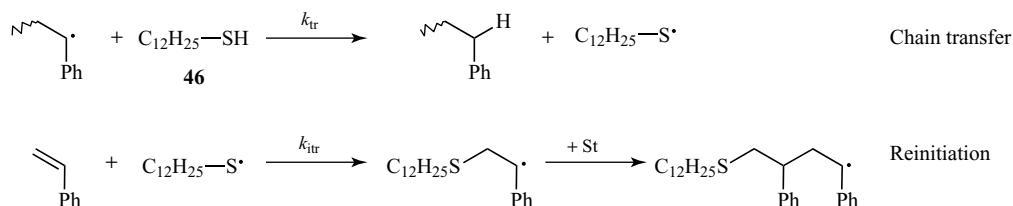
where $\bar{X}_n$, $\bar{X}_{n0}$ are the number-average degree of polymerization in the presence or absence of chain transfer, respectively, and C_{trT} is the chain transfer constant of T.

The added transfer agent is said to behave ideally if its chain transfer constant is equal to unity. In this case, the ratio of the rates at which the monomer and transfer agent are consumed by the growing radicals is constant and equal to the ratio of the molar concentrations of the monomer to

transfer agent. This means that $\bar{X}_n$ remains constant throughout the polymerization. On the other hand, a transfer agent with $C_{trT} \gg 1$ will be rapidly consumed in early stages of the polymerization. In the case of $C_{trT} \ll 1$, the ratio $[T]/[M]$ increases with conversion, leading to a decrease in $\bar{X}_n$ as the polymerization progresses. Polymers with a broad molecular weight distribution result in both cases. Continuous addition of the monomer or transfer agent during polymerization to maintain a constant the $[T]/[M]$ ratio may help to overcome these problems. The control of the molecular weight of the polymer with the transfer agent translates into control of the viscosity of the reaction mixture and, through mitigation of the gel or the Norrish–Trommsdorff effect,^{123,124} into control of the polymerization rate and exothermicity.

Typical chain transfer agents used in industrial synthesis of variety of polymers (PS, poly (methyl methacrylate) PMMA, ABS, acrylic-, styrene-butadiene-, or acrylonitrile-butadiene copolymers) include mercaptans such as *n*-octyl mercaptan, *n*-dodecyl mercaptan, or 2,2-dimethyldodecyl mercaptan (*tert*-dodecyl mercaptan). Technical information¹²⁵ on mercaptans, as well as examples¹²⁶ of their use as chain transfer agents, can be found on the web site of their producers. Chain transfer with *n*-dodecyl mercaptan **46** in the styrene polymerization is exemplified in Scheme 17.

Primary mercaptans are more active chain transfer agents than secondary or tertiary ones. Apolar mercaptans are lipophilic and odiferous compounds of moderate toxicity. Examples of water-soluble and practically odor-free chain transfer agent are mercaptoacetic acid (thioglycolic acid) and 2-mercaptoethanol. Moreover, these agents introduce functionalities (COOH or OH) into the chains providing access to monofunctional^{120,127} polymers. A special case of chain transfer is the reversible addition fragmentation chain transfer (RAFT), which is an important method of controlled RP



Scheme 17 Polymerization of styrene with chain transfer with *n*-dodecylmercaptan.

(see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).

2.7 Chain Termination

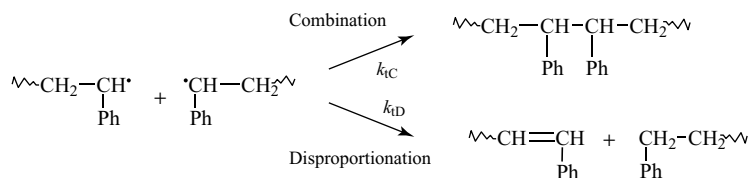
The propagating radicals in RP add a monomer unit every ~ 1 ms on average and typically terminate after about ~ 1 s. Polymeric chains with high $\bar{X}_n$ are formed during this short time. Termination of growing radicals occurs via coupling (k_{tc}) or disproportionation (k_{td}) (Scheme 18). The corresponding rate constants are very high, $k_t \sim 10^7$ – 10^9 M $^{-1}$ s $^{-1}$, approaching the diffusion-controlled limit.

Sterically undemanding radicals terminate preferentially through coupling (styrene), whereas radicals derived from 1,1-disubstituted monomers generally undergo disproportionations (methyl methacrylate). The self-termination of growing macroradicals is a diffusion-controlled process. Therefore, the termination rate constants depend strongly on the chain lengths, and k_t decreases with increasing viscosity of the polymerizing mixture. The increase of viscosity in bulk polymerizations at medium to high conversions slows down the movement of large chains to such a level that their self-termination becomes very slow. On the other hand, monomer molecules may still diffuse rapidly. As a consequence, an autoacceleration phenomenon known as the Norrish–Trommsdorff or gel effect^{123,124} may occur.

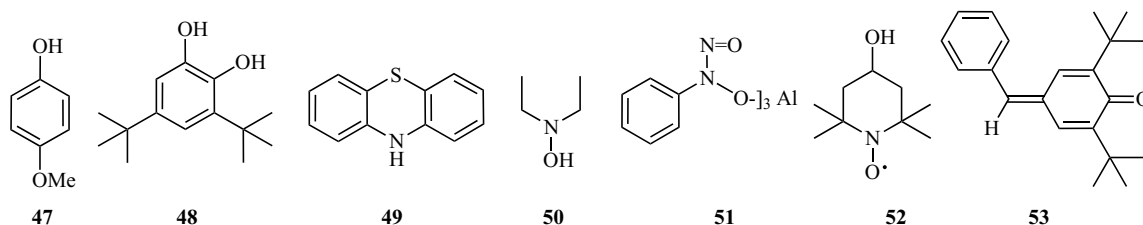
Macroradicals can also terminate by reaction with radicals derived from the initiator. Finally, another very important source of termination reactions is the deliberately added molecules called *inhibitors* or oxygen (oxygen inhibition).

2.7.1 Inhibitors

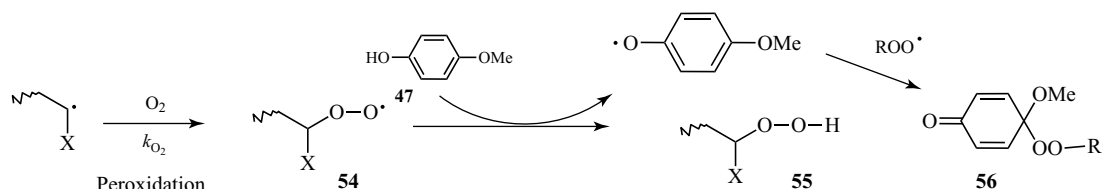
Pure monomers must be protected during storage from polymerization by mixing them with small amounts of polymerization inhibitors, species able to rapidly and efficiently scavenge propagating and/or primary radicals. Moreover, the presence of inhibitors is also necessary during the synthesis and purification (e.g., distillation) of monomers. In fact, a distinction between storage and in-process stabilizers is sometimes made. An ideal inhibitor will prevent polymerization during what is termed an *induction period*. Once consumed, polymerization proceeds at a normal rate. Species that do not show a distinct induction period but rather slow down polymerization are called *retarders*. This topic was reviewed by Bovey and Kolthoff¹²⁸ and Tüdös and Földes-Berezsnich.¹²⁹ Common inhibitors include stable radicals such as galvinoxyl, nitroxide radicals, diphenylpicrylhydrazyl, phenols, quinones, nitrones, nitro and nitroso compounds, phenothiazine, and salts of transition metals which can trap C-centered radicals by electron transfer. Examples of industrially important inhibitors (Scheme 19) are *p*-methoxyphenol **47**, 2,4-di-*t*-butyl catechol **48**,



Scheme 18 Termination of polystyrene macroradicals by combination and disproportionation.



Scheme 19 Examples of polymerization inhibitors.



Scheme 20 Inhibition of polymerization with *p*-methoxyphenol.

phenothiazine **49**, *N,N*-diethylhydroxylamine **50**, salts of *N*-nitroso phenylhydroxylamine **51**, and 4-hydroxy-TEMPO **52**. An example of a retarder is 2,6-di-*t*-butyl-7-phenyl quinone methide **53**, which is used in combination with nitroxide radicals as a storage stabilizer¹³⁰ for radiation-curable coating or ink compositions.

The phenolic inhibitors **47–48**, which are used mostly as storage stabilizers, require^{131,132} traces of oxygen in order to be fully effective. The phenols themselves are rather poor scavengers of C-centered radicals. The latter, however, react very rapidly with oxygen, affording peroxy radicals **54** which are efficiently transformed into nonradical products, namely, hydroperoxides **55** and cyclohexadienones **56**, by reaction with phenols (Scheme 20).

For this reason, the oxygen content in large storage tanks containing acrylic or methacrylic acid and *p*-methoxyphenol (100–200 ppm) as polymerization inhibitor is continuously monitored and maintained at a specific level. An illustrative case of a runaway acrylic acid polymerization caused by insufficient inhibition was reported¹³³ by Levy and Penrod.

On the other hand, phenothiazine **49** is a good hydrogen donor to both C-centered and peroxy radicals and, therefore, an excellent inhibitor^{132,134} even in the absence of oxygen.

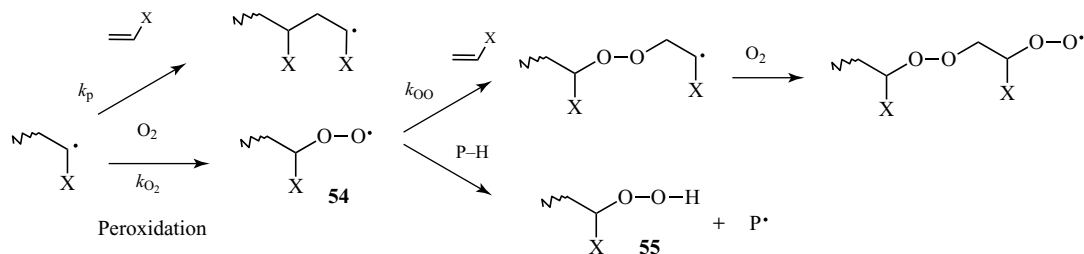
The liquid and rather volatile (bp 125 °C) *N,N*-diethylhydroxylamine **50** is used as in-process inhibitor in distillations of monomers such as styrene, divinylbenzene, isoprene, and butadiene.

In precise laboratory work with monomers, the inhibitors are often removed by distillation, by

filtration over a pad of aluminum oxide, or by a suitable extraction procedure. In industrial polymerizations, such purifications would be too expensive. Therefore, in most cases, the inhibitor is not removed but consumed by the additional initiator.

2.7.2 Oxygen Inhibition

RPs are tolerant to protic solvents but suffer from oxygen inhibition when conducted in air-saturated media or under an air atmosphere. The dioxygen molecule, due to its biradical ground state character, reacts with carbon-centered radicals to give peroxy radicals **54**. The rate of this peroxidation reaction is much greater¹³⁵ ($k_{O_2} \sim 10^8\text{--}10^9\text{ M}^{-1}\text{ s}^{-1}$) than the typical rates⁵⁴ of propagation ($k_p \sim 10^2\text{--}10^4\text{ M}^{-1}\text{ s}^{-1}$). Hence, at equal monomer and oxygen concentrations, the peroxidation would be $10^4\text{--}10^7$ faster than propagation (Scheme 21). The concentration of dissolved oxygen in monomers is on order¹³⁶ of 10^{-3} M , whereas the concentration of monomers is generally in the range of 0.1–10 M. Even so, the vast majority of carbon-centered radicals in air-saturated monomers are converted into the peroxy radicals **54**. The latter add only very sluggishly¹³⁷ ($k_{OO} \sim 0.1\text{--}3\text{ M}^{-1}\text{ s}^{-1}$), in what is now a rate-determining step, to monomers affording new C-centered radicals. As these C-radicals react again preferentially with oxygen, the result is an alternating copolymer with oxygen. The normal polymerization will be possible only when the majority of dissolved oxygen is consumed. This can



Scheme 21 Oxygen inhibition.

occur if the rate at which it is replenished from the air-exposed surface is sufficiently low. The oxygen copolymers are polymeric peroxides that are thermally and photochemically unstable and thus impair the properties of the final polymer. Moreover, peroxy radicals¹³⁸ abstract H atoms from the surrounding substrates (PH) to yield new radicals and the hydroperoxides **55**. The latter are potential sources of new radicals, which may further complicate the polymerization.

The influence of oxygen on radical and other polymerizations has been reviewed by Bahanu and Kishore.¹³⁹ To prevent these detrimental effects, measures must be taken to exclude oxygen by conducting the polymerization under vacuum or nitrogen, or in a refluxing solvent. Oxygen inhibition is a serious problem and is much more difficult to avoid in the photopolymerization of thin films and coatings due to the very large surface. Here, it leads to incompletely cured, tacky surfaces with poor mechanical properties. Different methods to overcome oxygen inhibition in these applications were reviewed¹⁴⁰ by Scranton and coworkers. Latest strategies involve an admixture of oxygen-scavenging additives,^{141,142} use of monomers with high functionality,¹⁴³ or singlet oxygen¹⁴⁴ sensitizers. It should be noted that oxygen inhibition is not a problem for every RP process. The radical thiol–ene click reaction, which is becoming an important tool for polymer synthesis,^{145–147} is much less sensitive to oxygen.

3 POLYMERIZATION PROCESSES

3.1 General Comments

Rather than listing the complete literature dealing with industrial polymerization processes and the

related reactor technology, we refer the reader to good introductory texts.^{148–150}

Industrial polymerizations differ from the processes used for synthesis of low molecular compounds in several respects. For one, it is usually not possible to purify the final polymer by standard distillation or crystallization techniques. Polymers obtained by classical RP are always mixtures of macromolecules with varying degrees of polymerization and deviation from the idealized structure. Separation of these mixtures is not possible on an industrial scale. Elimination of residual monomers, initiators, or solvents can also be a difficult and costly task requiring special methods and equipment.

The properties of the polymer, for example, its molecular weight distribution which influences its mechanical properties and processability, often strongly depend on the method (e.g., suspension polymerization or EP) by which it is prepared.

An important feature of polymerization in solution or in a melt is the dramatic increase, often by several orders of magnitude, of the viscosity during the reaction. This viscosity increase is the cause of the autoacceleration effect called the Norrish–Trommsdorff effect.^{123,124} It complicates mixing and pumping of the reaction mass and significantly reduces the rate of heat transfer and, therefore, the efficiency of the reactor cooling. Temperature control of industrial polymerizations is a very critical task because of the highly exothermic nature of RPs. In many cases, a rapid and, therefore, almost adiabatic runaway polymerization would cause temperature increase of many hundreds of degrees,¹⁵¹ leading to serious consequences such as fire, reactor rupture, or environmental contamination. For example,¹⁵² the adiabatic temperature increase at 100% conversion of monomer into polymer is

1810 °C for ethylene, 721 °C for acrylonitrile, 542 °C for vinylchloride, and 336 °C for styrene.

In fact, the average heat of polymerization ΔH_p of a vinylic monomer is about -82 kJ mol^{-1} , which is the difference between the sum of the energies of the two C–C single bonds ($\sim 2 \times 346 \text{ kJ mol}^{-1}$) formed in the polymer and the bond energy of a C=C bond ($\sim 610 \text{ kJ mol}^{-1}$) of the monomer. The actual heats of polymerization vary as a result of secondary effects such as steric strain in the polymer or differences in the resonance stabilization or hydrogen bonding, and solvation between the monomer and polymer. For example, ΔH_p varies¹⁵³ from -35 kJ mol^{-1} for α -methyl styrene to -163 kJ mol^{-1} for tetrafluoroethene (25 °C, liquid monomer $\rightarrow$ solid polymer). Detailed discussion of the thermodynamics of polymerization is provided in the monograph¹⁵³ of Sawada. Data on the heats, entropies, free-energy changes, and ceiling temperatures of polymerization of many monomers can be found there or in the *Polymer Handbook*.⁶⁷

3.2 Polymerization Techniques

The different polymerizations according to the classification on Figure 4 can be carried out in several ways: bulk polymerization, precipitation polymerization, solution polymerization, slurry polymerization, gas-phase polymerization, suspension polymerization, or EP. The polymerization techniques that are important for industrial RP are briefly highlighted.

3.2.1 Bulk Polymerization

The only components of a bulk polymerization mixture are monomers, the initiator, and, optionally, a chain transfer agent. The initiator may be omitted in the case of thermal autoinitiation of styrene. The main advantage of bulk polymerization is that a very pure polymer is produced. Furthermore, as the polymer is not diluted, the volume yield of the polymer is high. However, the high increase of viscosity during the polymerization makes the stirring and removal of the heat of polymerization difficult. A special type of bulk polymerization is precipitation polymerization. Here, the polymer is not soluble

in its own monomer (e.g., PVC in vinylchloride) and precipitates during the polymerization. Examples of polymers prepared by bulk polymerization are PMMA, general-purpose (or crystalline) PS, and LDPE.

3.2.2 Solution Polymerization

Solution polymerization is related to bulk polymerization but the components are dissolved in a suitable solvent. Both the heat generation and viscosity of the polymerization mixture are lower because of dilution. The thermal control of the reactor is also facilitated because the lower viscosity allows more efficient cooling. Optionally, cooling can be achieved by refluxing the solvent. The drawback of solution polymerization is that the polymer must be freed from the solvent if it is needed in pure form.

3.2.3 Suspension Polymerization

Suspension polymerization enjoys the advantages of bulk polymerization but is not plagued with problems of high viscosity and difficult thermal control. In this technique, pure monomers containing the dissolved initiator and, optionally, chain transfer agent are dispersed (suspended) in a continuous water phase (1–1.5 times by mass) in form of small droplets in the size range of 50–1000 μm . Both monomer and coreactants must be insoluble in water. The dispersion of the organic (or oil) phase in water is effected by stirring in the presence of added surfactants. Frequently used surfactants are amphiphilic polymers such as poly(vinyl alcohol), partially hydrolyzed poly(vinyl acetate), or hydroxypropyl methyl cellulose. Micronized inorganic powders such as CaCO_3 , MgCO_3 , or $\text{Ca}_3(\text{PO}_4)_2$ are also used. The advantage of these inorganic “pickering dispersants” is that they can be easily removed from the polymer by treatment with diluted acid. The droplet size and size distribution are complex functions of the type and concentration of the dispersant, stirring parameters, reactor, and stirrer geometry, as well as the physical properties of the dispersed and continuous phases. From a kinetic point of view, each droplet behaves as a small bulk polymerization reactor. The droplets are transformed during

the polymerization into rigid spherical polymer particles which are easily isolated by filtration. The main advantage of suspension polymerization is the easy thermal control of the reactor and virtually constant viscosity of the reaction mass as a whole. The purity of polymers prepared by this technique is higher than that obtained in EP and is comparable to that of bulk or solution polymerization. Examples of polymers made by suspension polymerization are PS and PMMA. The most important production process¹⁵⁴ for PVC is suspension polymerization of vinylchloride in pressurized (8–12 bar, because of the low boiling point of vinylchloride) reactors. PVC is not soluble in vinylchloride and precipitates in the monomer droplets which are finally transformed into porous polymer particles (“powder” suspension polymerization).

3.2.4 Emulsion Polymerization

EP, like suspension, mini emulsion, and microemulsion polymerization, is a type of heterogeneous polymerization. It should be noted that heterogeneous polymerizations are not only radical in nature. Heterogeneous polymerizations in aqueous dispersed media have been reviewed¹⁵⁵ by Charleux and Ganachaud.

EP provides polymer particles of 50–1000 nm dispersed in a continuous medium, most often water. Such polymeric dispersions are called *latexes*. Synthetic latexes were known already in 1930s but it was the work during the United States Synthetic Rubber Program¹⁵⁶ (1939–1945) which established EP as a unique and industrially viable technique. In the second half of the twentieth century, the method was further developed and attained a high level of technical and theoretical understanding. Today, about 10% of all synthetic polymers or some 20% of those prepared by RP ($>20 \times 10^6$ tons per year) are made by EP.¹⁵⁷ The process is named *emulsion polymerization* for historical reasons because it was originally targeted with the polymerization of emulsified monomer droplets, and only later it was realized that polymerization occurs not in the monomer droplets but mainly within the monomer-swollen latex particles. Among the abundant literature, the excellent monograph of Herk¹⁵⁸ which covers the history, mechanism, as well as industrial applications of EP; the books of Asua^{150,159}; or the recent

book of Chern¹⁶⁰ which additionally treats the related mini emulsion and microemulsion polymerizations can be highlighted. Therefore, only the key aspects of classical EP will be discussed here. The simplest EP system consists of a continuous aqueous phase, a practically water-insoluble monomer, a water-soluble initiator, and a colloidal stabilizer (emulsifier or surfactant). The monomer is dispersed to form small (0.01–0.1 mm) droplets which are stabilized against coalescence by a layer of surfactant molecules. It is important to note at this point that “water-insoluble” monomers used in EP in reality have a very small but measurable solubility in water: for example, the solubility of styrene at 50 °C is 4.3×10^{-3} M (see p. 78 of Ref. 158 for the water solubility of industrial monomers). If the concentration of the surfactant is above the critical micelle concentration (CMC), the formation of micelles occurs. These generally spherical micelles with a diameter of a few nanometers contain $\sim 10^2$ surfactant molecules and are swollen by the monomer which migrates from the “reservoir” droplets through the water phase. The number of micelles ($\sim 10^{17} - 10^{19} \text{ l}^{-1}$) is many orders of magnitude higher than the number of monomer droplets ($\sim 10^{10} \text{ l}^{-1}$). Consequently, the surface area of the micelles is 3–5 orders of magnitude larger than that of the droplets. The hydrophilic primary radicals formed in the water phase from the water-soluble initiator (e.g., ammonium persulfate) do not enter the lipophilic micelles. They preferentially add to and propagate with the monomer dissolved in water until the resulting oligomeric radicals are lipophilic enough to enter (nucleate) the micelles. Nucleation of the monomer droplets is insignificant because of the much larger surface of the micelles compared to the droplets.

Rapid propagation then follows in the monomer-swollen micelles leading to latex particles in a process called *heterogeneous nucleation*. A different process called *homogeneous nucleation* occurs if the amount of surfactant is below the CMC. In this case, the oligomeric waterborne radicals continue to propagate until they became insoluble enough that they undergo coil-to-globule transition. The resulting hydrophobic globules are swollen with monomer and became latex particles, too. Both heterogeneous and homogeneous nucleation may be operative in a given system. Monomer droplets, monomer-swollen micelles, and monomer-swollen latex particles coexist during the

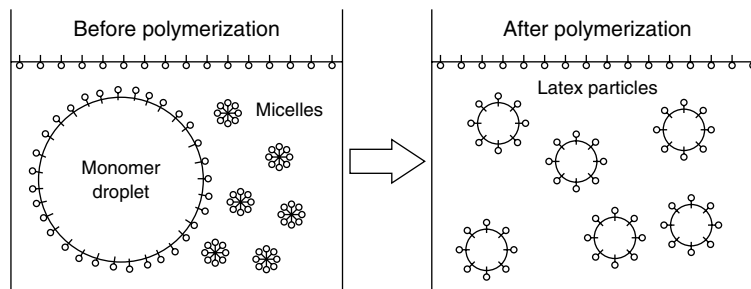


Figure 6 Emulsion polymerization.

nucleation phase. As the polymerization proceeds, the number of micelles decreases as they are either transformed into latex particles or dissociate to provide surfactant to stabilize the increasing surface area of the latex particles or globules formed by homogeneous nucleation. At the end of nucleation (monomer conversion of 5–10%), all micelles have disappeared and 10^{17} – 10^{18} latex particles per liter are present. They are now the main sites of polymerization. New monomer diffuses from the droplets into the latex particles to replace the monomer consumed there through polymerization. Consequently, the size of latex particles increases and that of droplets decreases until they disappear completely. The polymerization then continues in the monomer-swollen latex particles until the monomer is depleted. The result is a polymeric dispersion in water or a latex (Figure 6).

As the change of viscosity during the course of EP is very small (similar to suspension process), the control of the polymerization reactor is simplified. EP never proceeds to 100% conversion, but leaves some residual monomer in the waterborne polymer that must be removed. This can be performed either via stripping with steam or nitrogen, or through postpolymerization by addition of fresh initiator.

It is important to note that the basic mechanism of RP is the same in bulk, suspension, and EP. However, the distinctive feature of EP is the radical compartmentalization. In fact, the radicals that are situated in different particles cannot terminate by bimolecular termination. Because of the small size of the latex particles, only one propagating radical is inside at a given time. Hence, the polymer chain in the particle grows until a new radical enters and terminates with the growing one. Therefore, on average, 50% of particles contain one radical and the rest none. Nevertheless, due to the enormous number

of particles, the overall radical concentration in the latex is about one order of magnitude higher than in a typical bulk polymerization (10^{-8} M). Consequently, the polymerization rates are higher in EPs as compared to bulk or suspension process. Radical compartmentalization also allows longer radical life times, resulting in polymer chains of a higher degree of polymerization. The lifetime of the propagating radicals in the particles is inversely proportional to the frequency at which new radicals enter the particles and terminate with the growing ones. The entering frequency for a given concentration of the initiator decreases with the number of particles. Hence, it is possible to increase the rate of polymerization and the molecular weight of the polymer by simply increasing the number of particles, for example, by changing the monomer to surfactant ratio.

The continuous phase in conventional EP is water. Water-soluble monomers (e.g., acrylamide) can be polymerized via *inverse EP*. In this process, an aqueous solution of the water-soluble monomer and surfactant is dispersed in an organic phase (e.g., hexane) and the polymerization is initiated by lipophilic initiators. The process proceeds via a mechanism similar to aqueous EP and results in a dispersion of an aqueous solution of water-soluble polymer in an organic phase.

About 50% of emulsion polymers are commercialized as waterborne dispersions. It is important to note that emulsion polymers have in common the same state of aggregation but are diverse in chemical composition. A comprehensive overview of waterborne polymeric dispersions together with their applications and markets is available in the monograph¹¹ of Urban and Takamura and of Daniel and Pichot.¹² The main waterborne dispersions and their respective markets are shown in Table 5.

Table 5 Waterborne polymer dispersions by product class.

-
- Styrene–butadiene copolymers (paper coatings, paperboard, carpet backing, adhesives and sealants, additives for mortar and bitumen), 37%.
 - Polyacrylates, polymethacrylates, styrene–acrylate copolymers (paints, coatings, adhesives, inks, paper, and leather coatings), 30%.
 - Vinyl acetate homo- and copolymers (paints, adhesives for paper and wood), 28%.
-

A substantial part of emulsion polymers is commercialized as dry products. Examples are styrene–butadiene rubber (SBR), acrylonitrile–butadiene rubber (nitrile rubber), about 75% of ABS copolymer, a small part of PVC, water-redispersible powders¹¹ for the construction industry, and polymeric modifiers¹¹ for plastics (e.g., impact modifiers, processing aids, rheology modifiers, and so on). Diverse techniques for the isolation of the polymer from the dispersion are available: for example, direct spray-drying of the emulsion or its coagulation followed by drying of the filter cake.

Standard laboratory formulations for EP contain water, the monomer, the initiator, and the surfactant. Commercial recipes are often much more complicated, containing up to 20 components. A large number of monomers are used in EP either alone to give homopolymers or, more frequently, as mixtures to provide copolymers. In general, random copolymers are obtained with an inhomogeneous monomer distribution throughout the chains. Individual monomers impart specific properties to the final polymer. Acrylonitrile, for example, improves

solvent resistance, while vinyl chloride improves fire retardancy and acrylates provide good stability against light and heat. An important polymer property that must be controlled is the glass transition temperature T_g , which strongly influences the film formation from a latex and the mechanical properties of the film. The T_g of a copolymer can be estimated with the simple Fox equation (11) or with recently developed¹⁶¹ more sophisticated models.

$$\frac{1}{T_g} = \frac{W_{M1}}{T_{g1}} + \frac{W_{M2}}{T_{g2}} + \dots + \frac{W_{Mn}}{T_{gn}} \quad (11)$$

where T_g refers to the copolymer, T_{g1} , T_{g2} , ... refer to the individual homopolymers, and W_{M1} , W_{M2} , ... are the weight fractions of monomers M1, M2, ... in the copolymer.

In addition to the principal monomers that make up largest part of the latex (e.g., butadiene, styrene, and so on), small amounts (typically 2–5% based on the dry polymer) of the so-called functional monomers are often used. These important comonomers contain functional groups (COOH, NH₂, OH) that impart special properties to both the colloidal system and the polymer. As EP usually provides polymers of impractically high molecular weight, chain transfer agents, usually mercaptans, are often used. Other common additives include electrolytes (buffers) and metal ion sequestering agents. A typical list of the components of an industrial EP formulation is shown in Table 6.

Table 6 Components of an industrial emulsion polymerization recipe.

-
- **Monomers (50–55 wt%)**
Principal monomers leading to high T_g : methyl methacrylate, styrene, acrylonitrile, vinyl chloride, vinyl acetate
Principal monomers leading to low T_g : methyl acrylate, 2-ethylhexyl acrylate, *n*-butyl acrylate, 1,3-butadiene
Functional monomers: acrylic and methacrylic acid, itaconic acid, fumaric acid, 2-hydroxyethyl acrylate, acrylamide
 - **Initiators (0.3–0.5 wt%)**
Thermal initiators: sodium, potassium or ammonium persulfate, water-soluble azo-compounds
Redox initiators: *t*-BuOOH or persulfate + Na₂S₂O₅
 - **Surfactants (0.5–3 wt%)**
Ionic surfactants: sodium lauryl sulfate, sodium or potassium salts of fatty acids (soaps), salts of alkylbenzene sulfonates
Nonionic surfactants: *O*-polyoxyethyleneated long-chain alcohols or alkylphenols
 - **Chain transfer agents:** mercaptans
 - **Sequestering agents:** ethylenediamine tetraacetic acid (EDTA) (for complexing of adventitious metal ions, to prevent among other things their uncontrolled reaction with the redox initiator)
 - **Electrolytes:** alkali metal phosphates (to control the pH)
 - **Water, sometimes deionized (45%)**
-

3.2.5 Mini- and Microemulsion Polymerization

The majority of dispersion polymers are prepared by conventional EP. However, two variants of classical EP, *mini-* and *microemulsion polymerizations*, are of industrial interest and will, therefore, be briefly mentioned. A comprehensive discussion of the physicochemical and technological aspects of mini emulsion polymerization can be found in the monograph¹⁶² of Mittal. The size of the monomer droplets in a mini emulsion polymerization^{160, 162–166} is significantly reduced (30–500 nm) relative to that in EP ($>10^4$ nm). These small droplets are obtained by intensive homogenization in the presence of a surfactant and a small amount of extremely hydrophobic costabilizer, sometimes called *hydrophobe* (e.g., hexadecane or cetyl alcohol). The hydrophobe cannot migrate through the aqueous phase and thus prevents the diffusion of monomer molecules from smaller droplets to larger ones (Ostwald ripening) through establishment of counteractive osmotic pressure in the smaller droplets. As a result, kinetically stable mini emulsions are obtained which can be polymerized by both water- and oil-soluble initiators. In contrast to the classical EP, the locus of polymerization in a mini emulsion is within the emulsion droplets. The resulting latex can be viewed as a polymerized copy of the original mini emulsion. An important consequence for industry is that water-insoluble compounds (monomers, polymers, inorganic solids, pigments, carbon black, additives, etc.) can be directly incorporated/encapsulated^{165, 166} into the polymer particles by dissolving/dispersing them in the monomer prior to polymerization. A practical industrial example is the encapsulation of light stabilizers¹⁶⁷ to render them easily dispersible in coating formulations. This is not possible via classical EP since the monomer and the species dissolved/dispersed in it need to diffuse through the aqueous phase to the growing polymer particles. Mini emulsion polymerization bears some similarity to suspension polymerization. In both cases, the polymerizing droplet behaves as an individual batch reactor. The main difference is in the size and stability of the particles. Ostwald ripening is much less important in suspension polymerization because of the very large size of the particles; hence, addition of hydrophobes is not necessary.

The monomer droplets are even smaller (1–30 nm) in microemulsion polymerization.^{160, 168–171} Microemulsions are thermodynamically stable, isotropic, transparent, or translucent systems which are obtained upon intensive homogenization using a combination of an anionic surfactant (e.g., sodium dodecyl sulfate) and a nonionic cosurfactant (e.g., 1-pentanol). This special surfactant system creates an interfacial tension at the oil/water interface close to zero. The high amount of surfactant in microemulsion formulation leads to a complete surfactant coverage of the droplets. As in mini emulsion polymerization, the locus of polymerization is within the emulsion droplets. The result is very small (~ 5 –50 nm) polymer particles in coexistence with empty micelles. A particle contains only a small number of polymeric chains having a very high molecular weight not achievable via conventional emulsion or mini emulsion polymerization. Potential applications^{160, 171} of microemulsion polymerization include the synthesis of ultrafine latex particles, water-soluble polymers with very high molecular weights for use as flocculants, nanostructured porous materials, functionalized colloidal particles, and transparent colloidal systems for photochemical applications.

3.3 Types of Industrial Polymerization Reactors

Polymer reaction engineering along with the design of polymerization reactors is a huge discipline on its own. The excellent book¹⁵⁰ of Assua, the handbook¹⁴⁸ of Meyer and Keyrentjes, or the chapter of Cunningham and Hutchinson in Ref. 62 is recommended as introductory reading. Polymerization reactors can be grouped according to the method by which the reactants are added to the reaction vessel (Figure 7).

- In a *batch reactor*, all the reactants are charged to the reaction vessel at the beginning and no material is added to or removed from the reactor during polymerization. After its completion, the contents are discharged and the reactor is prepared for the next batch. Batch reactors are the simplest to operate, but offer the least control over the polymerization. Thus, copolymerization of monomers with different reactivity ratios or

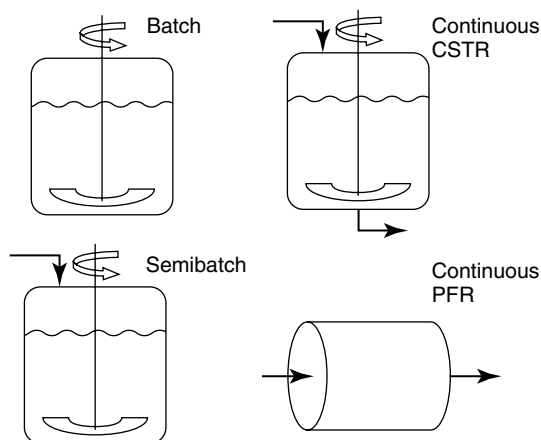


Figure 7 Types of reactors commonly used in radical polymerization.

outside the azeotropic monomer feed composition will result in a broad distribution of copolymer composition. On the other hand, batch reactors are readily adaptable to new set of reaction conditions and to new products.

- In a *semibatch* (or semicontinuous) reactor, the starting materials can be added, and/or the products removed, during the polymerization. Often, only a portion of the total amount of reactants is initially charged into the reactor. The polymerization is then started, and more reactants are added during reaction in order to control various parameters such as reaction rate, molecular weight, or copolymer composition distribution. Any reactant can be fed at a selected, individual rate.

Semibatch operation is commonly used to control the copolymer composition distribution. The compositional drift can be substantially reduced by maintaining a constant ratio of monomers in the reactor. Continuous feeding of initiator and monomers in the desired ratio helps to control the molecular weight and to minimize the risk of a thermal runaway reaction because the monomer concentration remains low throughout the polymerization (monomer-starved conditions). Semibatch reactors are widely used in EP: for example, stainless steel vessels ranging in size from 20 to 200 m³ and equipped with a stirrer.

- In a *continuous reactor*, the reactants are introduced and the products as well as unconsumed reactants are withdrawn continuously. Continuous

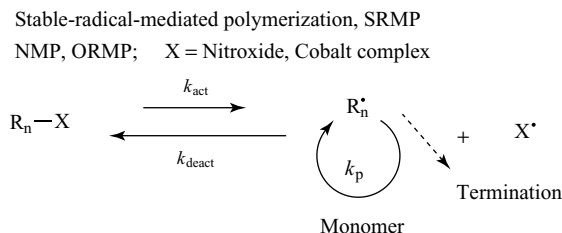
reactor systems include continuous stirred tank reactors (CSTR), plug flow reactors (PFR), or combinations of both. The polymerization may take place in a single reactor or in a cascade of reactors in which the monomer conversion gradually increases. Continuous reactors are preferred for large-volume polymers with a limited number of variations in polymerization conditions. They offer simplicity of operation, high throughput rates, uniform product quality, and, hence, relatively low operating costs.

4 CONTROLLED REVERSIBLE-DEACTIVATION RADICAL POLYMERIZATION

A 2010 IUPAC recommendation¹⁷² proposes the term *controlled reversible-deactivation radical polymerization* (CRDRP) for polymerizations previously called *controlled radical polymerization* (CRP) or *living radical polymerization* (LRP).

It was the pioneering discovery^{173,174} of living anionic polymerization by Michael Szwarc in 1956 that initiated the rapid development of this field, which has many important applications in industry. Over the years, other controlled and living polymerizations such as group-transfer polymerization, living carbocationic polymerization, living ring-opening metathesis polymerization, or living transition-metal-catalyzed alkene polymerization were developed. A review of the state of the art of controlled and living polymerizations in year 2010 was compiled¹⁷⁵ by Müller and Matyjaszewski. Its preface also gives clear definitions of the sometimes controversial terms “controlled” and “living”.

RP is one of the most important industrial polymerization techniques. However, prior to the mid-1990s, classical RP did not allow the synthesis of polymers with precisely designed molecular architectures such as block, comb, or star copolymers or polymers with defined terminal functional groups or with predetermined and narrow molecular weight distributions. This was, however, possible with the aforementioned nonradical processes. This situation started to change dramatically with the seminal work^{176,177} of Otsu, who in 1982 proposed a reversible deactivation of the growing chains in RP using the so-called iniferters.



Scheme 22 Stable-radical-mediated polymerization.

Today, a plethora of CRP techniques are available. All are based on reversible deactivation of growing chains. Most of these chains are in a dormant form and the period of chain growth of an individual propagating chain may be extended from ~1 s in conventional RP to a few hours in CRDRP. At any given instant, only a small fraction of chains are growing. However, as long as the interconversion of active and dormant forms is rapid compared to propagation, all chains are able to grow at the same rate. Therefore, the polymerization takes on much of the character of a living polymerization. Nonetheless, it is important to note that, even though chain termination and irreversible chain transfer are suppressed to a very low level in such RPs, they are not completely absent.

CRDRP makes possible the synthesis of block copolymers by sequential addition of different monomers. Moreover, if the initiating species are fully consumed prior to any appreciable chain growth, all chains grow at the same rate and the molecular weight distribution of the polymer is much narrower than in a conventional RP.

Presently, the most important CRDRP techniques are the following:

- *Stable-radical-mediated polymerization* (SRMP), which embraces the nitroxide-mediated RP

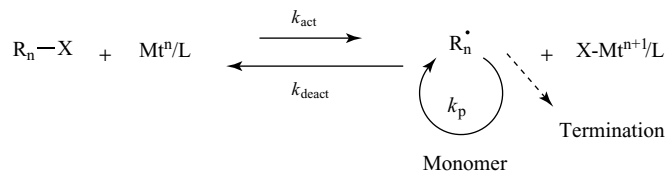
(NMP) (see **Nitroxide-Mediated Polymerization and its Applications**, note, however, that IUPAC recommends¹⁷² the term *aminoxyl* instead of *nitroxide*) and organometallic-mediated RP (ORMP). The deactivation involves reversible coupling with persistent (stable) radicals (Scheme 22).

- *Atom-transfer radical polymerization* (ATRP) (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**). The deactivation of the radicals involves reversible atom transfer or reversible group transfer catalyzed usually, though not exclusively, by transition-metal complexes (Scheme 23).
- *Degenerate-transfer RP* (DTRP) in which the deactivation of the radicals involves degenerative transfer of a group (or atom). Most prominent is the RAFT polymerization (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**) (Scheme 24).

A detailed treatment of CRDRP is beyond the scope of this article and the reader is referred to recent review articles,^{178–186} monographs,¹⁷⁵ and other articles in this encyclopedia (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**, **Nitroxide-Mediated Polymerization and its Applications**, **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**, **Sb, Bi, Te, and I-Transfer Polymerization and Applications**, and **Fundamentals of Controlled/Living Radical Polymerization**).

Atom-transfer radical polymerization, ATRP

X = Cl, Br; Mt = Cu, Ru, Ni, Fe, Mo...; L = Amines, Phosphines

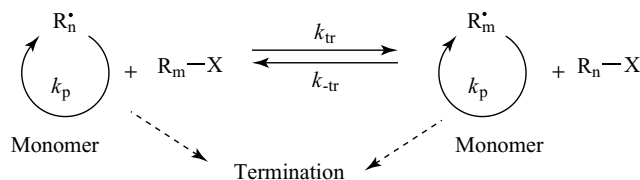


Scheme 23 Atom-transfer radical polymerization.

Degenerate-transfer radical polymerization, DTRP

$X = S-(C=S)Z$; RAFT: $Z = SR$; MADIX: $Z = OR$

Atom or group transfer: $X = I, TeR, SbR_2$



Scheme 24 Degenerate-transfer radical polymerization.

4.1 Industrial Applications of Controlled Reversible-Deactivation Radical Polymerization

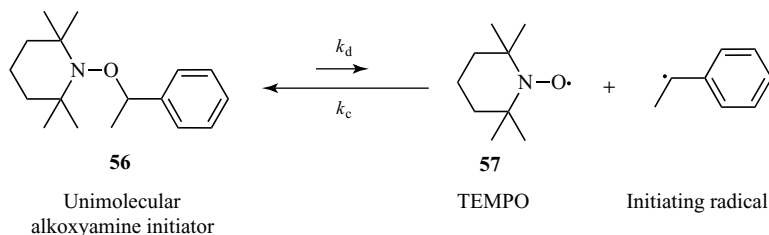
CRDRP opens completely new possibilities for the design and synthesis of novel materials via RP. As is often the case when revolutionary technologies emerge, very optimistic forecasts of their commercial potential appear. Thus, in 2000 the potential market for CRDRP products was anticipated to exceed 20 billion US\$ per year.¹⁸⁷ Today, 10 years later, the known industrial applications of CRDRP are very few. It is now clear that CRDRP will not replace classical RP for the production of large-volume commodity polymers. However, its potential for the development and production of high-value polymeric specialties remains intact. Possible target products include adhesives, binders, compatibilizers, cross-linkers, dispersants, emulsifiers, leveling agents, lubricants, sealants, and thermoplastic elastomers. These products are expected to find applications in various industries such as aerospace, aircraft and automobile, biomedical and cosmetic, coatings, electronics, home and personal care, and nanotechnology. The industrial obstacles and achievements of CRDRP were reviewed¹⁸⁷ recently in a very detailed manner by Destarac. Not all CRDRP techniques known today are equally well suited for upscaling from small laboratory experiments into large-scale industrial processes. For example, the controlling agent must be cost effective and ecologically sound. Furthermore, residual metals in ATRP or the chemical nature of the end groups (RAFT) may be an issue.

4.1.1 Nitroxide-Mediated Radical Polymerization

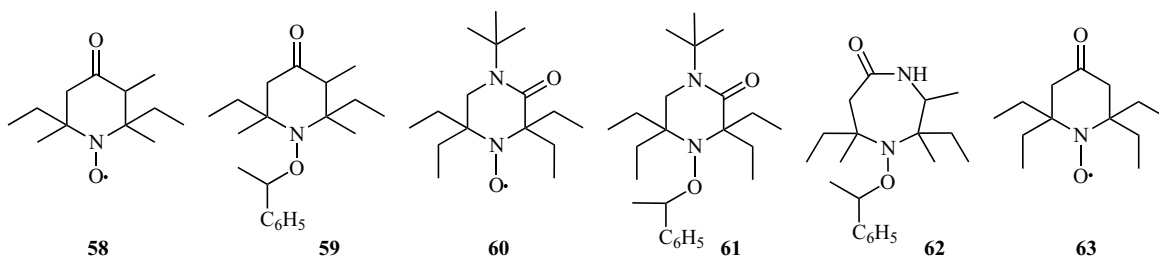
NMP can be performed using the combination of a nitroxide radical controller with a conventional radical initiator such as AIBN or dibenzoylperoxide. However, the initiator-to-controller ratio is slightly different for each polymerization system. In fact, due to the cage reactions of the primary radicals, excess of the initiator is required to ensure 1:1 stoichiometry between the nitroxides and *available* primary radicals. For this reason, unimolecular alkoxyamine initiators such as **56** are preferred because their homolysis along the relatively weak¹⁸⁸ ($\approx 110\text{--}140\text{ kJ mol}^{-1}$) NO–R bond affords the nitroxide and initiating radical in exactly 1:1 ratio (Scheme 25).

Yet another possibility is the so-called *in situ* NMP.¹⁸⁹ The required nitroxide radicals are synthesized directly in the polymerizing mixture by addition of radicals generated from conventional initiators to nitric oxide, nitroso compounds, or nitrones, or by the oxidation of suitable secondary amines or hydroxylamines. This method is of potential interest for industrial applications because the nitroxide precursors are cheap. However, a prerequisite for the process optimization is a thorough understanding of the underlying mechanisms.

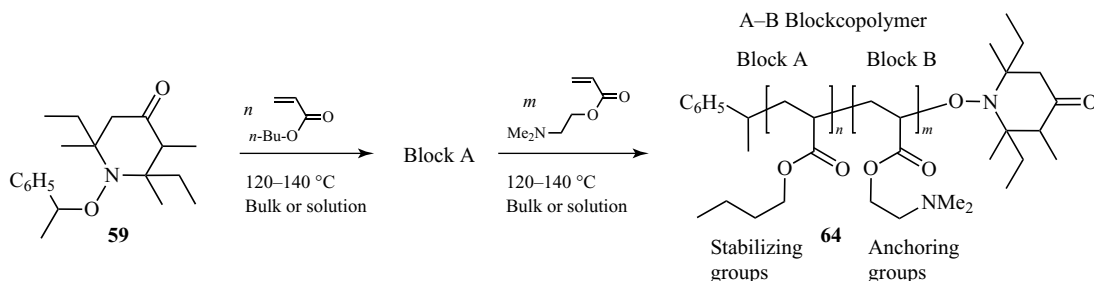
It should be noted at this point that 2,2,6,6-tetramethyl-piperidine-*N*-oxyl (TEMPO) **57** and the related alkoxyamines, for example, **56**, can only be used for controlled polymerization of styrene and not other monomers such as acrylates. To overcome this limitation, Ciba (now part of BASF) has developed a range of proprietary cyclic nitroxides and unimolecular alkoxyamine initiators



Scheme 25 Unimolecular alkoxyamine initiator.



Scheme 26 Sterically hindered cyclic nitroxides and alkoxyamine initiators.



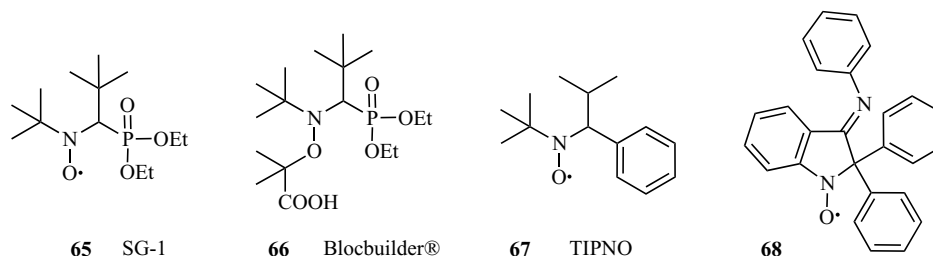
Scheme 27 Amphiphilic block copolymer as pigment dispersant.

that are suitable for controlled polymerization of both styrene and acrylates. Examples of these sterically highly hindered piperidine,¹⁹⁰ piperazinone,^{191–193} or diazepanone¹⁹⁴ nitroxides and alkoxyamines **58–62** are shown in Scheme 26.

The piperazinone nitroxide **60** belongs to the most effective¹⁹³ cyclic six-membered nitroxides for NMP known today and its synthesis^{191,193} is simpler than that^{195,196} of the equally effective¹⁹⁵ tetraethyl-piperidone-*N*-oxyl **63**. The industrial NMP process was reported¹⁹⁷ by Ciba in 2003. Using NMP, Ciba developed and commercialized a range of block copolymer pigment dispersants^{197–203} which offer advantages in rheology of pigment concentrates, their stability, and coloring properties. The optimal block copolymer pigment dispersant consists of (i) a B-block bearing

suitable anchoring groups (e.g., dialkylamino), which adsorb to the surface of a pigment particle; and (ii) an A-block with stabilizing groups which compatibilize the dispersant within the medium and prevent pigment agglomeration and coagulation. The design and synthesis of the amphiphilic blockcopolymer **64** by NMP using the alkoxyamine initiator **59** is exemplified in Scheme 27. The chemistry and physics of polymeric pigment dispersants have been reviewed²⁰² by Auschra and Pirrung.

In 2005, Elf Atochem (now Arkema) commercialized SG-1 (**65**), an acyclic phosphonylated α -hydrido nitroxide^{204,205} and BlocBuilder® MA²⁰⁶ (**66**), its related alkoxyamine^{206–208} which allows controlled polymerization of styrenic, acrylic, and some acrylamido monomers (Scheme 28).



Scheme 28 Acyclic and indolyl nitroxides and alkoxyamines.

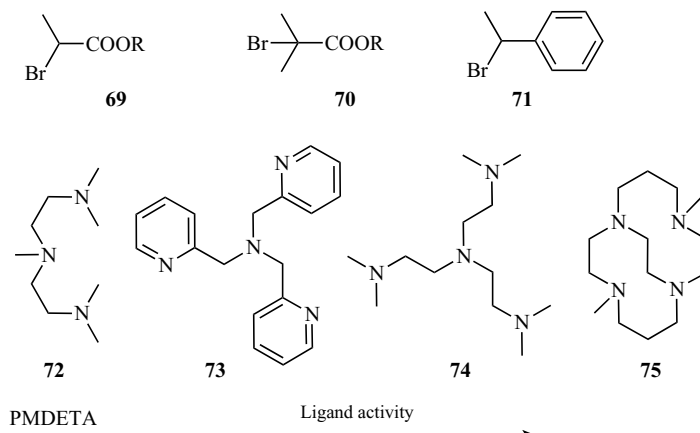
Recently, Arkema reported the development²⁰⁹ of NMP-based block copolymers (Nanostrength®) consisting of PMMA surrounding a center block of poly(butyl acrylate). However, only the central poly(butyl acrylate) block is controlled. These copolymers can be used as tough thermoplastics, thermoplastic elastomers, or toughening additives for epoxy thermosets. NMP is not suitable for polymerization of nonconjugated monomers such as vinyl acetate, vinyl chloride, or *N*-vinyl pyrrolidone. Also unsolved is the controlled homopolymerization of methacrylates although promising results were reported²¹⁰ with the indolyl nitroxide **68**. However, well-controlled and living copolymerization of methyl methacrylate with only 5–10% of styrene²¹¹ or acrylonitrile²¹² or as little 1% of 9-(4-vinylbenzyl)-9-*H*-carbazole²¹³ is possible. From the industrial point of view, it is important that NMP, ATRP, and RAFT are amenable^{155, 214–220} to aqueous emulsion or mini emulsion polymerization even though some issues²²¹ remain to be solved. One issue is that NMP requires relatively high temperatures, typically in the range of 100–140 °C. Interesting attempts have been made to use nitroxide mediators in radical photopolymerization.²²²

A low-cost and upscalable synthesis of nitroxides or the related alkoxyamines is necessary to allow their use in industrial NMP. For example, the relatively expensive TEMPO **57** can be replaced by the much cheaper and industrially available 4-hydroxy-2,2,6,6-tetramethyl-piperidine-*N*-oxyl or its readily available 4-alkoxy- or 4-acyloxy derivatives for polymerization of styrene. The nitroxides **58**,^{190,194} **60**,^{191,193} and **65**^{223,224} can be prepared by simple reactions without expensive organometallic reagents, as is the case for the TIPNO²²⁵ (*N*-tert-butyl-*N*-2-methyl-1-phenylpropyl nitroxide) nitroxide **67** which is very popular in academic laboratories.

Similarly, transformation of the nitroxide into the corresponding alkoxyamine initiator (e.g., **58** to **59** or **65** to **66**) must be industrially feasible. A variety of methods for the preparation of alkoxyamines exist,^{226–229} but only a few are suitable for large-scale, multiton synthesis. The reported industrially relevant methods rely on coupling of nitroxides with C-centered radicals, which, in turn, are generated from either activated alkyl halides with Cu or Cu(I) salts²³⁰ or from hydrocarbons and *t*-butylhydroperoxide.²³¹ In most cases, the nitroxide group remains covalently attached to the NMP polymer. This is usually not a problem, but, nevertheless, possibilities²³² for its removal exist.

4.1.2 Atom-Transfer Radical Polymerization

ATRP is arguably among the most versatile CRDRP method for building complex polymer architectures with a high degree of precision. It can be run over a large range of temperatures, starting at 0 °C or below, with a broad range of monomers (with the exception of acids) using relatively easily accessible (optionally functionalized) initiators. Despite this, the method was not readily accepted by industry because of the large amounts of metallic catalysts (0.1–1 mol% vs monomer) and ligands required. Even though several methods for catalyst removal²³³ exist, they are too expensive on an industrial scale. Significant progress was made possible with the invention of activators regenerated by electron transfer (ARGET)^{181, 234–236} and initiators for continuous activator regeneration (ICAR)^{181, 237} modifications of ATRP by Matyjaszewski and coworkers. In ARGET-ATRP, an excess of reducing agent (e.g., ascorbic acid, copper(0), or tin octoate) relative to catalyst is used to continuously regenerate the Cu(I) activator species



Scheme 29 Alkyl halides and ligands for ATRP.

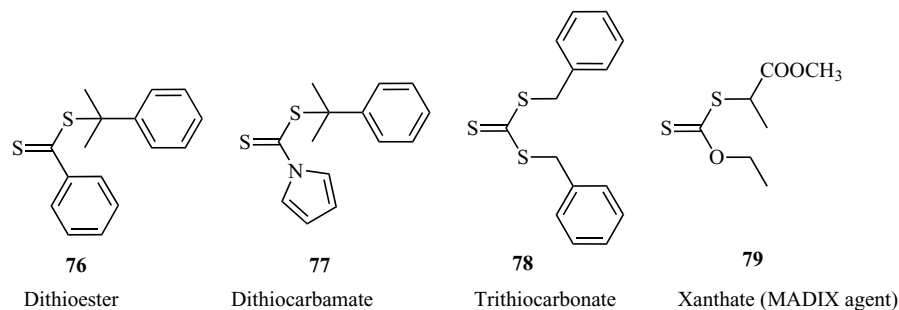
by reduction of Cu(II) products which are formed by unavoidable radical termination. In ICAR-ATRP polymerization, radicals are continuously generated by conventional initiators (e.g., AIBN) to reduce the Cu(II) species and thus regenerate the active Cu(I) activators. Using these techniques, the amount of Cu catalyst can be reduced²³⁸ by several orders of magnitude down to 10–50 ppm. This low amount of residual Cu catalyst may be acceptable for some applications. Use of ARGET to reduce the concentration of the Cu catalyst in solution-ATRP in batch, semibatch, and continuous reactors has been reviewed.²³⁹

A new dimension in the reduction of Cu catalyst in ATRP is represented by the single-electron-transfer-controlled radical polymerization (SET-CRP) developed by Percec *et al.*^{240–243} In this method, Cu(0) activates the polymerization and is converted by transfer of an electron to the alkyl halide (initiator or dormant chain) into a Cu(I) species. The latter rapidly disproportionates in polar solvents (H₂O, alcohols, dipolar aprotic solvents) in the presence of amine ligands into Cu(0) and the Cu(II) deactivator. The atomic Cu(0) catalyst is much more reactive than the Cu(I) species used in ATRP, so that only small amounts have to be used. SET-CRP allows rapid polymerization of both activated (acrylates, methacrylates) and nonactivated (vinyl chloride) monomers in environmentally friendly solvents at room temperature with even less catalysts than ARGET or ICAR. It is expected that these new advances will facilitate implementation of ATRP in industry, which up

to now, similarly to other CRDRP techniques, has not proceeded as fast as originally expected. Matyjaszewski at Carnegie Mellon University founded the ATRP Consortium (1996–2001) and the CRP Consortium (2001–present)²⁴⁴ with the goal to assist major industrial companies in this transfer. One success was registered by Kaneka, which commercialized^{180,187} moisture and photocurable telechelic polyacrylates prepared by ATRP for use as sealants and adhesives, or in coatings. In addition, at least two start-up companies, “ATRP Solutions,”²⁴⁵ and “Warwick Effect Polymers,”^{187,246} are fostering industrial ATRP. Finally, the availability of the ATRP reagents deserves a brief comment. Copper and Cu(I) salts as well as the typically used alkyl halides, for example, **69–71** (Scheme 29), are readily available. The situation is more complicated with the amine ligands. Only *N, N, N', N'', N''*-pentamethyl-diethylenetriamine (PMDETA) **72** is commercially available (e.g., BASF) in large quantities but not the most effective²³⁵ ligands, for example, **73–75**.

4.1.3 Degenerate-Transfer Radical Polymerization

By far the most important method of DTRP is RAFT, which is an extremely versatile tool for the synthesis of complex polymeric architectures in bulk, organic, or water solution or in dispersed media. It is compatible with the widest range of



Scheme 30 Examples of RAFT/MADIX agents.

polymerizable monomers of all CRDRP techniques. From the process point of view, a RAFT agent can simply replace the conventional chain transfer agent, requiring little or no change in established industrial setups. This broad applicability puts²⁴⁷ RAFT in the position to become a key industrial CRP method. All aspects of RAFT are covered in the “*Handbook of RAFT Polymerization*”²⁴⁸ and in recent reviews.^{209,247,249–251}

Similar to alkoxyamines in NMP, RAFT agents must be readily available. A recent overview²⁵² covers various RAFT agents and their synthesis. Scheme 30 shows examples **76–79** of typical RAFT agents. Note that RAFT using xanthates as controlling agents is called *macromolecular design by interchange of xanthates* (MADIX).²⁵³

The trithiocarbonate **78** (BlocBuilder® DB)²⁰⁶ was developed by Arkema to commercial stage, and the xanthate **79** (Rhodixan® A1) can be obtained under licence from Rhodia. However, RAFT polymers are always yellow to red in color, which is clearly not acceptable in many applications. Fortunately, a variety of methods^{251,254} are available to remove the thiocarbonylthio end group from the polymer or use it for further transformations, for example, for synthesis of block copolymers. Advances in synthesis of degradable “green” polymer materials via RAFT have been reviewed²⁵⁵ by Perrier and Semsarilar. Rhodia recently reported^{256,257} the use of MADIX for the development and commercialization of Rhodibloc® RS block copolymers for the stabilization of emulsions.

Last but not least, it should be mentioned that the first industrially applied CRP was most likely the iodine-transfer polymerization²⁵⁸ used by Daikin Industries for the preparation of fluorinated thermoplastic elastomers.¹⁸⁷

5 MAIN COMMERCIAL POLYMERS MADE BY RADICAL POLYMERIZATION

It is beyond the scope of this article to discuss the synthesis and properties of the individual polymers that are made by RP. A detailed overview appears, for example, in the “*Industrial Polymers Handbook*”¹⁷ or the book¹⁸ by Campo. The monograph²⁵⁹ of Scheirs and Priddy provides in-depth information on all aspects of styrenic polymers and copolymers. Excellent monographs^{11,12} on dispersion polymers are also available. Abundant information on PVC can be found in the “*Practical Guide to Polyvinyl Chloride*”²⁶⁰ and in the special issue (2002, vol. 27(10)) of *Progress in Polymer Science*. The technical processes of PVC production have been reviewed¹⁵⁴ by Saeki and Emura. Development of PVC from its discovery to mass production is recounted by Braun.²⁶¹ Comprehensive information on polyethylenes, including LDPE which is made by RP, is available in “*Practical Guide to Polyethylene*”²⁶² or in Ref. 121.

6 CONCLUSION

Conventional RP has reached a very high level of sophistication and is among the most important industrial polymerization techniques; about 45% of all synthetic polymers are made via this method. The most rapidly developing area of synthetic polymer chemistry today is CRP. Even though considerable progress has been made in CRP during the last two decades, only a very small part of its tremendous potential could be put into industrial practice up to now. However, the recent advances in CRP give reason to expect that new, high-valued products, rather than replacements for existing polymers, will be developed in the very near future.

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Spin Labels and Spin Probes

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1 INTRODUCTION

Free radicals are neutral or charged compounds with an open-shell configuration resulting from an electronic structure characterized by the existence of one (monoradical) or several (polyradical) single occupied molecular orbitals. The highly reactive, often transient nature of radicals reflects the fact that their major reactivity pathways (dimerization, hydrogen abstraction, and disproportionation) are strongly favored thermodynamically and usually occur with little activation barrier. Then, most free radicals are very short-lived species rather difficult to characterize; however, some can be strongly stabilized by electronic and steric effects, making them stable, “that can be isolated and handled as pure compounds,” according to Griller and Ingold’s definition.¹ The properties exerted by the specific combination of open-shell configuration and chemical stability have been exploited to develop many applications^{2–4} involving stable radicals such as reporter molecules, chemical reagents, building blocks for new magnetic materials (see **Physical Properties of Thiazyl Radicals Toward Conductive and Magnetic Materials**), spin polarization transfer agents, and so on.

Nitroxides and to a lesser extent trityl radicals constitute the two major classes of stable radicals used as reporter molecules. Nitroxides^{2–6} are easily the most well-known class of radicals including a large number of stable structures such as the popular TEMPO **1** ($Y = H$, Figure 1) and its derivatives (see **Nitroxides in Synthetic Radical**

Chemistry). The electronic structure of nitroxides is characterized by the existence of a stabilizing π_{N-O} three-electron bond with an unpaired electron in a π^* orbital and substantial spin density on both N and O. The dimerization of nitroxides does not result in a gain of bonding electrons, and at room temperature, the formation of symmetric dimers R_2NOONR_2 has never been observed, demonstrating the inherent stability of the $R_2NO^{\bullet}$ framework.

Gomberg’s discovery of the triphenylmethyl (trityl) radical **2** (Figure 1) was a landmark discovery as it marked the beginning of organic free radical chemistry (see **The History of Free Radical Chemistry**).⁷ Under anaerobic conditions, **2** is highly persistent, this stability is ascribed largely to steric protection of the central carbon by the three phenyl groups that adopt a propellor conformation, with the rings twisted by $\sim 30^\circ$ with respect to the plane containing the central carbon and the three *ipso* carbons. Partial delocalization of the unpaired electron into the phenyl rings decreases the electronic energy, but it induces radical reactivity at the *para* carbons. Substitution of the *para* hydrogens and introduction of bulky substituents on the phenyl rings can lead to stable trityl radicals such as **3** (Figure 1).

The shape of the electron paramagnetic resonance (EPR) spectrum of a free radical depends on the motional dynamics of the radical and on various parameters (polarity, molecular oxygen concentration, pH, etc.) characterizing the free radical microenvironment. Moreover, EPR spectroscopy is

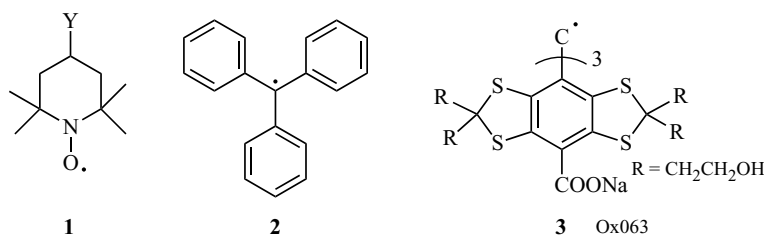


Figure 1 Structure of TEMPO **1** (Y = H), triphenylmethyl radical **2** and Ox063 **3**.

a sensitive method that allows one to get easily spatial (distance between radical centers) and temporal (tumbling rates) information (see **Analysis of Radicals by EPR**). Thus, EPR proved to be immensely useful to the characterization of complex chemical and biological systems, including free radicals as reporter molecules. Different techniques have been developed that provide a wealth of information on systems into which either covalently (spin labels) or noncovalently (spin probes) bound stable radicals have been introduced. Whatever the mode of bonding of the reporter molecule to the system under investigation, these techniques are usually named spin labeling. This field of research has undergone a tremendous development during the past 30 years and results have been gathered and discussed in different books and reviews. In the space allowed in this article, we cannot provide an exhaustive survey of each technique but rather a brief presentation of their background and recent developments involving nitroxides or trityl radicals as reporter molecules.

Although EPR is a very sensitive technique, it is very rare that the steady-state concentration of transient radicals intervening in chemical reactions reaches the EPR detection threshold. A coupled EPR/spin trapping (EPR/ST) technique has been developed to overcome this limitation. Basically, EPR/ST consists of adding a transient radical of interest to a diamagnetic spin trap, this addition giving rise to an EPR detectable spin adduct (usually a nitroxide spin adduct). A successful EPR/ST experiment not only supports strongly the formation of a transient radical in a chemical reaction but it can also provide detailed information on its chemical structure.

2 SPIN LABELING

The basic idea underlying the spin labeling approach is to tag a material (organic polymer, biological macromolecule or system, supramolecular assembly, etc.) with a specific label whose properties make it possible to collect information on the material by an appropriate physical method. Although the method could use any free radical or paramagnetic metal ion or even a group with a long-lived triplet state, at least 99% of the reported spin labeling studies employ nitroxides either as spin labels or spin probes and EPR to collect information.

2.1 Spin Labels and Spin Probes in Biological Systems and Organic Polymers

Spin labeling, introduced by H. McConnell,⁸ who coined the name, has been an accepted physical biochemical technique for over 40 years and is nowadays recognized as an important tool for the determination of structural characteristics of biological membranes and a wide range of both soluble and membrane proteins of arbitrary molecular weight.^{9–17}

Several EPR approaches can be used to detect and follow changes or dynamic interactions with either proteins, peptides, or substrates and to measure distances between two labeled sites.¹⁸ Hundreds of nitroxide spin labels or spin probes have been tailored for biological spin labeling,^{5,6,9,10,19–22} the great majority belongs to the following classes (Figure 2):

- the 2,2,6,6-tetramethyl-piperidine-*N*-oxyl nitroxides (**A**), in which the substituents are typically at C4;

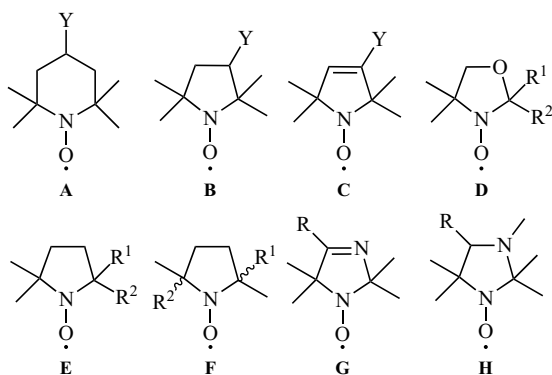


Figure 2 Principal classes of nitroxides used as spin labels or spin probes.

- the 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl nitroxides (**B**) and the 2,2,5,5-tetramethylpyrroline-*N*-oxyl (**C**) nitroxides in which the substituents are typically at C3;
- the 5,5-dimethyl-oxazolidine-*N*-oxyl nitroxides (**D**, doxyl), which are attached to the labeled compound at the 2 position;
- the proxyl (**E**) and azethoxyl (**F**) nitroxides;
- the imidazoline-*N*-oxyl (**G**) and imidazolidine-*N*-oxyl (**H**) nitroxides.

All these stable nitroxides bear no hydrogen atoms on the carbons attached to the nitroxyl nitrogen, that is, the α -carbons; many typical examples are depicted in figures shown herein.

2.1.1 Spin Probes for the Study of Biological Membranes

Since the very beginning of the development of spin labeling, numerous studies have been devoted to study biophysical properties of biological membranes.^{16,23–30} These include structural and dynamic parameters,^{23–26} protein–lipid interactions,^{16,27–29} polarity and proticity,^{28,30} penetration depths of metal ions, and so on.²⁸ The main spin probes used for these studies are shown in Figure 3, the *n*-DSA and *n*-PCSL probes provide a number of unique approaches for determining several membrane properties as a function of bilayer depth. The orientation-dependent behavior of various nitroxide spin labels incorporated into aligned membrane systems has also been investigated.^{31–34}

2.1.2 Spin Labels for the Study of Proteins

A few of the nitroxide spin labels developed^{35–48} to investigate the structure and dynamics of proteins are shown in Figure 4. They can be covalently attached to proteins through various functional groups,³⁷ the amino acid residue that is labeled varies with both the label and the protein but typical targets include cysteine, serine, and lysine. Spin-labeled unnatural amino acids such as the 2,2,6,6-tetramethyl-piperidine-1-oxy-4-amino-4-carboxylic acid (TOAC), **27**,^{38–43} **28** (β -TOAC),^{44,45} or **29** (POAC)⁴⁶ and **30**⁴⁷ were developed as a means for spin labeling the backbone of peptides.

In the late 1980s, thanks to the design of **26** (MTSL)⁴⁸ and the outstanding work of Hubbell and coworkers,^{49–51} who recognized that site-directed mutagenesis makes it possible to obtain specific attachment sites for spin labels at any desired position in a protein, a major breakthrough occurred with the development of site-directed spin labeling (SDSL). MTSL is a sulfhydryl-specific spin label that reacts specifically with the accessible cysteine residues of a protein.⁴⁸ SDSL utilizes site-directed mutagenesis to replace the residue of interest with a cysteine and all reactive native cysteine residues with a suitable substitute. The unique cysteine residue of the recombinant protein is then specifically reacted with MTSL (Figure 5a) to generate a nitroxide side chain sensitive to the local environment. Since its finding SDSL has been widely used for *in vitro* studies on both soluble and membrane proteins, and the topic has been regularly reviewed.^{12–14,16,17,52–54} Among the impressive amount of pertinent results obtained using SDSL, those concerning information on structural aspects of bacteriorhodopsin^{51,55–68} illustrate particularly well the very high potential of the SDSL technique.

SDSL can be challenging for proteins that contain functionally important native cysteine residues or disulfide bonds. To make SDSL amenable to any protein, an orthogonal labeling strategy, that is, one that does not rely on any of the functional groups found in the common 20 amino acids, was developed. In this approach, a genetically encoded unnatural amino acid is reacted chemoselectively with an especially designed spin label.⁶⁹ For example, the genetically encoded unnatural amino acid *p*-acetyl-L-phenylalanine is

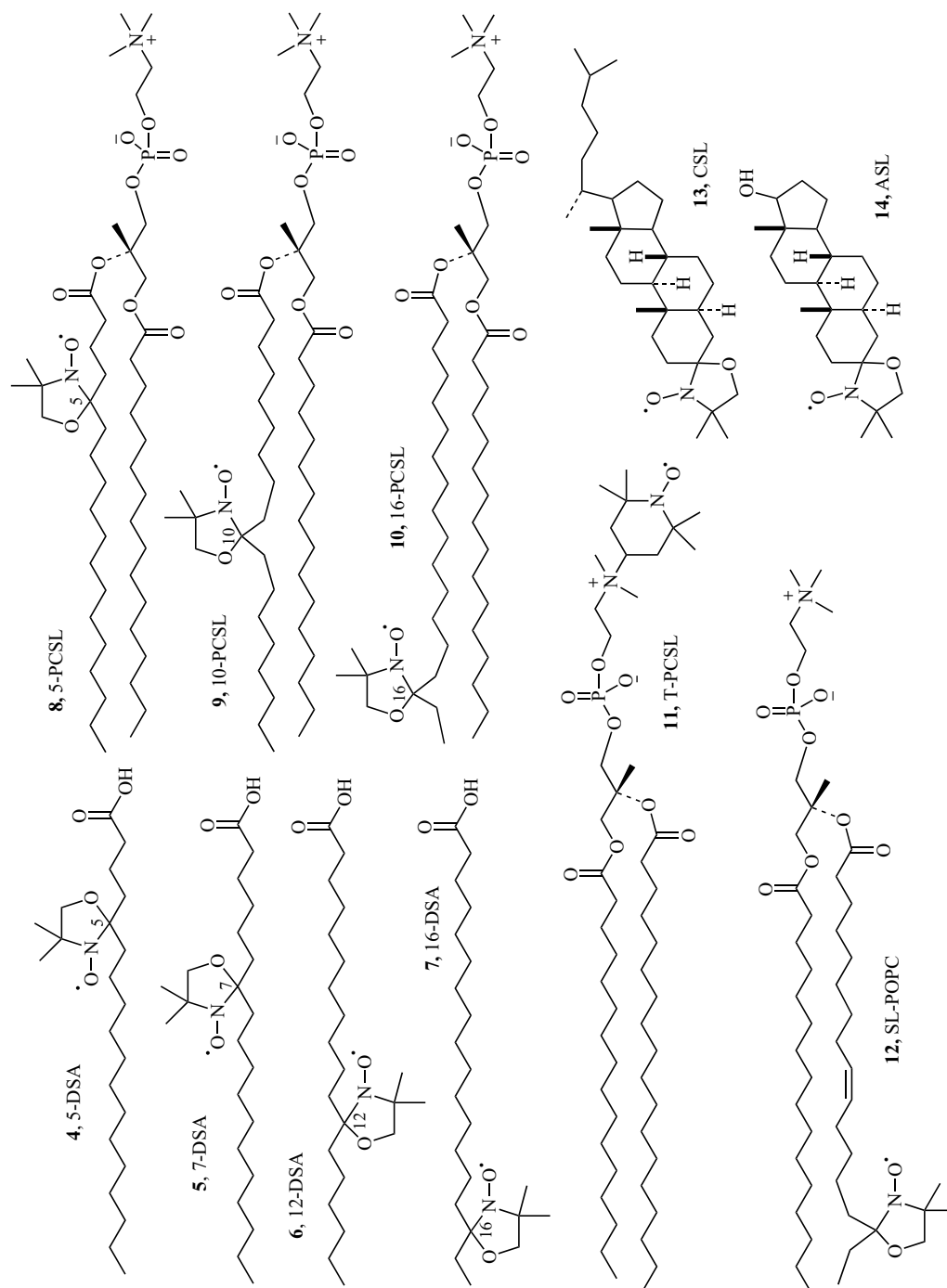


Figure 3 Main spin probes used to investigate biological membranes.

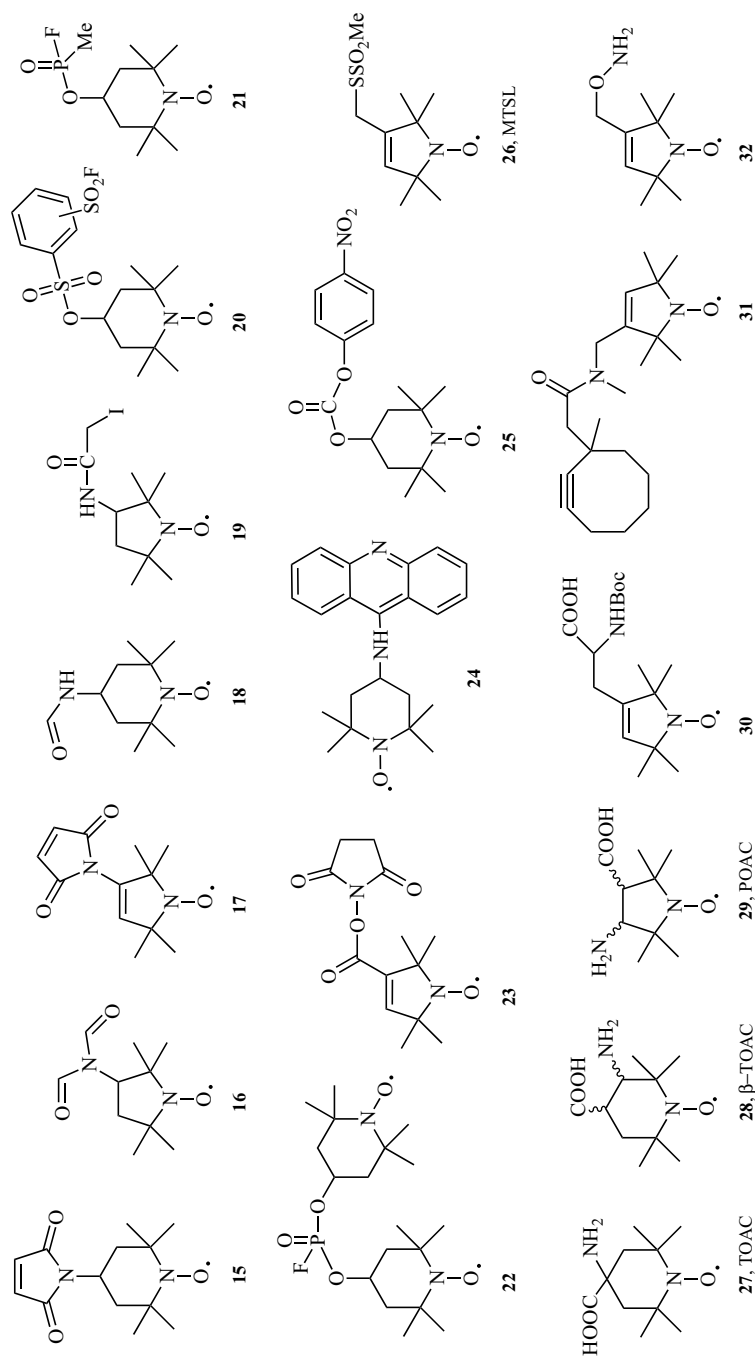


Figure 4 Main spin labels used to investigate proteins.

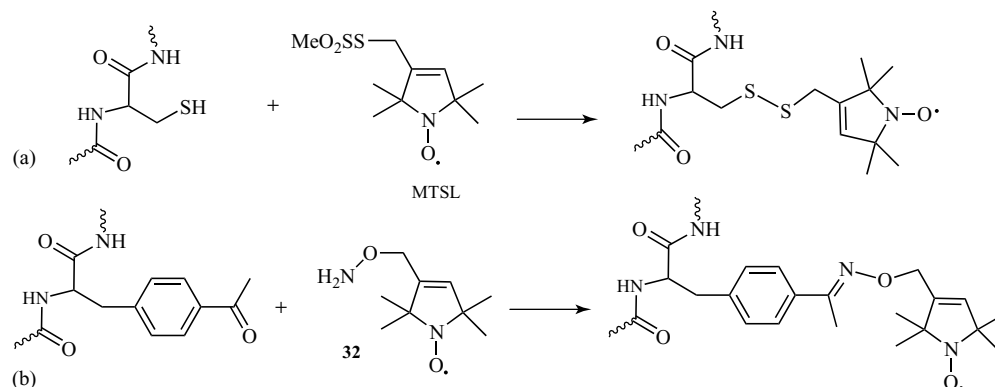


Figure 5 (a) Labeling of a cysteine residue with MTSL. (b) Orthogonal labeling of *p*-acetyl-L-phenylalanine, a genetically encoded unnatural amino acid.

reacted with **32** to generate a ketoxime-linked spin label (Figure 5b). Other nitroxides designed for orthogonal SDSL, such as **31**, have been prepared.⁷⁰

2.1.3 Spin Labels for the Study of DNA and RNA Molecules

Spin labeling of nucleic acids has been used since the early 1970s to get structural and dynamic

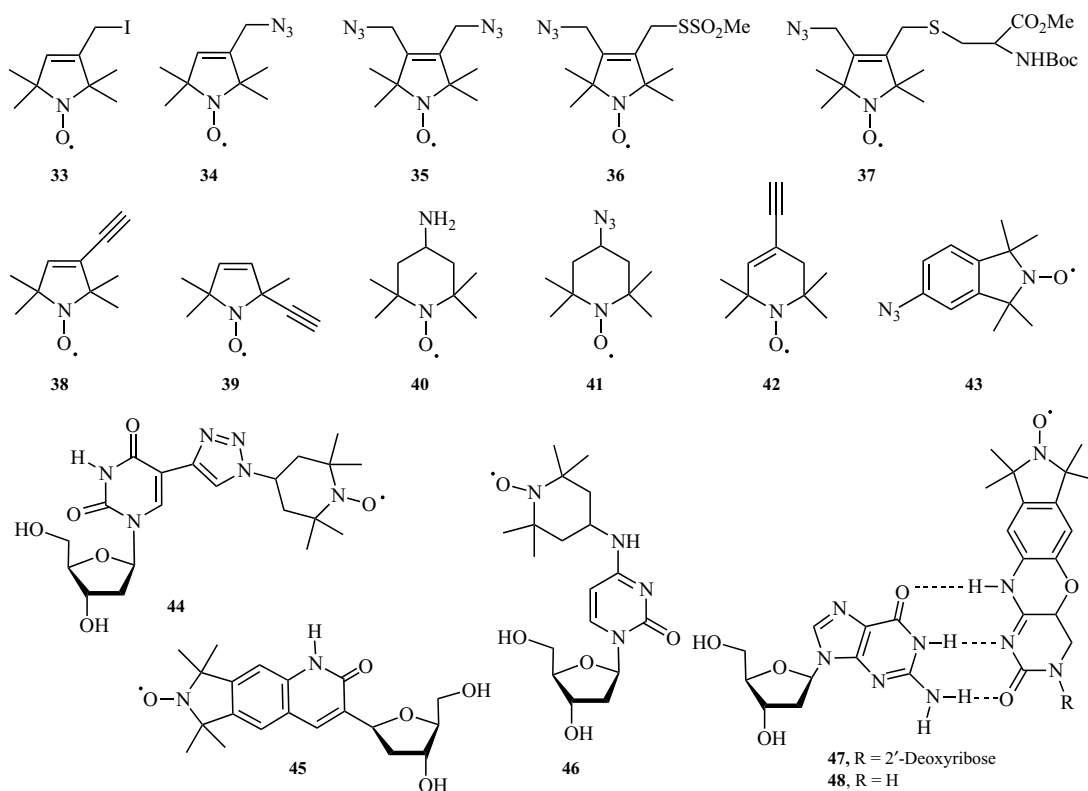


Figure 6 Examples of nitroxides used to spin label DNA and RNA molecules.

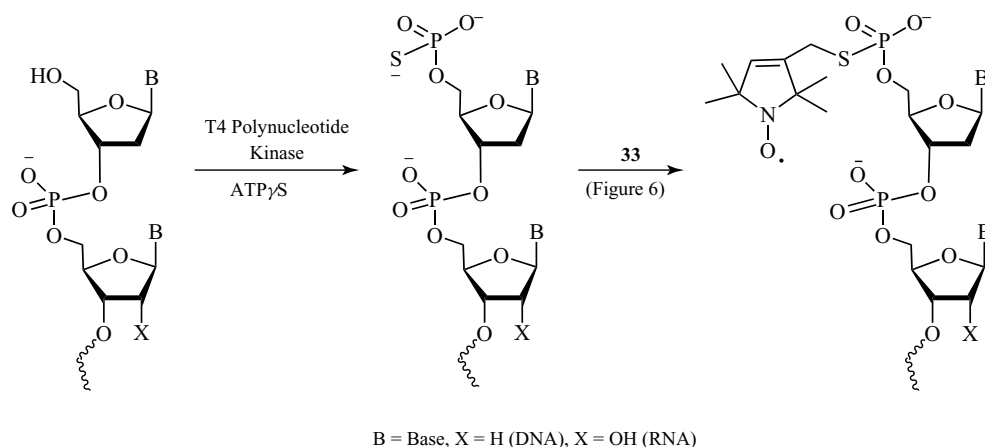


Figure 7 Biochemistry of the 5' ps labeling scheme according to Grant and Qin.⁸⁴

information on RNA/DNA architectures under biological conditions, and the early works have been reviewed by Bobst⁷¹ and Keyes and Bobst.⁷² Over the past decade, several strategies have been established to site-specifically spin label oligonucleotides.⁷³ Some nitroxide spin labels tailored for this purpose are shown in Figure 6. Strategies were developed to attach nitroxides at specific backbone,^{74–76} sugar,^{77,78} and base^{79–82} positions. Methods have also been reported for attaching nitroxides at the 5'-terminus of RNA and DNA molecules.^{83,84} For example, Grant and Qin⁸⁴ developed the 5' ps labeling scheme that utilizes T4 polynucleotide kinase to transfer the γ -phosphorothioate group of adenosine-5'-O-(3-thiotriphosphate) (ATP γ S) to the 5'-terminus of DNA or RNA molecules (Figure 7).

Spin labeling of DNA molecules^{85–87} can also be performed using the highly chemoselective azide-alkyne “click” reaction.⁸⁸ For example, after its automated synthesis, an oligonucleotide incorporating modified nucleobases bearing ethynyl side chains can be spin labeled (Figure 8), with nitroxides bearing an azido function.⁸⁹

Noncovalent SDSL of nucleic acids has been introduced by Shelke and Sigurdsson,⁹⁰ using nitroxide **48** (Figure 6). Nitroxide **48** is an analog of cytidine, with a nitroxide-bearing isoindol moiety fused to cytosine by an oxazine linkage, and forms a stable base pair with guanine (Figure 6).

2.1.4 Distance Measurements in the Nanometer Range (1.5–8 nm)

Distance of 1.5–8 nm between two spin labels can be measured in macromolecules and supramolecular assemblies by pulse EPR techniques,⁹¹ namely pulse electron double resonance (PELDOR) or double quantum coherence.⁹² PELDOR is frequently used during SDSL structure determination of biomacromolecules,^{14,17,81,93–95} it has also been used to investigate the structure of organic polymers. Various new spin labels and model spin labels (Figure 9) have been prepared to optimize and test the reliability of distance measurements by the PELDOR approach.^{96–102} Using nitroxides **49–53** as models, Schiemann and coworkers⁹⁷ showed that a single PELDOR data set yields not only distances and thereby precise geometric information on the nanometer scale but also the number of spins n in a molecule.

Godt and coworkers⁹⁸ developed nitroxides **54** as conformationally unambiguous spin labels. Spin labels **54** can be attached through cross-coupling to the macromolecules of interest and provide access to data that are unbiased by conformational flexibility within the spin label.¹⁰² The spin label **56** exhibits slow enough spin-echo dephasing to permit accurate distance measurements at temperature up to 125 K in 1 : 1 water/glycerol.¹⁰¹

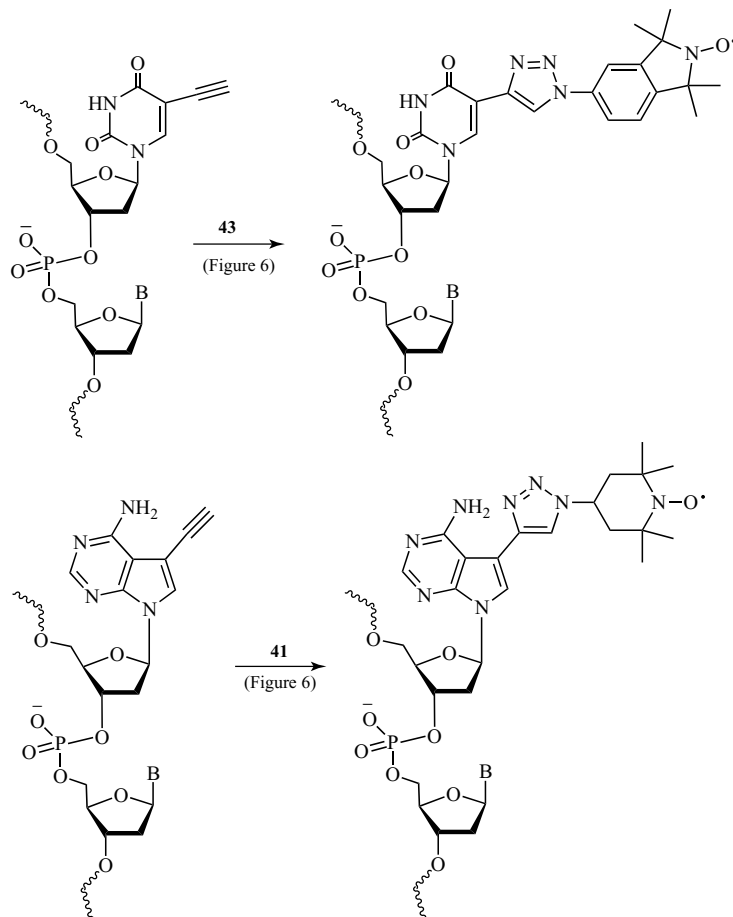


Figure 8 Use of click-chemistry to spin label RNA or DNA molecules.

2.1.5 Spin Labels and Spin Probes for the Study of Organic Polymers

Spin labeling has been used to address various structural problems of organic polymers. The implemented techniques, spin labels, and spin probes are almost identical to those presented above and only some books and reviews are mentioned herein.^{102–111}

2.1.6 Spin Probes for Imaging Techniques (MRI, EPRI, PEDRI, DNP)

Nitroxides as MRI Contrast Agents

Nitroxides have unpaired electrons that confer them the ability to enhance image contrast in

magnetic resonance imaging (MRI) via a proton T_1 -shortening effect, similar to the one observed for the well-known gadolinium-based contrast agents. Nitroxides were evaluated as potential contrast agents in MRI in the mid-1980s, and due to their slower reduction rate in biological systems, 3-carbamoylPROXYL (**153**, Figure 21) and 3-carboxyPROXYL (**134**, Figure 17) were the most used and studied nitroxide contrast agents.¹¹² However, due to their low relaxivity ($0.15\text{--}0.20\text{ mM}^{-1}\text{ s}^{-1}$ at 25°C and 1.5 T for mononitroxides) compared to gadolinium complexes ($2.5\text{--}5.5\text{ mM}^{-1}\text{ s}^{-1}$ at 25°C and 1.5 T for monomeric Gd(III) complexes) and their rapid bioreduction to the corresponding diamagnetic hydroxylamines, nitroxides were classified as nonoptimal compared to the metal-based contrast agents.^{113–117}

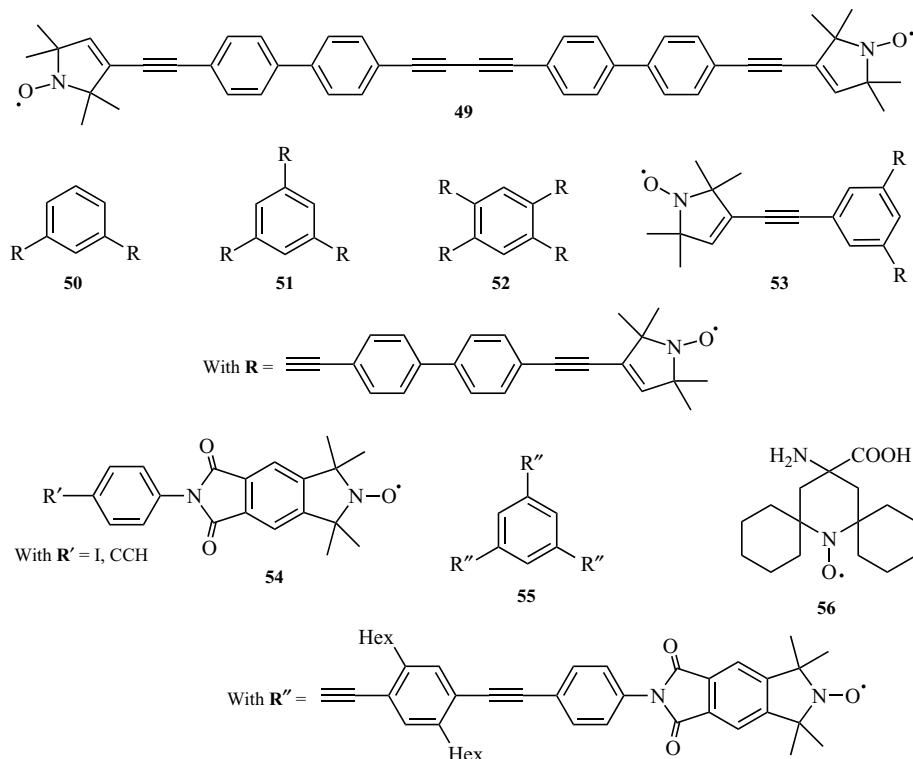


Figure 9 Model spin labels used to optimize and test the reliability of distance measurements by the PELDOR approach.

Nevertheless, because of their easy conjugation to biomolecules or particles, allowing tissue or articular targeting,^{118,119} the potential blood–brain barrier permeability of some nitroxides,¹²⁰ and their low toxicity,¹²¹ nitroxides have proved to be useful for specific applications.

The effect of combining several nitroxides (up to three) on relaxivity in a molecule was studied and a good linear relation between the T_1 —contrast enhancement and the concentration of nitroxide groups was found.¹²² Several nitroxide-labeled dendrimers were described in the past two decades and it was shown that dendritic polynitroxides exhibited higher relaxivity per nitroxide compared to monomeric nitroxide, this enhancement being attributed to an increase in the rotational correlation time.^{118,123–125} Recently, hyperbranched polymers carrying 20 TEMPO units have been prepared by postfunctionalization, which exhibited high relaxivity improvement with regard to monomeric TEMPO.¹²⁶

Spin Probes for EPRI and PEDRI

With the recent developments and technological advances in low-field EPR imaging (EPRI), nitroxides and trityl radicals have shown to be promising candidates for imaging applications.¹²⁷ EPRI is unique for free radical imaging and is a very sensitive technique. However, its applications to living organisms are limited by different characteristics (half-life time in biological milieu, linewidth, and distribution) of the spin probes. To overcome these limitations, strategies have been developed based on

- the use of free radicals with improved resistance to bioreduction,¹²⁸
- the use of trityl radicals^{129,130} and isotopically labeled nitroxides^{131,132} exhibiting narrow linewidths,
- the selective delivery of nitroxide probes^{133,134} (Figure 10).

Proton electron double resonance imaging (PEDRI, also named Overhauser-enhanced magnetic resonance imaging, OMRI) has shown to be

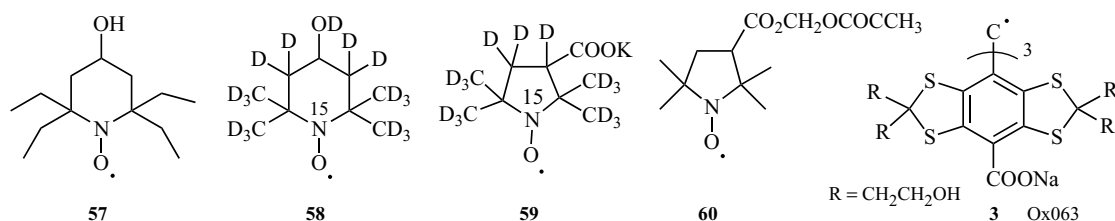


Figure 10 Spin probes for imaging applications.

a promising alternative due to the combination of sensibility to high resolution.^{135–140} In PEDRI experiments, an EPR resonance of the free radicals is irradiated during the acquisition of a magnetic resonance image. The polarization transfer from electron spins to the proton spins results in the enhancement of the nuclear magnetic resonance (NMR) signal in regions of the sample containing the free radical probes, bringing information on its spatial distribution in the final image. As observed for EPRI, isotopically labeled nitroxides and bioreduction resistant nitroxides are promising candidates for PEDRI (Figure 10).

Spin Probes for DNP

The development of dynamic nuclear polarization (DNP) technique associated to NMR and MRI has witnessed a large interest in the past decade and new free radicals and dinitroxides have been designed and studied as polarizing agents.^{141–143} In a typical DNP experiment, the larger polarization of the electron spin system is transferred onto the nuclear spin

system by microwave irradiation of EPR transitions. Hyperpolarization provides a means to increase the nuclear polarization by several orders of magnitude (up to 100 000) from the Boltzmann polarization. The maximum theoretical enhancement achievable is given by the gyromagnetic ratio (γ_S/γ_I), being ~ 660 for ^1H nuclei and ~ 2600 for ^{13}C nuclei. DNP is the extension of the original Overhauser effect and its applications to high fields proved to be challenging till high-power high-frequency microwave sources were made available and the theory better understood. DNP technique rapidly appeared as a breakthrough in NMR/MRI, notably for the studies on protein structures¹⁴⁴ and for real-time metabolic imaging.¹⁴⁵

At high magnetic field (5 T) in the solid state (90 K) and pumping at 140-GHz microwave frequency, Griffin reported that using TEMPO-based biradicals as polarizing agents improved polarization compared to monoradical TEMPO.^{146,147} Thus, the highest enhancements so far measured were obtained using TOTAPOL¹⁴⁸ **61** and bTbK¹⁴⁹ **62**

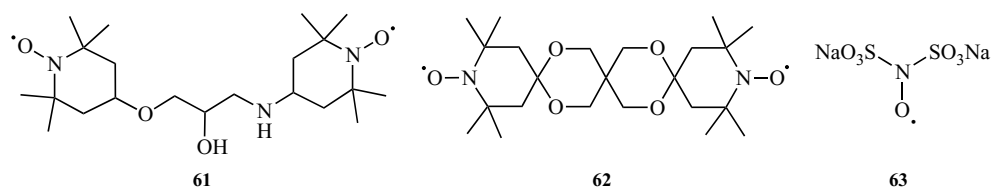


Figure 11 Nitroxides as polarizing agents for DNP applications.

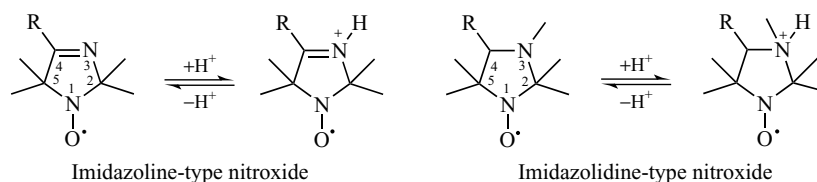


Figure 12 Reversible protonation of imidazoline and imidazolidine-type nitroxides (IMSTSL, **112**, $A_N = 1,575$ mT, **112-H⁺**, $A_N = 1.434$ mT, $\Delta A_{\text{iso}} = 0.141$ mT).

dinitroxides, with enhancement values of 230 and 325, respectively (Figure 11).

Recently, Prisner and coworkers demonstrated that DNP is possible also in liquids at high magnetic fields (400-MHz NMR frequency and 260-GHz microwave source) using Fremy's salt **63**.¹⁵⁰ Ardenkjaer-Larsen *et al.*¹⁵¹ were involved early in the design of polarizer for the generation of hyperpolarized spin systems in the solid state at very low temperatures (2–5 K) followed by a rapid dissolution process and sample transfer to the NMR/MRI apparatus. This approach has gained a tremendous interest in the MRI field allowing real-time metabolic studies, and trityl radicals such as Ox063 **3** (Figure 1) have been largely used as polarizing agents in such systems.

It has been reported that using ^2H and ^{15}N isotope-labeled TEMPONE (**132**, Figure 17), the effective saturation factor can be increased¹⁵² in ^1H -DNP experiments (water solution and pumping at 9.7-GHz microwave frequency in a 0.34-T NMR field).

2.1.7 Spin Probes for pH Measurements

Nitroxides as pH-Sensitive Spin Probes

Proton concentration measured as pH is of fundamental importance in the biochemistry of living systems and pH changes have been associated with many physiological and pathological processes. Thus, *in vitro* and *in vivo* measurements of pH in noninvasive way could provide useful information about clinical diagnostic applications. EPR has been shown to be an appropriate technique to perform such measurements, the principle is based on the monitoring of EPR parameters (A_N and g factor) of nitroxides bearing functional groups, adjacent to the nitroxyl function, that can be reversibly protonated (Figure 12).

Imidazoline as well as imidazolidine-type nitroxides containing a nitrogen at position 3 of the heterocycle are considered to be the most suitable for pH-sensitive spin probes due to the high sensitivity of their EPR parameters to pH changes.

Keana *et al.*¹⁵³ and Volodarsky and coworkers¹⁵⁴ first reported the pH dependence of the EPR spectra of imidazolidine-type nitroxides. Khramtsov *et al.* and Weiner *et al.* considered the conditions for fast and slow exchange between unprotonated and

protonated forms of nitroxides, they showed that at X-band, the slow exchange condition is $3 < \text{p}K_a < 11$.^{155–157} They also showed for the intermediate pH values that at X-Band, only the high-field line of the EPR spectrum splits into two lines whose intensities changed reversibly with pH (Figure 13c). Using higher frequencies (35.5 GHz, Q-Band and 140 GHz, G-band), all the lines of the nitrogen triplet were split, proving that the use of higher frequencies improves the precision in g -factor determination, making this parameter a good alternative to ΔA_{iso} measurements *in vitro* (Figure 13a and b).^{158,159} However, the use of high-frequency EPR is limited for *in vivo* experiments.

Further works on the imidazoline ring have shown that, depending on substitution at position 4, the $\text{p}K_a$ of the molecules can vary from 1 to 12.5. During the past decades, a large number of pH-sensitive nitroxides have been synthesized with

- different ranges of pH sensitivity (**64–72**, **76–87**, and **91–96**),^{160–163}
- different degree of lipophilicity (**82–87**, **97–111**, and **118–121**),^{160, 164–166}
- different stability toward bioreduction (**73–75**, **88**, **113**, and **122**),^{167–171}
- different functional groups (**89–90**, **112**, and **114–117**).^{172–176}

Chemical structure, $\text{p}K_a$ values, and ΔA_{iso} for some of these nitroxides are listed in Tables 1 and 2.

As an illustration, a few applications of pH-sensitive spin probes to biological system are described herein, further information can be found in review articles published recently.^{156,157,176}

Ptushenko *et al.*¹⁷⁷ measured intrathylakoid pH in chloroplast suspension using nitroxides **64–67**, **71**, and **77** (Table 1). Tikhonov *et al.*¹⁷⁸ used **64–67** to measure the light-induced change in the intrathylakoid pH in isolated bean chloroplasts.

Potapenko *et al.*¹⁶⁸ studied the localization and monitored the acidity in the rat stomach using imidazoline-based nitroxide **88**. The combination of bulky groups at the α -position of the nitroxyl group to enhance the stability toward bioreductant agents and the two ionizable groups to extend the range of pH sensitivity make **88** a good candidate for pH measurements in the rat stomach. Using PEDRI, the authors monitored the distribution of **88**. The use of longitudinally detected EPR (LODEPR), and field-cycled dynamic nuclear

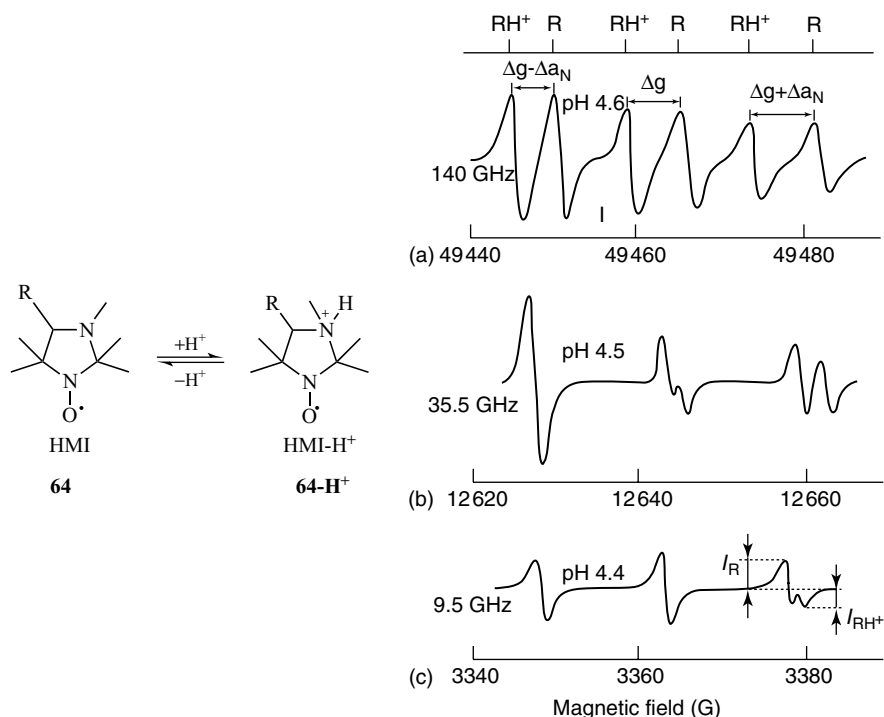


Figure 13 The EPR spectra of an aqueous solution of HMI **64** at $\text{pH} \sim \text{p}K_a$ performed at different microwave frequencies. [With kind permission from Springer Science+Business Media: Appl. Magn. Reson., Stable nitroxyl radicals as pH, thiol and electron transfer probes, 31, 2007, 357, L. M. Weiner.]

polarization (FC-DNP) techniques was to follow the drug-induced perturbation of acidity in the stomach. Previously, the same authors studied the successful use of low-field EPR-based techniques to detect **64** in the rat stomach.¹⁷⁹

Also, **112** derivatives were used as pH-sensitive nitroxides to determine interfacial $\text{p}K_a$ and local electrostatic field in phospholipid membranes and micellar solutions.^{159,180}

Further applications have illustrated the usefulness of these pH-sensitive nitroxide probes in different systems such as in liposomes,¹⁷⁵ in drug release tablets,¹⁸¹ and in gold nanoparticles.¹⁸²

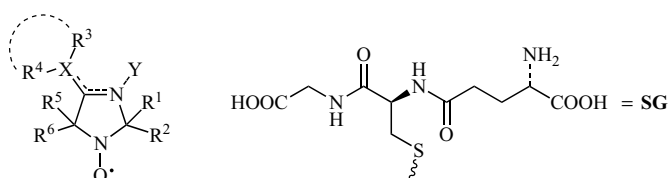
Recently, a self-assembled amphiphilic copolymer (PEG-*b*-PS-aminoTEMPO) was designed and evaluated as a pH-sensitive probe (Figure 14).¹⁸³

Trityl Radicals as pH-Sensitive Spin Probes

Water-soluble triarylmethyl (TAM) radicals are also used for pH measurements, thanks to their higher stability compared to nitroxides in living tissues,¹⁸⁴ their narrow single EPR line width, and their pH-sensitive magnetic resonance parameters.

The study of the pH dependence of the EPR spectra of Ox063 **3**, cTAM₀ **123**, cTAM₁ **124**, and cTAM₂ **125** were performed by Bobko *et al.*¹⁸⁵ (Figure 15). The authors showed that the additional A_H coupling constant of cTAM derivatives facilitates the pH measurement at low frequencies allowing *in vivo* experiments. However, the low $\text{p}K_a$ of the above TAM derivatives limited the experiments at physiological pH. In order to overcome this problem, the incorporation of ionizable groups such as amino groups was developed by Dhimitruka *et al.*¹⁸⁶ and allowed the pH measurement in a range of pH from 6.8 to 9.0 using aTAM_{1–5} (**126–130**, Figure 15).

TAM derivatives bearing a dendritic moiety were prepared and tested as pH spin probes by Liu *et al.*¹⁸⁷ They showed the highest sensitivity and stability of these probes in acidic conditions and in the presence of reactive oxygen species (ROS) compared to CT03 **137** (Figure 19). Moreover, in acidic media, **131** (Figure 15) did not show self-aggregation. The acid-induced release of Cu^{2+}

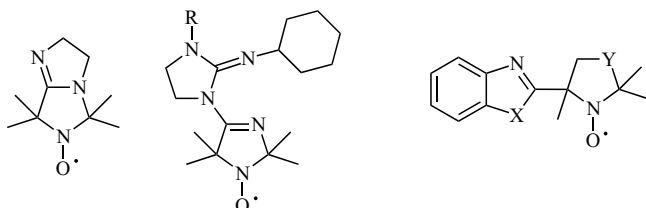
Table 1 Structures of pH-sensitive spin probes.

- 64, $R^1 = R^2 = \text{Me}$, $X = \text{Me}$, $Y = \text{Me}$, $R^5 = R^6 = \text{Me}$: **HMI**
 65, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{H}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$: **ATI**
 66, $^{161}\text{R}^1 = R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = \text{Me}$, $R^6 = \text{Me}$: **KG-4**
 67, $^{161}\text{R}^1 = R^2 = \text{Et}$, $R^3 = R^4 = (\text{CH}_2)_4$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$: **KG-5**
 68, $^{161}\text{R}^1 = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 69, $^{161}\text{R}^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = R^4 = (\text{CH}_2)_5$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 70, $^{161}\text{R}^1 = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{HO}(\text{CH}_2)_2$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 71, $^{161}\text{R}^1 = 2\text{-Py}$, $R^2 = \text{Et}$, $R^3 = \text{Me}$, $R^4 = \text{H}$, $X = \text{N}$: **KG-2**, $R^5 = R^6 = \text{Me}$
 72, $^{161}\text{R}^1 = m\text{-H}_2\text{NC}_6\text{H}_4$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 73, $^{167}\text{R}^1 = R^2 = \text{Et}$, $X = \text{Me}$, $R^5 = R^6 = \text{Et}$
 74, $^{167}\text{R}^1 = R^2 = \text{Et}$, $X = \text{Me}$, $Y = \text{Me}$, $R^5 = R^6 = \text{Et}$
 75, $^{167}\text{R}^1 = R^2 = \text{Et}$, $R^3 = R^4 = (\text{CH}_2)_4$, $X = \text{N}$, $R^5 = R^6 = \text{Et}$
 76, $^{162}\text{R}^1 = p\text{-Me}_2\text{NC}_6\text{H}_4$, $R^2 = \text{Et}$, $R^3 = R^4 = (\text{CH}_2)_5$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 77, $^{162}\text{R}^1 = 4\text{-Py}$, $R^2 = \text{Et}$, $R^3 = R^4 = (\text{CH}_2)_5$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$: **KG-1**
 78, $^{162}\text{R}^1 = p\text{-Me}_2\text{NC}_6\text{H}_4$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 79, $^{162}\text{R}^1 = 4\text{-Py}$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 80, $^{162}\text{R}^1 = 4\text{-Py}$, $R^2 = p\text{-Me}_2\text{NC}_6\text{H}_4$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 81, $^{162}\text{R}^1 = p\text{-OHC}_6\text{H}_4$, $R^2 = \text{Et}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 82, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{COOH}$, $R^4 = \text{Ph}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 83, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{CONHCH}_3$, $R^4 = \text{Ph}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 84, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{CONHCH}_3$, $R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 85, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{COOH}$, $R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 86, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{COOCH}_3$, $R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 87, $^{160}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CH}_2\text{COOCH}_3$, $R^4 = \text{Ph}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 88, $^{168}\text{R}^1 = \text{Et}$, $R^2 = 4\text{-Py}$, $R^3 = R^4 = \text{HO}(\text{CH}_2)_2$, $X = \text{N}$, $R^5 = R^6 = \text{Et}$: **API**
 89, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = (\text{CH}_2)_2\text{N}^+(\text{Me})_3$, $\text{CH}_3\text{OSO}_3^-$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$: **NR1**
 90, $^{175}\text{R}^1 = \text{Me}$, $R^2 = p\text{-C}_6\text{H}_4\text{SG}$, $R^3 = R^4 = \text{Me}$, $X = \text{N}$, $R^5 = R^6 = \text{Et}$: **NR2**
 91, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = (\text{CH}_2)_2\text{N}(\text{Me})_2$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 92, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = (\text{CH}_2)_2\text{NH}_2$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 93, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = \text{CH}_2\text{CO}_2\text{Et}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 94, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = (\text{CH}_2)_2\text{N}_3$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 95, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, $R^4 = (\text{CH}_2)_2\text{CN}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 96, $^{163}\text{R}^1 = R^2 = \text{Me}$, $R^3 = R^4 = (\text{CH}_2)_2\text{NHCS}$, $X = \text{N}$, $R^5 = R^6 = \text{Me}$
 97, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{COH}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 98, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{COCH}_3$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 99, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{CO}t\text{-Bu}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 100, $^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{COCO}_2\text{Me}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 101, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{COCF}_3$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 102, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{CO}_2\text{Et}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 103, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{COPh}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 104, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{CO}4\text{-Py}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 105, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{CON-C}_{17}\text{H}_{35}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 106, $^{164}, ^{165}\text{R}^1 = R^2 = \text{Me}$, $R^3 = \text{CN}$, $R^4 = \text{CO}(\text{CH}_2)_8\text{CO}_2\text{H}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$
 107, $^{165}\text{R}^1 = \text{Me}$, $R^2 = \text{C}_8\text{H}_{17}$, $R^3 = \text{CN}$, $R^4 = \text{COH}$, $X = \text{C}$, $Y = \text{H}$, $R^5 = R^6 = \text{Me}$

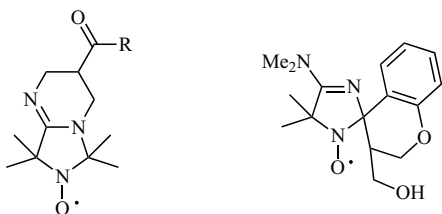
(continued overleaf)

Table 1 (continued)

- 108**, $^{165}\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{C}_8\text{H}_{17}$, $\text{R}^3 = \text{CN}$, $\text{R}^4 = \text{COCH}_3$, $\text{X} = \text{C}$, $\text{Y} = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{Me}$
109, $^{165}\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{C}_8\text{H}_{17}$, $\text{R}^3 = \text{CN}$, $\text{R}^4 = \text{CO}t\text{-Bu}$, $\text{X} = \text{C}$, $\text{Y} = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{Me}$
110, $^{165}\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{C}_8\text{H}_{17}$, $\text{R}^3 = \text{CN}$, $\text{R}^4 = \text{COCF}_3$, $\text{X} = \text{C}$, $\text{Y} = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{Me}$
111, $^{165}\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{C}_8\text{H}_{17}$, $\text{R}^3 = \text{CN}$, $\text{R}^4 = \text{COPh}$, $\text{X} = \text{C}$, $\text{Y} = \text{H}$, $\text{R}^5 = \text{R}^6 = \text{Me}$
112, $^{172}, ^{173}, ^{176}\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{X} = \text{CH}_2\text{SSO}_2\text{Me}$, $\text{Y} = \text{Me}$, $\text{R}^5 = \text{R}^6 = \text{Me}$: **IMSTL**



- 113**, $^{170}, ^{171}$ **114**, **115**, $^{163}\text{R} = \text{Me}$, **H** **116**, $^{174}\text{X} = \text{NH}$, $\text{Y} = \text{CH}_2$; **117**, $^{174}\text{X} = \text{NH}$, $\text{Y} = \text{CH}_2\text{-CH}_2$



- 118**, $^{166}\text{R} = p\text{-C}_6\text{H}_4\text{-(OC}_{10}\text{H}_{21})$; **122**, 169
119, $^{166}\text{R} = p\text{-C}_6\text{H}_4\text{-(OCH}_2\text{-CO}_2\text{Et)}$;
120, $^{166}\text{R} = p\text{-C}_6\text{H}_4\text{-(OCH}_2\text{-CO}_2\text{H)}$;
121, $^{166}\text{R} = \text{OH}$

from the **131**- Cu^{2+} complex was used to measure the pH by EPR (Figure 15c).

2.1.8 Spin Probes for Oximetry

Nitroxides as Oximetric Spin Probes

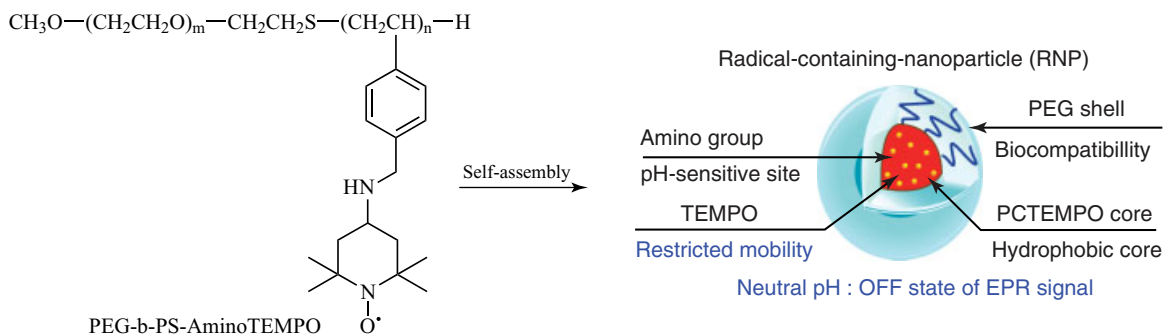
Molecular oxygen plays a crucial role in cellular metabolism and abnormal tissue oxygenation is involved in a number of diseases (cancer, ischemic diseases, etc.).²⁵ As a result, the measurement of oxygen concentration *in vitro* and *in vivo* is fundamental to study many physiological and pathological processes. There are different oxygen measurement techniques and among them, spin probes coupled to EPR (EPR oximetry) is a noninvasive technique widely used in biological systems. The principle is based on the interaction of molecular oxygen and the paramagnetic spin probes (Heisenberg exchange). This interaction has shown to be sensitive and reliable to allow the quantification of the oxygen concentration in various systems (Figure 16).

The two main types of spin probes used in EPR oximetry are soluble spin probes¹⁸⁸ and stable paramagnetic particles (lithium phthalocyanine (LiPc),¹⁸⁹ charcoals,^{190,191} India ink,¹⁹² etc.). In this brief report, we will focus on the development and use of soluble nitroxide and trityl radical spin probes. The specifications for a useful oximetric spin probe are a narrow line shape EPR signal, oxygen sensitivity, stability, solubility, and low toxicity.

Nitroxides (Figure 17)^{193,194} were first used as spin probes for oximetry, to increase their sensitivity to O_2 concentration, various deuterated nitroxides derived from **133** and **132** were prepared and used for *in vivo* applications.^{121, 195–197} Nitroxide **136** (Figure 18) exhibits a six line EPR spectrum with very narrow lines due to the coupling with nitrogen and the hydrogen attached to C4 (0.05 mT). Analysis of the broadening of the doublet lines allowed oxygen concentration measurements in tissues and animals.^{195,198,199} More recently, Burks *et al.*¹³¹ synthesized the fully isotopically labeled (^2H , ^{15}N) nitroxide **59**, which was designed for oxygen mapping of tumor using EPRI.

Table 2 pK_a values and ΔA_{iso} of various pH-sensitive nitroxides from Table 1.

pH probes	pK_a	ΔA_{iso} (mT 10^{-1})	pH probes	pK_a	ΔA_{iso} (mT 10^{-1})	pH probes	pK_a	ΔA_{iso} (mT 10^{-1})	pH probes	pK_a	ΔA_{iso} (mT 10^{-1})
64	4.7	1.27	79	5.08	0.81	94	5.47	0.89	109	10.08	1.06
HMI				2.86	0.53						
65	6.2	0.79	80	5.03	0.61	95	5.06	0.86	110	7.5	0.40
ATI				3.95	0.68						
				2.29	0.61						
66	7.3	1.04	81	5.9	0.82	96	2.82	0.72	111	9.3	0.90
KG-5				9.8	0.12						
67	6.9	1.12	82	5.94	0.73	97	—	—	112 IMSTL	2.42	1.41
KG-4											
68	6.0	0.79	83	4.3	0.88	98	9.7	0.71	113	7.2	0.9
69	5.6	0.90	84	5.2	0.89	99	—	—	114	12.5	0.17
70	4.8	0.93	85	6.63	0.88	100	6.5	0.69	115	10.2	0.15
71	5.4	0.81	86	5.0	0.92	101	6.6	0.80	116	—	0.6
KG-2											
72	6.0	0.80	87	3.5	0.85	102	10.1	0.72	117	—	0.6
73	1.2	0.9	88	4.91	1.39	103	—	—	118	8.5	0.55
			API	2.82	0.86						
74	4.95	1.3	89	3.80	0.94	104	8.1	0.75	119	8.85	0.59
			NR1								
75	7.4	0.9	90	6.2	0.9	105	9.1	0.82	120	8.67	0.6
			NR2								
76	6.1	0.83	91	3.73	0.87	106	10.1	0.85	121	9.4	0.5
	3.4	0.35								5.05	0.1
77	4.8	0.8	92	4.11	0.81	107	7.2	0.73	122	5.09	1
KG-1	2.8	0.6									
78	6.25	0.77	93	4.76	0.90	108	8.6	0.86			
	3.50	0.26									

**Figure 14** Schematic illustration of a pH-sensitive radical-containing-nanoparticle. [Adapted with permission from T. Yoshitomi, R. Suzuki, T. Mamiya, H. Matsui, A. Hirayama, Y. Nagasaki, *Bioconjugate Chem.*, 2009, **20**, 1792–1798. Copyright 2009 American Chemical Society.]

Trityl Radicals as Oximetric Spin Probes

Applications of nitroxides in oximetry are limited by their sensitivity to bioreduction and the large EPR linewidth of their EPR spectra. Researchers from Nycomed Innovation's company developed TAM derivatives and showed that their stability *in vivo*

and the shape of their EPR signals make them very interesting as oximetric probes for biomedical applications.²⁰⁰ CT-03 **137**, perdeuterated CT-03 **138** (Figure 19), and Ox063 **3** show very narrow EPR linewidths and are less sensitive to bioreduction than nitroxides. Moreover, the broadening of

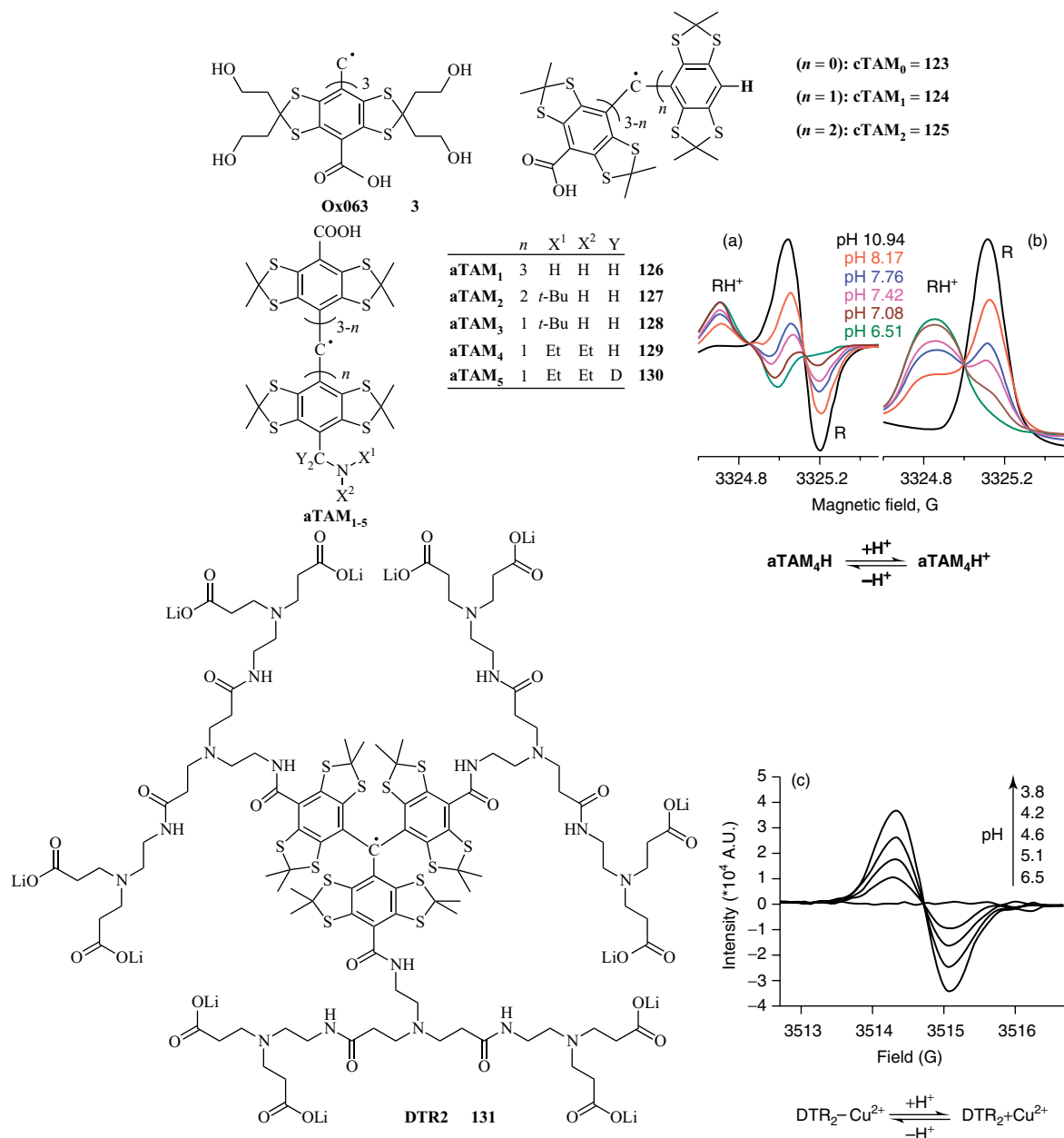


Figure 15 Trityl radicals as pH-sensitive spin probes. (a) High-field components of the EPR spectra of aTAM₄ (50 mM) radical in 1.5 mM pyrophosphate buffer at various pH values, 37 °C. (b) Integrated spectra demonstrate isosbestic point characteristics for the chemical equilibrium between protonated and unprotonated aTAM₄ radicals. [Adapted with permission from I. Dhimitruka, A. A. Bobko, C. M. Hadad, J. L. Zweier, V. V. Khramtsov, *J. Am. Chem. Soc.*, 2008, **130**, 10780–10787. Copyright 2008 American Chemical Society.] (c) pH dependence of the EPR spectra and intensity of the complex of **131** with Cu²⁺. [Ref. 187 - Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/B807406B>.]

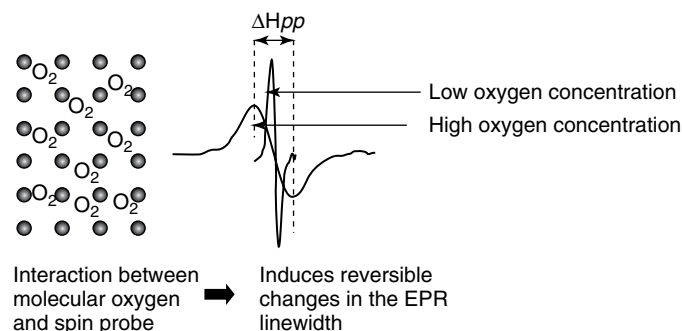


Figure 16 Effect of oxygen on exchange-narrowed line shape. Black dots represent spin probe molecules. Introduction of O_2 induces line broadening measured by peak-to-peak line width ΔH_{pp} . [Reprinted with permission from Ref. 188. Copyright 2010 American Chemical Society.]

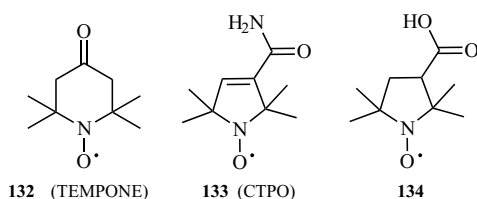


Figure 17 Structure of some nitroxides used as oximetric spin probes.

EPR lines due to oxygen is almost the same for trityl radicals and nitroxides (45 mT mM^{-1} of O_2); however, in oxygen-free medium, the broadening due to spin exchange is about 10 times lower for trityl radicals (1 mT mM^{-1}) than for nitroxides.^{157,184,201} These properties make TAM radicals spin probes of choice for oximetric applications.

Efforts have been made to synthesize new halogenated TAMs, taking advantage of the higher oxygen solubility in lipophilic environments compared to water. TAMs bearing fluorinated side chains (F15T-03 **139** and F45T-03 **140**, Figure 19) and possessing a high affinity for fluoruous media were prepared and used to follow subtle changes in oxygen concentration after induced ischemia in rodents.^{202,203}

PTM-TE **141** (Figure 19), a perchloro TAM, used by Dang *et al.*²⁰⁴ has proven to be highly sensitive to dissolved oxygen. *In vivo* oximetry and imaging of oxygen concentration in fibrosarcoma (RIF-1) tumor transplanted into C3H mice were performed using **141** dissolved in hexafluorobenzene as injectable probe.²⁰⁵

To improve sensitivity to oxygen concentration and intracellular permeability, Liu *et al.*²⁰⁶ synthesized various esterified trityl radicals. Among them, BT-03 **142** showed the highest sensitivity to molecular oxygen (linewidth = 0.0102 mT), whereas AMT-02 **143** and AMT-03 **144** (linewidth = 0.0203 and 0.0171 mT , respectively) showed interesting potential as intracellular probes. Experiments performed in bovine aortic endothelial cells showed the uptake of **143** by cells and its hydrolysis to **137**. Measurements of intracellular oxygen have been performed using these esterified trityl radicals.²⁰⁷

Taking into account that the presence of *para*-hydrogen on aromatic rings of TAMs limits their stability,²⁰⁸ Bobko *et al.*²⁰¹ prepared TAM-H **145** (Figure 19) containing one aldehyde and two carboxylic groups. EPR spectrum of **145** exhibits a doublet resulting from the coupling with the aldehydic hydrogen and a linewidth of 0.0105 mT in anoxic conditions. Experiments using **145** and Ox063 for oxygen consumption in Met-1 cancer cells demonstrated that **145** allowed EPR measurements at very low oxygen concentration (1 mm Hg), whereas Ox063 **3** is almost insensitive to oxygen pressures lower than 20 mm Hg (Figure 20).

More recently, Dhimitruka *et al.*²⁰⁹ described the synthesis and characterization of deuterated derivatives of Finland trityl radicals (cTAM* **146**, cTAMe* **148**, aTAM* **150**, and aTAMe* **152**) and evaluated their sensitivity to oxygen concentration. Additionally, Finland trityl radicals substituted with linkers suitable for further derivatization have been synthesized.²⁰⁹

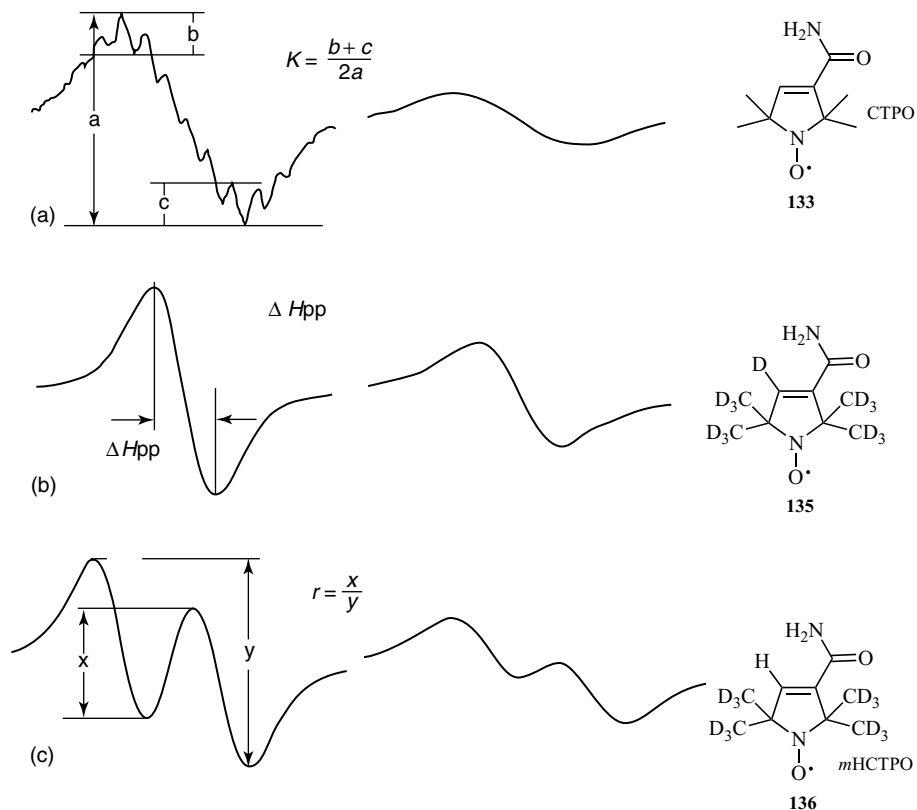


Figure 18 EPR spectra equilibrated with either pure nitrogen (left part) or with air (21% O₂, right part). (A: **133**, B: **135**, and C: **136**) [Reprinted from Ref. 199, Copyright (2000), with permission from Elsevier.]

2.1.9 Spin Probes for Redox Status Determination

Nitroxides and Trityl Radicals

The study of the biochemical profile variation is an important tool for biomedical diagnosis and for the evaluation of tissue activity. One of the biochemical profiles attracting a large interest is the redox status of cells since cellular energy production is linked to a series of oxidation reactions. Endogenous redox species, such as glutathione (GSH), ascorbate anion, thioredoxins, and NAD(P)H contribute to the overall redox control of cells. These redox species are responsive to parameters characteristic of a change in cell activity, such as oxygenation status, blood flow, oxidative stress, and mitochondrial dysfunction and altogether provide a good indication of the redox activity. Interestingly, in biological systems, nitroxide spin probes react with these

redox species to yield EPR-silent hydroxylamines as illustrated in Figure 21.

In most biological systems, one-electron reduction of the nitroxides predominates and the equilibrium is shifted toward the corresponding hydroxylamines (Figure 21) after a 10th of a minute. This feature has limited in many cases the applications of nitroxides as imaging agents in biological systems; however, monitoring the decay rate of nitroxide spin probes can provide information on the redox capacity of tissues.

Conventional EPR as well as NMR and EPRI techniques have been used in the past decade to monitor the changes in the reduction rate of spin probes in various tissues that may display different redox status.^{128,140,210–220} In the late 1990s, Kuppusamy *et al.*²²¹ measured the nitroxide reduction profiles in RIF-1 tumor-bearing mice by *in vivo* EPR spectroscopy and showed that

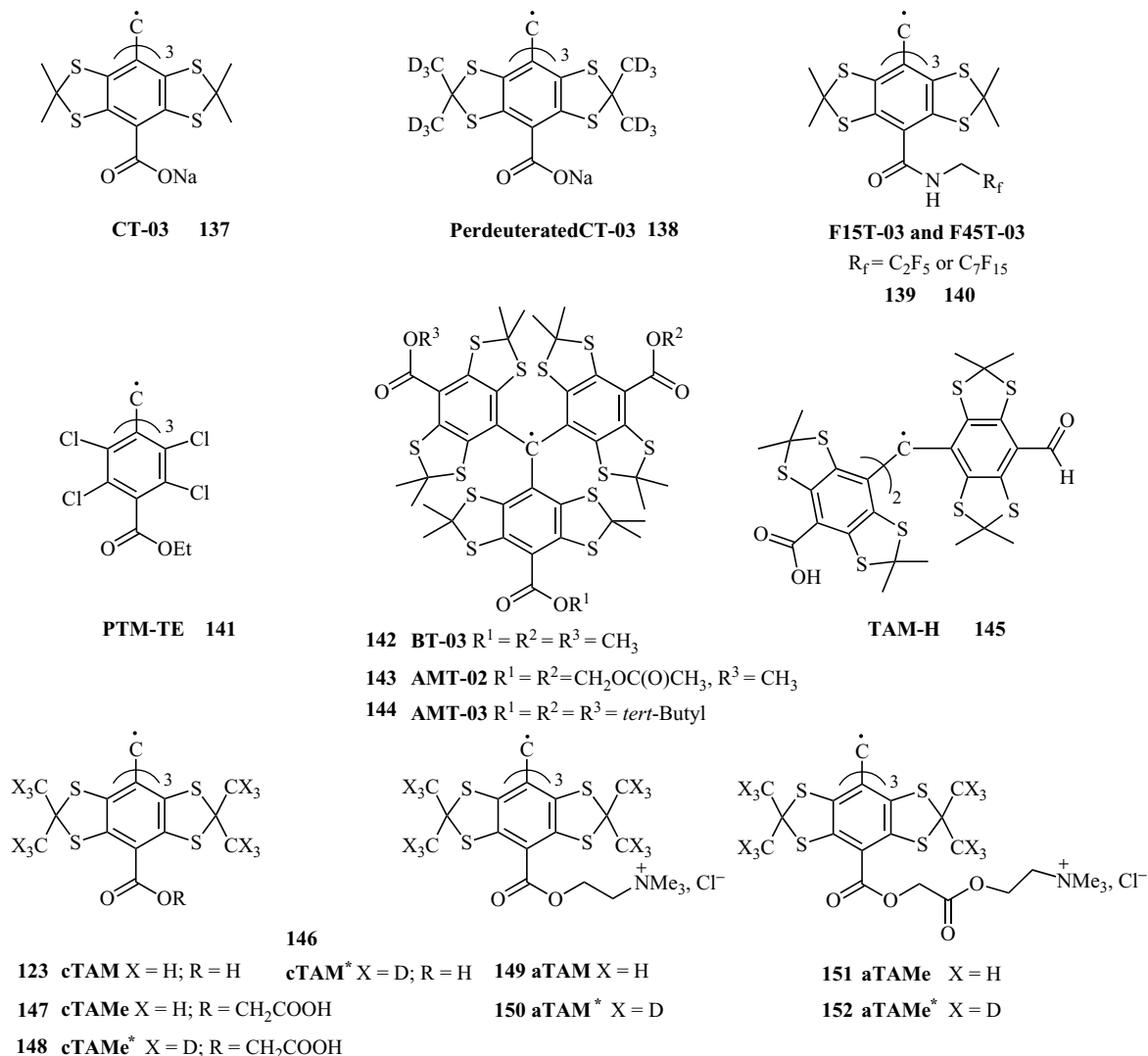


Figure 19 Oximetric soluble trityl spin probes.

tumor tissues were hypoxic and highly reducing when compared with normal tissues. In 2002, the same team reported the noninvasive measurements and spatial mapping of tumor redox status in tumor-bearing mice using **153** (Figure 21) as spin probe, low-frequency (1.3 GHz) spectroscopy, and (L-band EPRI) imaging techniques.²²² On the basis of their results, the authors highlighted the dominant role of GSH in the redox status of cells and the existence of heterogeneity of redox status in tumor tissue compared with normal tissue.

The influence of the nitroxide structure (Figure 22) on the reduction rate was also investigated using two cell-permeable nitroxides, **156** and **153**, and a cell-impermeable nitroxide **134**.²²³

The pharmacokinetic distribution of these spin probes was evaluated by MRI in normal tissue, tumor, kidney, and arteries in mice (Table 3). From these studies, the authors concluded that the differential reduction of cell-permeable nitroxides in normal tissue and tumor is due to intracellular processes and thus offer a noninvasive means

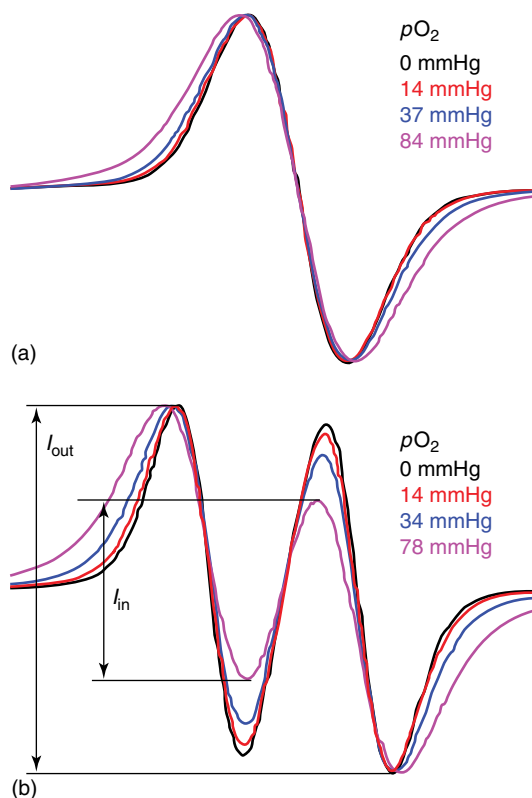


Figure 20 EPR spectra of aqueous solutions of (a) 100 μM Ox063 **3** and (b) 50 μM TAM-H **145** radicals measured at 37 $^{\circ}\text{C}$ and various oxygen concentrations. The spectra are scaled to the same maximum lineheight in the plots. [Reprinted from Ref. 201. Copyright 2009, with permission from Elsevier.]

to monitor redox status in various tissues using T_1 -weighted MRI.

PEDRI has been used at 0.02 T to assess the ability to image the *in vivo* distribution and redox-dependent clearance of nitroxide probes in different organs of a mice.¹³⁹ In this work, the best enhancement (-7) was observed in living mouse using **134**.

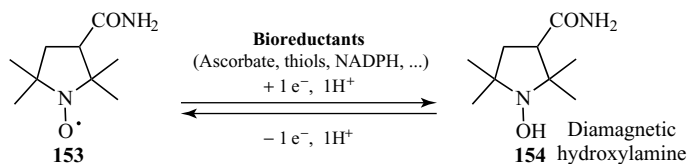


Figure 21 Redox status spin reporter.

More recently, the relation of the redox status to the partial pressure of oxygen in a tumor model was studied by EPRI using **155** and LiPc microcrystals implanted in the tumor.²²⁴

A series of trityl-nitroxide biradicals were developed as spin probes for the potential simultaneous measurement of redox status and oxygenation.^{225,226}

Thiol-Specific Nitroxide Labels for GSH Detection/Quantification

Important as actors of protein-mediated signaling pathways and as critical antioxidants, thiols and notably GSH are important regulators of the redox status in cells.²²⁷ The concentration of GSH is an important indication of many physio- and pathological situations, and since many years, methods and assays have been developed to monitor and determine the GSH concentration in tissues. An EPR method based on specific labeling of thiols was proposed using thiol-specific paramagnetic reagents as shown in Figure 23.^{156,213}

The first developed spin labels were mononitroxides in the early 1960s^{228,229}; however, limitations arose rapidly due to the small difference in the EPR parameters between the labeled and unlabeled thiols. Thus, the labeling methods required an additional purification step and *in vivo* applications were hampered.

Disulfide nitroxide biradicals such as **160** (Figure 23) exhibiting intramolecular spin exchange interactions were then developed to overcome these limitations.^{230,231} The reaction of the biradical label with a thiol such as GSH is accompanied by an EPR spectral change. Using disulfide nitroxide biradicals, the GSH concentrations were determined *in vivo* in cisplatin-resistant and cisplatin-sensitive tumors.²³²

Besides thiol-specific spin probes, a large series of reactive functional nitroxides have been developed for specific labeling applications and some of them are commercially available (Figure 24).

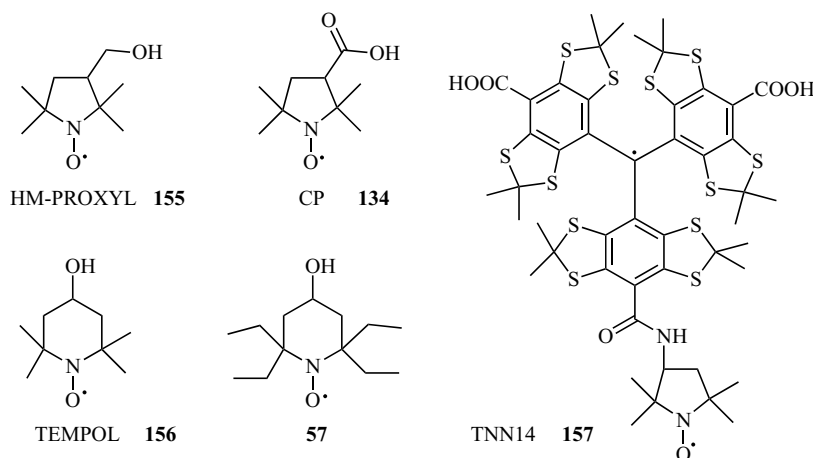


Figure 22 Structure of spin probes used in redox status determination.

Table 3 Decay rate of nitroxide contrast agents in various tissues from T_1 -weighted images.

Tissue	Decay rate (min^{-1})		
	TEMPOL	153	134
Normal leg	0.32 ± 0.03	0.056 ± 0.013	0.029 ± 0.014
Tumor leg	1.1 ± 0.2	0.107 ± 0.020	0.020 ± 0.014
Blood	1.0 ± 0.2	0.364 ± 0.008	0.4 ± 0.2
Left kidney	1.5 ± 0.2	0.30 ± 0.05	0.046 ± 0.006
Right kidney	1.2 ± 0.3	0.29 ± 0.04	0.050 ± 0.005

^a A solution of nitroxide contrast agents in PBS (1.5 mmol g^{-1} body weight) was injected via tail vein cannulation, 2 min after starting the MRI scan. *Source*: Adapted and reprinted by permission from the American Association for Cancer Research: F. Hyodo, K. Matsumoto, A. Matsumoto, J. B. Mitchell, M. C. Krishna, Probing the Intracellular Redox Status of Tumors with Magnetic Resonance Imaging and Redox-Sensitive Contrast Agents, *Cancer Research*, 2006, **66**(20), 9921–9928.

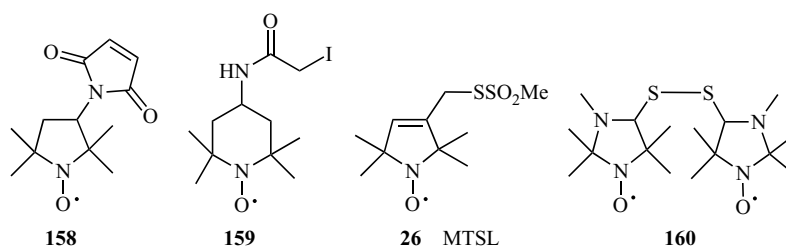


Figure 23 Structures of nitroxide spin labels used for the specific labeling of thiols.

2.1.10 Profluorescent Spin Probes

Nitroxides and to a lesser extent trityl radicals are routinely used as spin labels or spin probes for the EPR investigation of biological systems. However, in living systems such as cell cultures, tissues, and small animals, these spin labels and spin probes can react with various endogenous

biocomponents to form EPR-silent diamagnetic products.^{233–235} Nowadays, the loss of EPR signals and the low spatial resolution of EPRI techniques are the main limitations in the use of spin labels and spin probes to the EPR investigation of living systems. During the past two decades, a complementary approach using a spin probe (or a spin label) covalently linked to a fluorophore

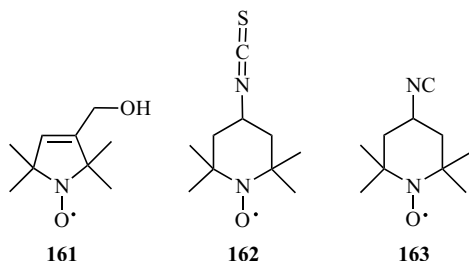


Figure 24 Structures of some reactive nitroxide spin labels.

moiety has been developed.^{236–238} This approach is based on the efficient quenching of fluorescence emission by the close free radical center. The hydroxylamine/nitroxide redox pair acts as an on/off switch of the fluorescence. The fluorescence quenching results from an enhanced intersystem crossing of the fluorophore excited singlet state to its triplet state through electron exchange interactions with the free radical centers.²³⁹

The hybrid probe can thus report at the same time on the redox status and the presence of free radicals in the studied system. On the basis of the distance dependence of the fluorescence quenching efficiency, approaches using a nitroxide and a fluorescent probe noncovalently linked have also been used to study dynamic and aggregating systems.

Nitroxides have been successfully used for the detection of carbon-centered and peroxy radicals by high performance liquid chromatography (HPLC) via a postderivatization step of the resulting alkoxyamine adducts with fluorescamine. The technique has shown to be highly sensitive and versatile but limited to simple systems.^{240–242}

For the study of more complex systems, including enzymatic systems, aggregates, and cell cultures, a more direct strategy was developed by combining a fluorescent moiety linked to a nitroxide to prepare prefluorescent probes (Figure 25). The reduction or trapping of a radical by the nitroxide group restores the fluorescent properties of the hybrid probes, allowing characterization, quantitative evaluation, and kinetic studies.^{240, 243–251}

For instance, this strategy has also been used for the evaluation of the local reactivity of phenol antioxidants in micellar systems,²⁵² for the mapping of radicals photogenerated through a mask in polymer films,²⁵³ for imaging the thermo-oxidative

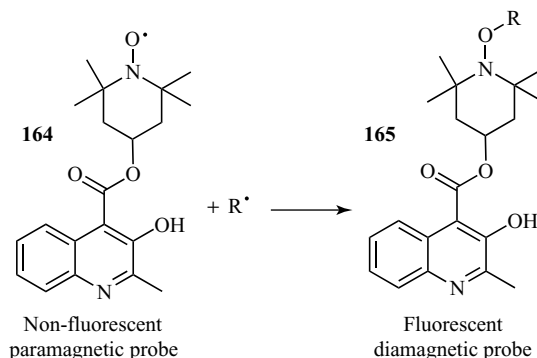


Figure 25 Profluorescent nitroxide spin probe.

degradation of polypropylene,²⁵⁴ for the quantitative analysis of vitamin C in fruit juices,²⁵⁵ for the *in vivo* detection of singlet oxygen production during photoinhibition of photosynthesis,²⁵⁶ and for probing ROS production and the redox status of cells.²⁵⁷

Perchlorotrityl radicals conjugated to a fluorophore moiety were developed as probes of superoxide radical, the spin probe exhibiting an enhancement of the fluorescence emission in the presence of KO₂ in DMSO (Figure 26).²⁵⁸

The reversible fluorescence quenching of quantum dots by nitroxides bearing ligand groups has been studied by EPR and fluorescence techniques.^{259–261} A detailed study on the quenching of terbium emission in the sensitized complex Tb(III)-carbostyryl-DTPA by TEMPOL **156** in aqueous solution has been reported.²⁶²

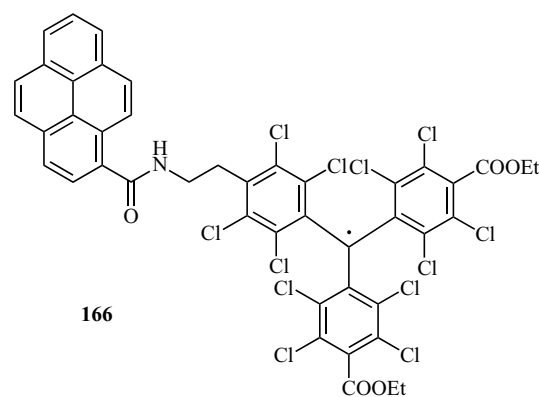


Figure 26 Profluorescent trityl spin probe.

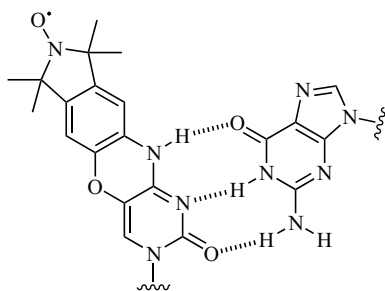


Figure 27 Prefluorescent nitroxide probe base paired to guanine in DNA.

Using both the EPR spin labeling and fluorescence (after nitroxide reduction) techniques,^{263,264} the folding of the DNA cocaine aptamer was studied by incorporating a prefluorescent nitroxide probe (Figure 27) in the aptamer chain.²⁶⁵ This probe has also been used to report the identity of its base-pairing partner in duplex DNA due to the different fluorescence signals observed for the different base pairs.²⁶⁶

The intramolecular fluorescence quenching of 5-carboxytetramethylrhodamine by TEMPO both linked at various positions on a DNA strand was studied in order to evaluate a method to measure short distance changes within single molecules.²⁶⁷ This approach was used earlier to study the binding of hirudin analogs to thrombin.²⁶⁸

In membrane and lipid raft studies, TEMPO nitroxide has been used as quenching molecule of a fluorescent group incorporated into lipid bilayers to detect the presence of coexisting ordered and disordered state lipid domains in model membranes.²⁶⁹ This approach was developed earlier to study the immersion of fluorophores in membranes.^{270,271}

Structural studies and aggregation processes of biomacromolecules, including proteins, RNA, and DNA, have been largely performed by analyzing

the fluorescence quenching of chromophores by nitroxide spin probes and spin labels.^{272–275}

2.2 Spin Labels and Spin Probes in Supramolecular Systems

Since the award of the Nobel Prize in chemistry in 1987 to Cram, Lehn, and Pedersen for the development and use of molecules with structure-specific interactions of high selectivity, supramolecular chemistry, often defined as the *chemistry beyond the molecule*, has never ceased to expand its frontiers, its scope, and the field of its applications. Approximately at the same time, some scientists started to explore the interface between free radicals and macrocycles often containing cavities amenable for guest inclusion (Figure 28). In this context, the use of EPR spectroscopy proved to be immensely useful to the characterization of the paramagnetic supramolecular systems (see **Analysis of Radicals by EPR**).

The first systems to have been investigated are probably micelles, crown-ethers, and cyclodextrins. Recently, more sophisticated systems, including cucurbiturils, self-assembled cages (metal-organic polyhedra—MOPs), or self-assembling free radicals, appeared in which the degree of prediction of the arrangement of free radicals by means of the assembling building blocks raised to unprecedented levels. We can notice that after a period of time where most chemists focused on the inclusion properties of well-known macrocycles as cyclodextrins or calixarenes, the “design concept” started to be a very important component of the systems investigated. The “design concept” comes within the scope that asks for predetermined properties to be reached experimentally by a very careful determination of the structural building blocks *and* supramolecular

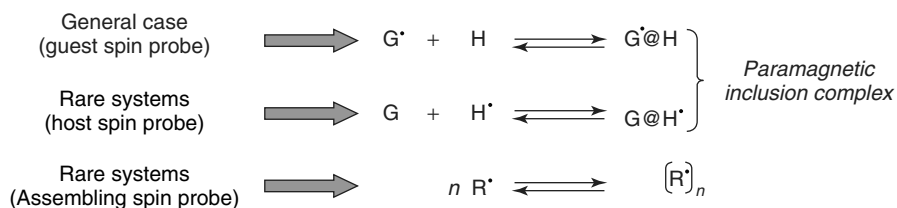


Figure 28 Different situations depicting the general and more peculiar role that can play radicals in systems involving molecular recognition.

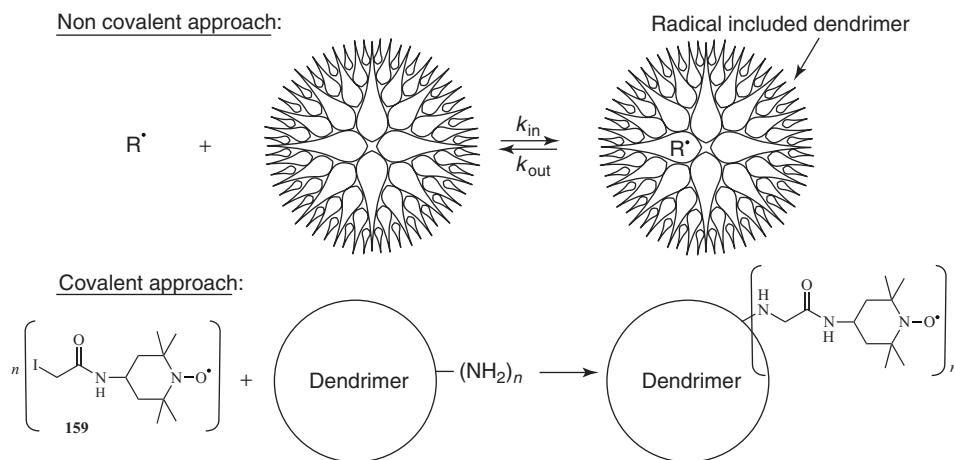


Figure 29 The two approaches involving nitroxides to investigate dendrimers and their supramolecular interactions with other large objects.

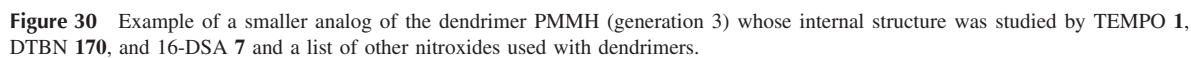
interactions mediating their assemblies into systems of higher complexity. Our aim is to present the most important aspects of the developing interface between free radicals and supramolecular chemistry/concepts. As will be seen, nitroxides hold a great part of the discussion, likely due to their stability and easiness of functionalization.²⁷⁶ Since this expanding topic has recently been the object of many book chapters,^{277–279} we will focus on the main results in the context of spin probes and assembled radicals. We have to mention that trityl radicals hold a special part of radical solid-state supramolecular chemistry/recognition^{280–282} with crystalline materials that can combine porosity with interesting magnetic and molecular recognition properties. Finally, micelles, vesicles, liposomes, surfactants, and some polymers can also be considered as supramolecular systems based on amphiphile molecules self-assembling in water and creating local hydrophobic pockets amenable to lipophilic guest inclusion according to the hydrophobic effect. A large part of the scientific literature is dedicated to the study on these systems by the spin probe-EPR technique and has recently been reviewed.^{283–292}

2.2.1 Nitroxides and Dendrimers

Dendrimers are generally prepared by a bottom-up approach and are covalent, most often spherical, sea-urchin-shaped architectures. Concerning

spin probes, two approaches have been considered (Figure 29). The first that benefits from the small size of nitroxides to explore the dynamic cavities inside dendrimers (noncovalent approach) and the second that consists of branching several nitroxides on the surface of a presynthesized dendrimer to investigate its recognition properties toward a large variety of other quite large covalent assemblies.

Smith and coworkers²⁹³ reported the binding of 4-amino-TEMPO **40** to the carboxylic acid function at the focal point of a dendrimer, whereas the groups of Ottaviani and coworkers used nitroxide probes CAT-1 **169** and CAT-12 **174** (Figure 30) to explore the interior and exterior of Gd(III)-containing dendrimers that are believed to be promising candidates as contrast agents for MRI.²⁹⁴ Recently, Sueishi *et al.*²⁹⁵ reported the formation of inclusion complexes of TEMPO **1**, DTBN **170**, and 16-DSA **7** with cyclotriphosphazene-phenoxymethyl-(methylhydrazono) dendrimer G 4.5 (PMMH, **167**, Figure 30). In 1996, the surfactant spin probe CAT-16 **175** was used to explore this interface with starburst dendrimers.²⁹⁶ It was concluded that for low-generation dendrimers, they are the guests with the micelle forming CAT-16 **175** acting as a host, whereas for higher generation ones, the nitroxide is the guest and the bigger dendrimer now plays the role of the host. The same team also reported the use of ruthenium(II) phenanthroline complexes labeled with a nitroxide (**176** and **177**) to investigate the binding of the complexes on the surface of starburst



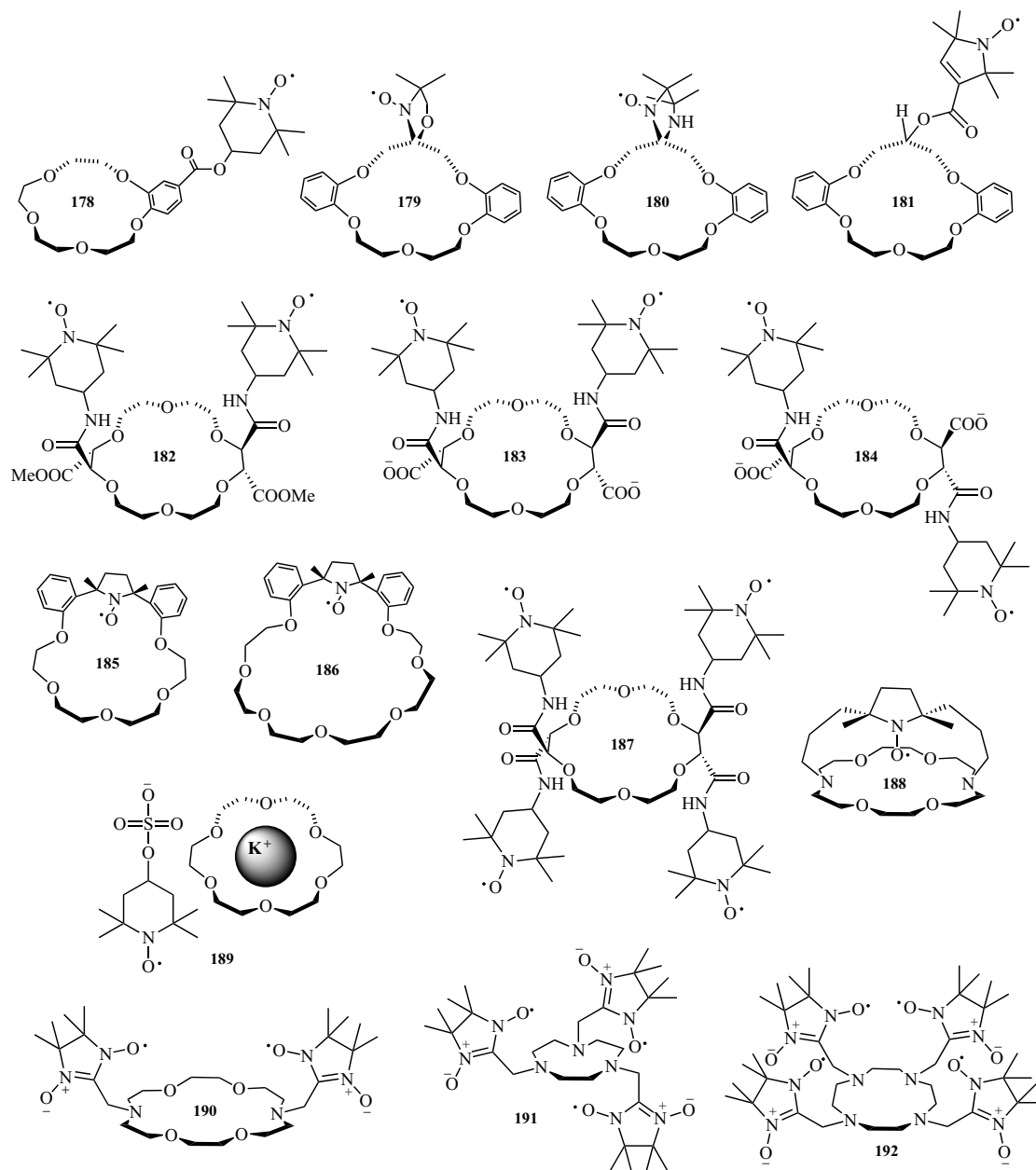


Figure 31 Covalently and noncovalently bound nitroxides with crown-ethers, polyazamacrocycles, and cryptands for the monitoring of cation recognition by EPR spectroscopy.

dendrimers.²⁹⁷ One year later, they studied the partitioning of spin probes C12T **171**, CAT-9 **173**, and CAT-16 **175** between the surface of dendrimers and micelles and they also could gain information about the interaction between these

two self-assembled and molecularly assembled systems.²⁹⁸

Janssen and coworkers²⁹⁹ later followed by Singel and coworkers studied the distribution of nitroxides on the surface of dendrimers.³⁰⁰ On the

other hand, the research group of Ottaviani have been very active in this field³⁰¹ and especially according to the second approach, they studied the interactions of spin-labeled dendrimers with (i) other dendrimers,³⁰² (ii) vesicles,^{303,304} (iii) polynucleotides,³⁰⁵ (iv) DNA,³⁰⁶ (v) porous materials,³⁰⁷ and (vi) peptides and proteins.^{308,309} A noncovalent approach has also been used recently (CAT-8 **172**) to investigate the recognition of phosphorous dendrimers with aggregating peptides involved in neurodegenerative diseases.³¹⁰

2.2.2 Nitroxides with Crown-Ethers and Cryptands

The process of cation recognition by crown-ethers and analogs has been monitored by means of EPR spectroscopy, thanks to macrocycles carrying various numbers of nitroxides (Figure 31). The benzo-15-crown-5 macrocycle **178** bearing a TEMPO dimerizes in the presence of potassium affording EPR spectra in line with the 1:2 complex K^+ @ **178**.³¹¹ On the basis of a study on the changes in their EPR parameters, the dibenzo-16-crown-5 derivatives **179**, **180**, and **181** were shown to be rather poor complexing agents of cations.³¹² The di- and tetranitroxides **182**, **183**, **184**, and **187** carrying TEMPO moieties (Figure 31) have been synthesized and the binding of potassium investigated.^{313,314} The *syn*-isomer of the two stereochemically distinct chiral dinitroxides **183** and **184** showed interesting spin–spin interactions mediated by the presence or the absence of potassium, making **183** a good candidate as a cation-sensitive ionophore.

The crown-ether and cryptand nitroxides **185**, **186**, and **188** have also been prepared and did not show evidence of complex formation in the presence of alkali metal cations in methanol.³¹⁵ However, 1:1-type complexes were observed in chloroform for the cryptand-PROXYL cage **188** in the presence of $NaBH_4$. The 18-crown-6-complexed potassium salt of **189** (Figure 31) exhibited an increased solubility in ionic liquids and organic solvents of different polarity and is believed to be a useful probe to investigate these media.³¹⁶ In 1996, Turek and coworkers reported the synthesis of a di- (**190**), a tri- (**191**), and a tetra-radical (**192**), with each nitronylnitroxide moiety being

appended on a nitrogen-containing macrocycle.³¹⁷ Among them, the polyazamacrocyclic dinitroxide **190** was shown to be very sensitive to the presence of alkali metal cations in organic solvents. This phenomenon was ascribed to the ability of the complexed cation to modulate the spin–spin exchange interactions between the two neighboring radicals. A structural analog of 18-crown-6 labeled with a phenoxyl radical³¹⁸ and other crown-ethers having five to eight oxygen atoms in the ring and bearing a benzoquinone moiety³¹⁹ were prepared, which also showed molecular recognition properties toward small size alkali metal cations that were monitored by EPR. One example of a verdazyl radical appended on benzo-15-crown-5 has been reported and its dimerization in the presence of Na^+ followed by EPR.³²⁰ Finally, nitroxide-labeled crown-ethers have also been used in crystal engineering to construct molecular organic magnets³²¹ and supramolecular analogs to generate radical triplet pairs with a C_{60} appended crown-ether recognizing an ammonium bearing nitroxide.^{322,323}

2.2.3 Nitroxides with Cyclodextrins

Paton and Kaiser³²⁴ were the first to study the inclusion of a nitroxide **194** in the cavity of natural β -CD as well as the grafting of a structural analog on the macrocycle (**193**) in 1970 (Figure 32). The fact that one nitroxide grafted on a cyclodextrin (*the structures of cyclodextrins mentioned hereafter are shown in Figure 32*) has been studied at the same time as its supramolecular, noncovalent counterpart shows that these two aspects arose interest very early. However, most of the studies reported after 1970 concerned the inclusion of small spin probes almost exclusively composed of nitroxides inside the cavities of several CDs. Only 35 years later, in 2005, will the spin labeling of cyclodextrins by nitroxides be investigated again with several compounds carrying one or two nitroxides, able to self-include or not and useful to probe interactions with other entities. In these systems, the spin label is useful to monitor supramolecular interactions thanks to EPR spectroscopy.

Three years later, solid-state EPR studies on the dynamics of polycrystalline enclathrated DTBN **170** in thiourea, nitroxide **198** ($n = 5$) in β -CD,³²⁵ and 7-DSA **5** in γ -CD were reported.³²⁶ The inclusion

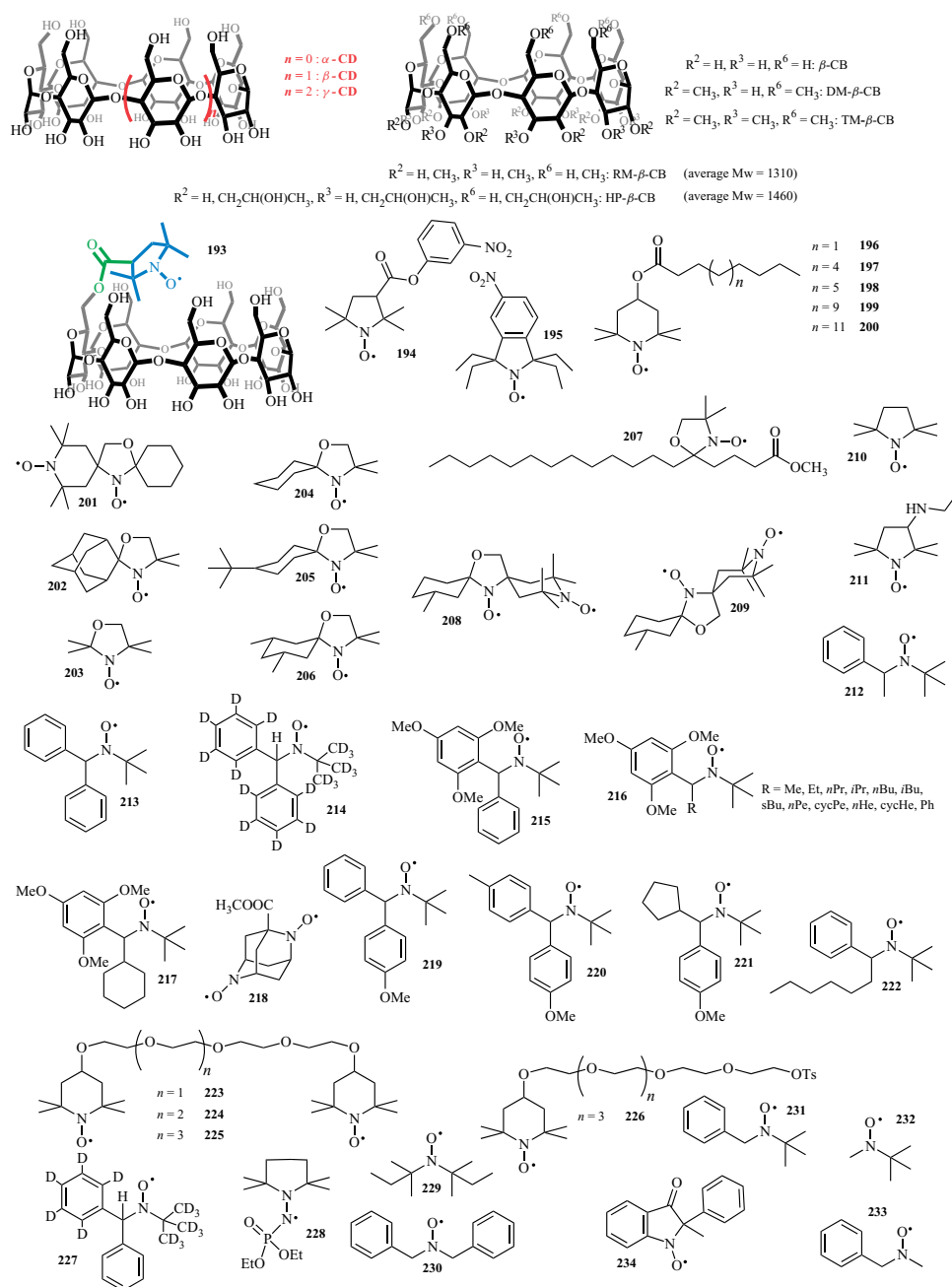


Figure 32 Mono- and dinitroxide spin probes used for EPR monitoring of recognition by cyclodextrins.

of TEMPONE **132** in α -CD and β -CD has also been observed quite early.³²⁷ Then, the research groups of Rassat and Janzen have extensively studied cyclodextrins by means of a large variety of spin probes. In 1975, Rassat and coworkers reported

the use of spin probes **1**, **132**, **156**, **195**, and **201–206** to study aqueous solutions of α -CD and β -CD (Figure 32).³²⁸ Chiral dinitroxide biradical **208** and **209** have then been used to study chiral recognition by β -CD.^{329,330} Inclusion complexes of

DTBN **170** in β -CD and γ -CD (solution)^{331,332} and those of TEMPO **1**, TEMPOL **156**, TEMPONE **132**, and TEMPAMINE **40** with α -CD and β -CD have been studied (solid³³³ and solution).³³⁴ β -CD has shown some protective effects regarding the kinetic of reduction of the PROXYL radical **210** by ascorbate anion in water^{335,336} as well as for DTBN and TEMPOL but not for TEMPO.³³⁷ Eastman *et al.*³³⁸ showed that nitroxides DTBN **170**, CAPRO **153**, and AMPRO **211** (Figure 32) form weak complexes with α -CD ($K_a \leq 6 \text{ M}^{-1}$) with respect to other spin probes or higher size macrocycles for which the binding constants are usually in the range 10^2 – 10^3 M^{-1} .^{339,340} In 1988, Kotake and Janzen published a series of papers describing the use of spin probes based on nitroxide **213** carrying hydrophobic *tert*-butyl and phenyl groups and functionalized analogs **214** and **215** (Figure 32). They showed that depending on the cyclodextrin added (α -CD, β -CD, and γ -CD), the nitroxides experience different environments depending on the side group included in the CD cavity (*tert*-butyl-in or phenyl-in for a bimodal-type inclusion).^{341–343} Interestingly, using the ENDOR technique, the use of prochiral spin probe **213** allowed detecting supramolecular diastereomer (two types of phenyl-in inclusion complexes) due to the inherent chiral nature of the β -CD hydrophobic cavity.³⁴⁴

Then, the same authors used α -CD, β -CD, γ -CD, and 2,6-di-*O*-methyl- β -CD (DM- β -CD) with functionalized spin probes keeping the nitroxide skeleton of **215** and replacing one phenyl group by various alkyl and cycloalkyl groups (**212**, **214**, **216** series, and **217**) to further study the bimodal-type inclusion^{345–347} and the effect of pH, pressure, and salt concentration on this phenomenon.^{348,349} The use of other probes (**212**, **219**, **220**, **221**, and **222**) even allowed identifying up to trimodal inclusion phenomena for spin probes carrying three hydrophobic, size complementary groups recognized by β -CD.³⁵⁰ An inclusion complex with an adamantanoid dinitroxide of stoichiometry 2 β -CD @ **218** has also been prepared³⁵¹ and spin–spin interactions of dinitroxide biradicals **223–225** modulated by the presence of γ -CD and various ions.³⁵² Differential pressure effects have been detected using EPR spectroscopy (β -CD spin probe **227**) with a shift of the bimodal inclusion-type complexation in favor or the *tert*-butyl group when the external pressure

increased.³⁵³ It appears that the only solvent usable for these studies is water, largely due to (i) the necessary occurrence of the hydrophobic effect and (ii) the release of “high energy” water molecules from the hydrophobic CD cavities on complexation, except in one case where ethanol was used.³⁵⁴ A good spectral resolution between the EPR signals of free and included radicals was obtained with spin probes **231–233** to investigate the cavities of α -CD, β -CD, γ -CD, DM- β -CD, and TM- β -CD, which allowed exploring the effect of several experimental parameters on the molecular recognition phenomenon.³⁵⁵ In this line, the strong sensitivity of the phosphorous splitting of hydrazyl radical **228** was exploited to study its inclusion in DM- β -CD, and a competitive method to determine the binding (association constant) of diamagnetic species based on the predetermined value of K_a of the **228** @ DM- β -CD system has been proposed.³⁵⁶ An interesting study explored the kinetics of crystal complex formation by EPR using spin probes **196**, **197**, and **200** with cyclodextrins α -CD, β -CD, and γ -CD.³⁵⁷ Lucarini *et al.* used symmetric spin probes **229** and **230** to monitor the pH-sensitive formation of the ternary complex **229** @ 2CDs and **230** @ 2CDs with β -CD, which tends to dimerize in the presence of these spin probes. The increased solubility and the protection against photodegradation of indolinone-*N*-oxyl radical **234** in the presence of RM- β -CD proved to be useful in enhancing its radical scavenging efficiency.³⁵⁸ Chiral spin probes **235–243** have also been investigated as a mean to better understand chiral recognition by inherently optically active CDs.³⁵⁹ Then, a series of papers were published about covalent nitroxide-CD architectures (i) to see whether the formation of self-included probes could be prepared and (ii) to investigate spin-labeled macrocycles to monitor the binding of other species regarding a free CD cavity. Chechik *et al.* synthesized monofunctionalized spin probes **247**, **248**, and **250** (Figure 33) based on a β -CD scaffold carrying TEMPO-type nitroxide on the narrow rim and showed that they are good candidates to monitor recognition events involving large guest molecules such as dendrimers,³⁶⁰ polymers,³⁶¹ or hydrogels.^{362,363} In 2006, a paper reported the attachment of the persistent nitroxide TIPNO on permethyl- β -cyclodextrin (TM- β -CD). The primary methoxy crown of **249** has been shown to have a pronounced effect in stabilizing the appended guest

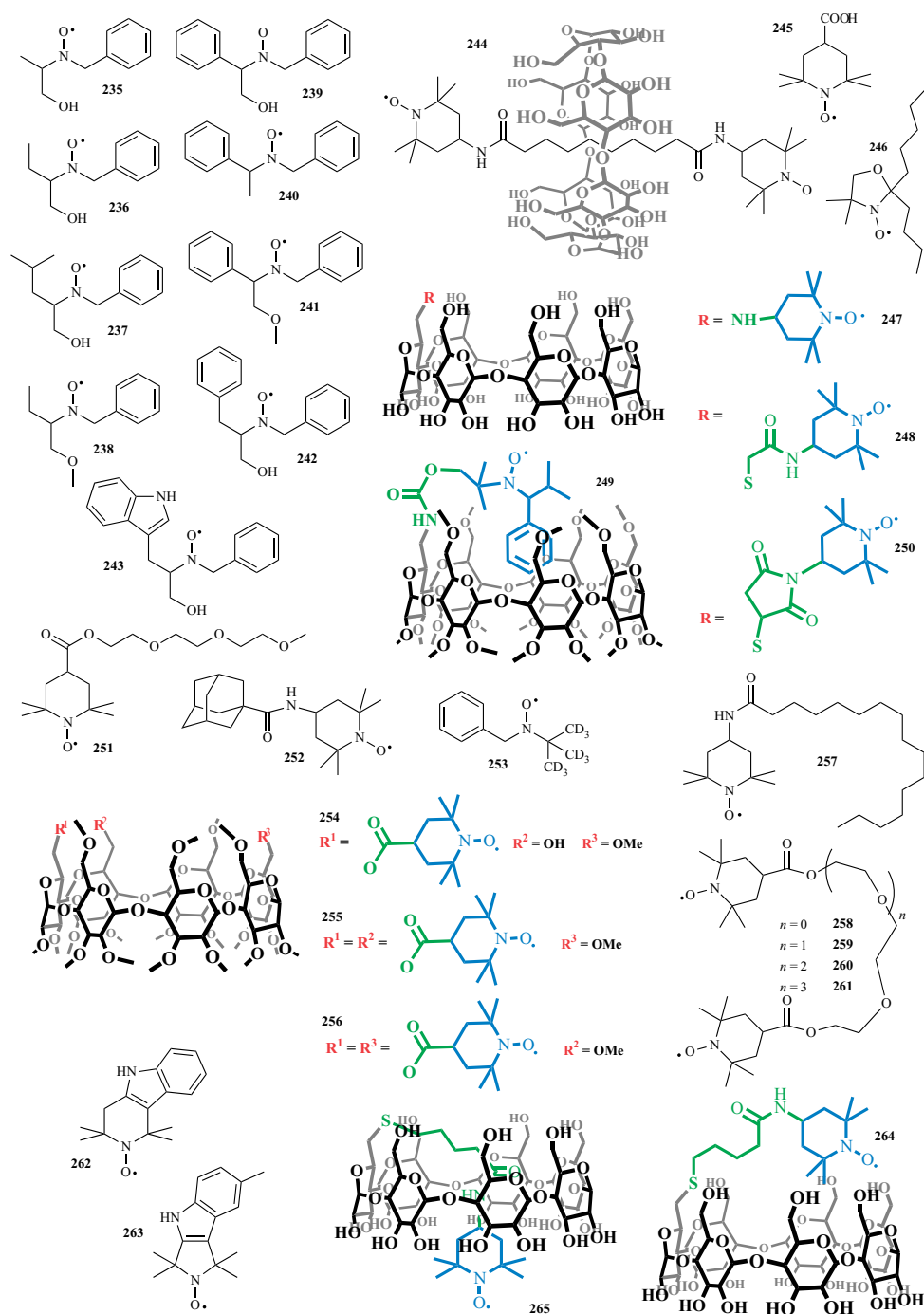


Figure 33 Mononitroxide spin probes used for EPR monitoring of CD recognition, and covalent nitroxide appended cyclodextrins.

within the methoxy groups or perhaps hampering (steric reasons) the self-, weak inclusion of the aromatic group inside the cavity.^{364,365} The same year, Lucarini and coworkers reported the first spin-labeled dumbbell-shaped rotaxane with a bis-TEMPO stoppered axle and α -CD as the wheel component (**244**).³⁶⁶ 5-DSA **4**, 7-DSA **5**, 12-DSA **6**, 16-DSA **7**, and 5-DMS **207** were used to explore the aggregation of β -cyclodextrin in water.³⁶⁷

Bis spin-labeled cyclodextrins with TEMPO moieties attached on the primary rim, **255** and **256**, have been prepared and their host guest binding properties investigated in water by EPR, particularly the modulation of the distance between the spin centers as a consequence of guest binding inside the CD cavity.³⁶⁸ A similar approach was done using bis spin-labeled oligoethylene-glycol chains **258–261**.³⁶⁹ Lucarini and coworkers showed that it was possible to determine (i) the rate of distribution of organic substrates between cyclodextrin, micelles, and water³⁷⁰ and (ii) to explore the competitive binding of alcohols to β -CDs using **231** (Figure 32) and **253** (Figure 33).³⁷¹ A TEMPO-cyclodextrin-based rotaxane has also recently been prepared (**265**), which exhibited an improved persistency of the attached spin probe under reductive conditions.³⁷² TEMPO **1**, CAT-16 **175**, C12NO **198**, 5-DD **246**, 5-DSA **4**, and 16-DSA **7** were used to probe the cavities of α -CD, β -CD, HP- β -CD, RM- β -CD, and the water-soluble, disulfide-cross-linked, polymeric β -CD-based nanocapsules (CDS)_n.³⁷³ 5-DSA **4**, 16-DSA **7**, long alkyl chain esters derived from TEMPO **196** and **199**, and the amide analog **257** were used in a first study,³⁷⁴ and nitroxides **262** and **263** in a second,³⁷⁵ to prepare solid host guest complexes with β -CD and γ -CD and to study the temperature dependence of the guest dynamics by EPR in the solid state. Using 5-DSA **4** and the cholestane nitroxide **13**, Grammenos *et al.*³⁷⁶ investigated the action of RM- β -CD on living cells (HCT-116). EPR spectroscopy was used to explore the mobility of TEMPO **1**, 4-carboxy-TEMPO **245**, 4-amino-TEMPO **40**, and 4-hydroxy-TEMPO **156** spin probes in viscous cyclodextrin solutions.³⁷⁷ Radicals DPPH **332** (Figure 39) and CAT-16 **175** have also been used to study the interaction of human serum albumin with β -CD and sodium dodecyl sulfate.³⁷⁸

Cyclodextrins have also found an interesting application as stabilizing agents regarding nitroxide

spin adducts issued from the spin trapping of unstable free radicals by nitrones and others spin traps.^{379–382}

2.2.4 Nitroxides with Calixarenes

Calixarenes (or resorcinarenes) are phenolic (or resorcinol)-based molecules whose aromatic rings are connected by methylene bridges in a macrocyclic manner, having a relatively large variety of sizes and flexibility often distinguished by the number of repeating aromatic units inside the macrocycle.^{383–385} As for cyclodextrins, it seems that the first calixarene studies involved spin-labeled calix[4]- and calix[6]arenes **266** and **267** carrying two TEMPO-type nitroxides (Figure 34) and able to recognize alkali metal cations³⁸⁶ in a manner reminiscent of spin-labeled crown-ethers (see Section 2.2.2 above). The presence of the cation complexed by the multiple appended ethylene glycol chains modulate the distance and so the exchange interaction between the two nitroxides affording characteristic EPR patterns.

In this line, a series of nitronyl nitroxide grafted calix[4]arenes **270–273** were then developed with **272** being sensitive to Zn²⁺ complexation by two appended bipyridines,³⁸⁷ while the more spatially restricted analog **273** with two bipyridine bridging arms connecting the two calixarenes did not show cation complexation (Figure 34). Li *et al.* reported several studies of calix[4]arenes carrying one or two *tert*-butyl nitroxide moieties **274–279** in which the appended spin probes served (i) to monitor conformational exchange between the cone and the 1,2-alternate positions,³⁸⁸ (ii) to sense the presence of silver ions,³⁸⁹ and (iii) to investigate the influence of solvent, temperature, steric hindrance, and complexation of silver ions on molecular conformations of the macrocycles.³⁹⁰ Rebek and coworkers reported the use of the tetrasubstituted resorcinarene **268** with four TEMPO moieties for the recognition of small molecules and the process was followed by EPR spectroscopy.³⁹¹ The spin labeling of a calixarene analog in the 1,3-alternate conformation **280** allowed to reach new macrocyclic high-spin molecules (S = 2) with expected applications as molecular magnetic materials or magnetic chemical sensors.³⁹² As for cyclodextrins again, the noncovalent inclusion complexation

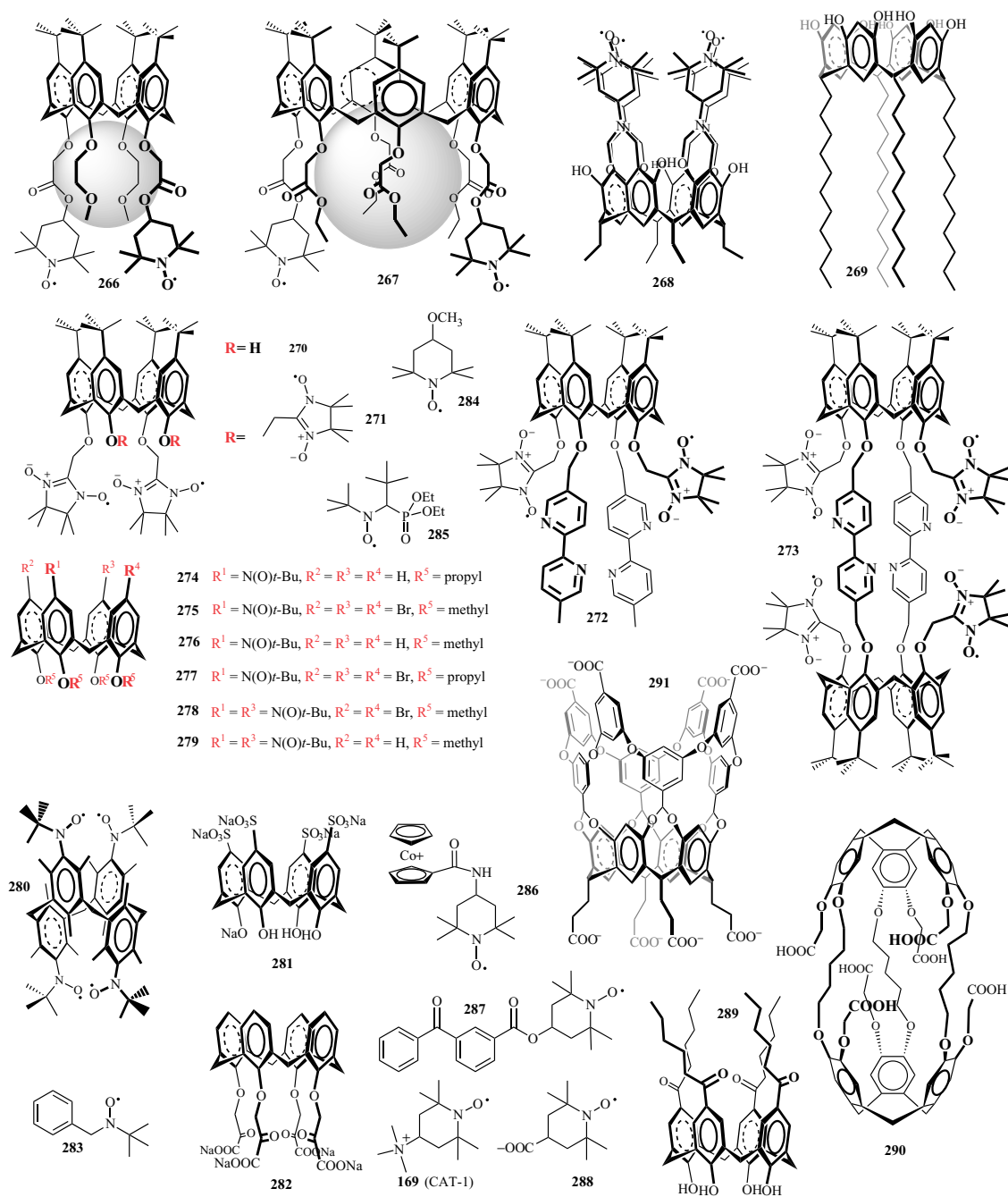


Figure 34 Covalently and noncovalently bound nitroxides for EPR monitoring of weak intra- and intermolecular interactions in calixarenes and resorcinarenes.

(exploring sizable cavities of macrocyclic cavitands) of nitroxide spin probes has been widely applied to calixarenes. In 1996, the hydrophobic cavity of **290**, a cryptophane-type facing, covalent dimer of a cyclotrimeratrylene molecule was explored by TEMPO **1**, TEMPONE **132**, TEMPAMINE **40**, and TEMPOL **156** (Figure 34).³⁹³ Later, Lucarini and coworkers used BTBN **231** to explore the cavities and binding properties of water-soluble calixarenes **281** and **282**³⁹⁴ and showed that the inclusion phenomenon of the probes produces marked differences in the EPR pattern corresponding to the included nitroxide with respect to the free radical. Solid-state supramolecular approaches featuring inclusion complexation of SG1 nitroxide **285** inside dimeric capsular hosts based on acyl-calix[4]arene **289** have also been described.³⁹⁵ Ananchenko and coworkers included TEMPO **1**, 4-methoxy-TEMPO **284**, and other 4-substituted TEMPOs in an organic zeolite host, made of crystalline **289**, and they diluted the probes with an organic counterpart fitting well the cavity of the repeating capsular assembly for expected applications as new magnetic materials, pH probes, or MRI contrast agents.^{396,397} Ramamurthy and coworkers reported nice examples of electron spin–spin superexchange³⁹⁸ and electron spin polarization transfer³⁹⁹ between included bulky

nitroxides **287** and structural analogs of **284** bearing linear alkyl chains from C2 to C10⁴⁰⁰ inside a dimerizing negatively charged capsule **291**₂ and the positively charged nitroxide CAT-1 **169** in the bulk solvent (Figure 34). A very nice and appealing self-assembling system based on resorcinarene **269**, which hexamerizes in water-saturated CH₂Cl₂ solutions, was studied by EPR using TEMPO-like spin probes **40**, **132**, **156**, **169**, and **286** to explore the inner space⁴⁰¹ and outer space⁴⁰² of the resulting giant cubic assemblies. Water-soluble calix[6]- and calix[8]arene analogs of **281** have been studied by EPR using spin probe **215** and structural analogs carrying cyclohexyl or cyclopentyl groups instead of the phenyl and for which several directional-type inclusions were identified (*tert*-butyl-in and phenyl-in and cyclohexyl-in or cyclopentyl-in inclusion complexes).^{403,404} The addition of alkali salts was observed to increase the binding of the probe toward the macrocyclic host.⁴⁰⁵ Calix[4]arene molecules carrying nitroxides are also currently being studied as new magnetic materials and contrast agents,^{406–409} but even though the radical center can be considered as a reporter of the magnetic information, it is not a spin probe in the sense developed so far in this article. There is also an example of structural analogs of **268** bearing linear alkyl chains of different length in which the four

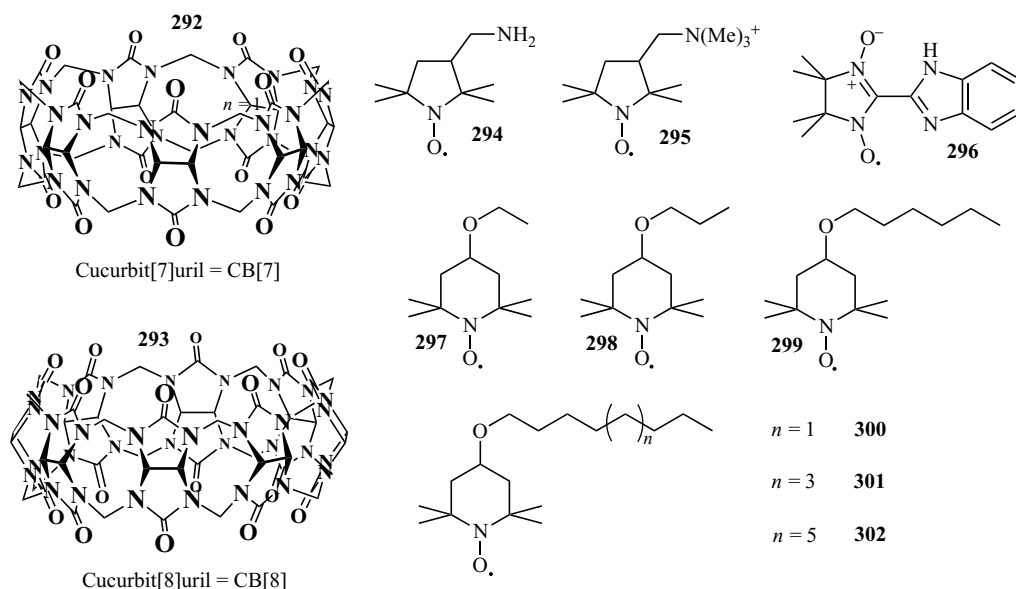


Figure 35 CB[7] and CB[8] macrocyclic hosts which have been investigated using nitroxides in aqueous solutions.

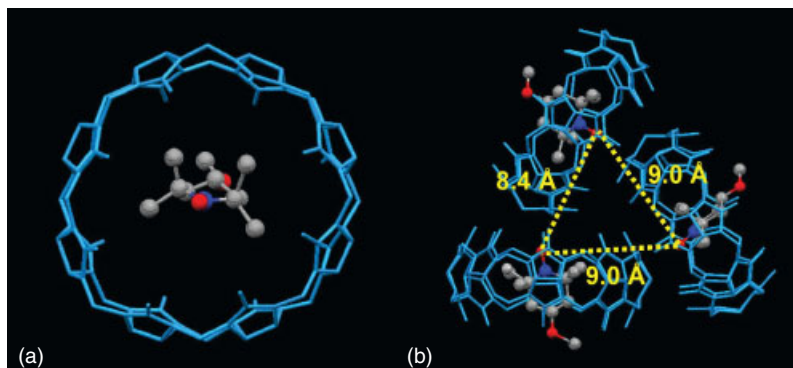


Figure 36 X-ray view of the inclusion complex of **284** in CB[8] and supramolecular formation of the **284** @ CB[8]₃ trimer supraradical. [Reprinted with permission from Ref. 417. Copyright 2009 American Chemical Society.]

TEMPO moieties are efficient radical scavengers and the resorcinarene displays interesting antioxidant and antiradical activities.⁴¹⁰ Verdazyl radicals have also been grafted onto calixarenes with the general idea of using the verdazyl-labeled macrocycles as spin probes to monitor recognition events of the newly prepared compounds.^{411,412}

2.2.5 Nitroxides with Cucurbiturils

Cucurbit[*n*]urils (CB[*n*], *n* = 5, 6, 7, 8, and 10) are a relatively new family of synthetic macrocycles possessing a hydrophobic cavity delineated with two identical carbonyl fringed portals.^{413,414} The constricted cavity tends to accommodate a variety of guests with higher selectivity and binding constants than with the corresponding cavitands of the CD or calixarene families. Mainly due to the principle of structural complementarity, only CB[7] and CB[8] have been used until now with nitroxides and nitronyl nitroxides (Figure 35).

Lucarini and coworkers first recognized the potential of using nitroxides to investigate the interior of these fascinating macrocycles. In 2007, they published a paper in which they showed that TEMPO **1** is included easily in the cavity of CB[7] **292** ($K_a \approx 2.0 \times 10^4 \text{ M}^{-1}$).⁴¹⁵ Then in 2009, three research groups published three papers about a new supramolecular architecture based on CB[8] **293** and several nitroxides. Lucarini and coworkers focused their attention on **1**, **40**, **132**, and **168** and discovered that in the presence of CB[8], a novel spectrum was observed with seven lines of respective intensities 1:3:6:7:6:3:1 taken as indicative of a

CB[8]-mediated supramolecular interaction of three nitroxides maintained artificially, spatially close to each other.⁴¹⁶ The same year, using CB[8] and nitroxide **284**, Bardelang *et al.*⁴¹⁷ obtained crystals of a supramolecular trinitroxide whose structure was determined by X-ray diffraction and corresponds likely to that of the trimer observed by Lucarini *et al.* in solution (Figure 36). These authors also showed that small nitroxide probes can monitor the assembly of cucurbiturils in water and that CB[7] is a very good agent to protect TEMPO against bioreduction. Finally, also in 2009, the teams of Ottaviani and coworkers published a systematic investigation of a large family of TEMPO such as nitroxide (**1**, **40**, **132**, **156**, **168**, **169**, **172**, **174**, **231**, **245**, **284**, and **297–302**, Figure 35) binding to CB[8]⁴¹⁸ in which they also easily observed the formation of the paramagnetic CB[8] trimer.

In 2010, Bagryanskaya and coworkers reported the use of five-membered ring nitroxides **64**, **65**, **155**, **294**, and **295** to probe the CB[7] cavity in water.⁴¹⁹ They showed that the apparent *pK* of the investigated CB[7] mixtures with these protonable nitroxides increased with CB[7] concentration presumably as a result of the strong tendency of cucurbiturils to stabilize positively charged guests via their two carbonyl crowns. They also showed that CB[7] is a very good candidate to protect several nitroxides toward biologically relevant reductive species such as ascorbate via guest inclusion inside its cavity. Finally, Vostrikova and coworkers recently published a study on the nitronyl nitroxide **296** with CB[8].⁴²⁰ Interestingly, depending on the preparation mode of the inclusion complexes, the stoichiometry is different. In the first complex

of 1:1 CB[8]:**296** type, the macrocycle suppress the ferromagnetic interaction of the guest when considered alone. However, in the second complex of 3:2 CB[8]:**296** type, one CB[8] molecule seems to “supramolecularly clip” two guests that π - π stack inside the cavity, whereas the expelled tetramethylimidazolidinyl fragments are capped by two other neighboring CB[8] molecules. In such a structure, the ferromagnetic interaction is recovered due to the structure directing effect of CB[8], which maintain the nitroxides close enough to overlap their phenyl π -orbitals.

2.2.6 Free Radicals with Metal-Organic Polyhedra (MOP)

In 2004, Fujita and coworkers reported the use of an MOP of the octahedral cage-type **303** to include and photooxidize adamantane **308** by means of a free radical mechanism proceeding by a guest-to-host photoinduced electron transfer (Figure 37).^{421,422} Since then, his research group has published several papers about spin cages, the probing of the interior of these elegant cages by stable radicals and cage effects with respect to self-assembled free radicals and how they can mediate through space spin interactions.

For example, the nitronylnitroxide **312** was used to probe the interior of MOP **306**.⁴²³ Two molecules of nitroxide **312** are also found in the cage as a result of weak hydrophobic forces. This is interesting because there seems to be a true cage effect which “forces” the nonassociative radicals to interact through space and produce spin–spin interaction mediated by the restricted cavity of MOP **306**. Using the pH-sensitive radical **313**, they showed that the spin interaction can be controlled by pH by means of the rate of included radicals in MOP **307**.⁴²⁴ Later, they investigated the inclusion of radicals **1**, **312**, **313**, and **314** in MOPs **306** and **307** and how the cage can modulate spin interactions by means of enforced supramolecular interactions inside the restricted cavities.⁴²⁵ Thus, they showed that the doublet state of the free radicals in aqueous solutions can be switched to the triplet state in the inclusion complex and added heat as a supplementary stimulus to control guest encapsulation and release from the MOPs and so mediate intermolecular spin interactions. Finally, a new ligand based on a verdazyl radical was developed for the construction of organic spin cages (Figure 38).

A new octahedral spin cage **316** (M_6L_4 type) was prepared and new host guest spin–spin interactions were identified based on the inclusion of radicals

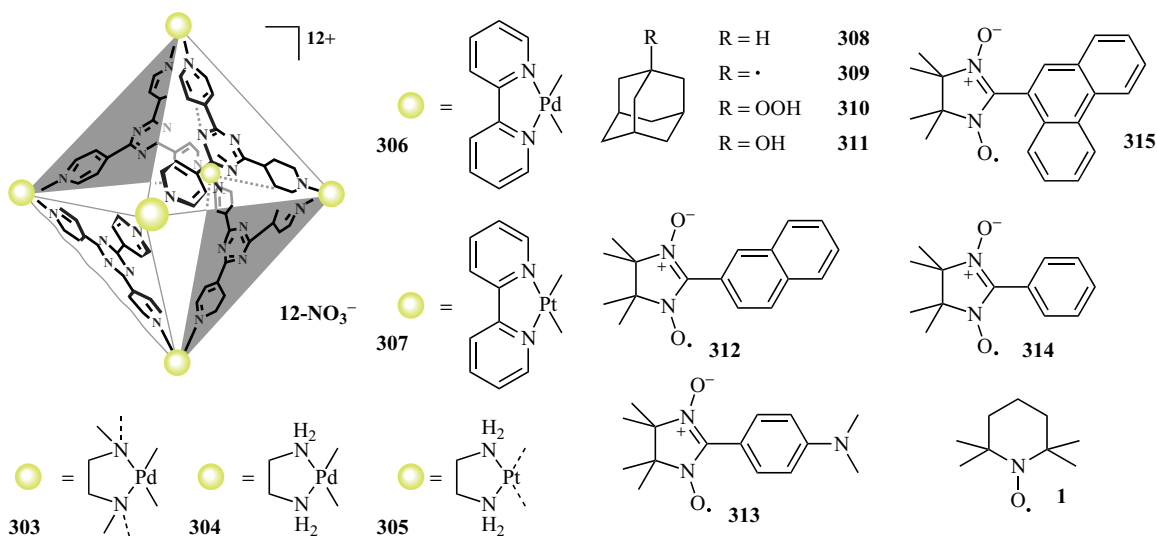


Figure 37 Structure of the metal–ligand cages used to encapsulate nitroxides, free radical precursors and photooxidized products. [Adapted with permission from M. Yoshizawa, S. Miyagi, M. Kawano, K. Ishiguro, M. Fujita, *J. Am. Chem. Soc.*, 2004, **126**, 9172–9173. Copyright 2004 American Chemical Society.]

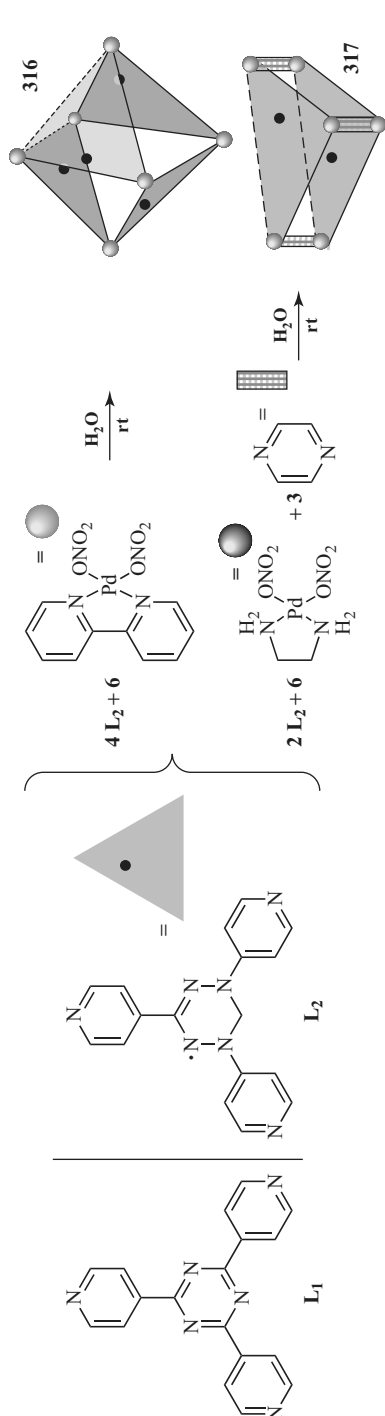


Figure 38 Ligand L_1 used in the first MOP cages developed by Fujita *et al.* and a verdazyl radical-type ligand L_2 for the preparation of organic spin cages (MOP type).

312 and **315**.⁴²⁶ These new complexes are expected to find applications as new spin probe reagents and MRI contrast agents. The reaction of ligand L_2 with a palladium precursor and pyrazine afforded a novel prism-shaped organic pillared spin cage **317** for the designed inclusion of open-shell metal complexes and the finding of guest tunable spin materials.⁴²⁷

2.2.7 Self-Assembling Free Radicals

Among the free radicals that have been reported to self-assemble, there is one class of compounds responding to the presence of metal ions that can induce the self-assembly to afford molecular architectures of higher complexity. This is the case for two molecules of iminonitroxyl diradical **318** that wrap around two silver(I) ions forming a double helical structure (Figure 39).⁴²⁸ Pyrazolate nitroxides **319** and **320** form trinuclear Ni(II) meso-helicates,⁴²⁹ and a μ -NO₃[−] bridged self-assembled two-dimensional silver(I) complex of iminonitroxyl monoradical **321** has also been described.⁴³⁰ Most of the metal ion-templated assembly of nitroxides has been the object of intense studies with respect to molecular magnetism.^{431,432} A C₆₀ molecule has been labeled with a pyrrolidininoxyl-type nitroxide bearing a charged component (**322**) to enhance its tendency to self-assemble due to the amphiphilic nature of the overall structure.^{433,434}

The oligopeptide nOct-Aib-Gly-Leu-Aib-Gly-Gly-Leu-Aib-Gly-Ile-Leu-Lol has been labeled with TOAC (**27**, Figure 4) (nOct-TOAC-Gly-Leu-Aib-Gly-Gly-Leu-TOAC-Gly-Ile-Leu-Ome, nOct-TOAC-Gly-Leu-Aib-Gly-Gly-Leu-Aib-Gly-Ile-Leu-Ome, and Fmoc-Aib-Gly-Leu-TOAC-Gly-Gly-Leu-Aib-Gly-Ile-Leu-Ome) and the possibility to form supramolecular dimers and tetramers investigated (**336**, Figure 39).⁴³⁵ Supramolecular events such as the folding of bis spin-labeled porphyrin one-dimensional (1D) wires induced by the recognition of a rigid planar star-shaped aromatic compound have also been described.⁴³⁶ In this context, this may be considered as spin labeling, but in the vast majority of cases reported, the strategy relied on the grafting of open-shell molecules on compounds previously known to self-assemble in established conditions. TEMPO **1**, 4-amino-TEMPO **40**, and 4-hydroxy-TEMPO **156**

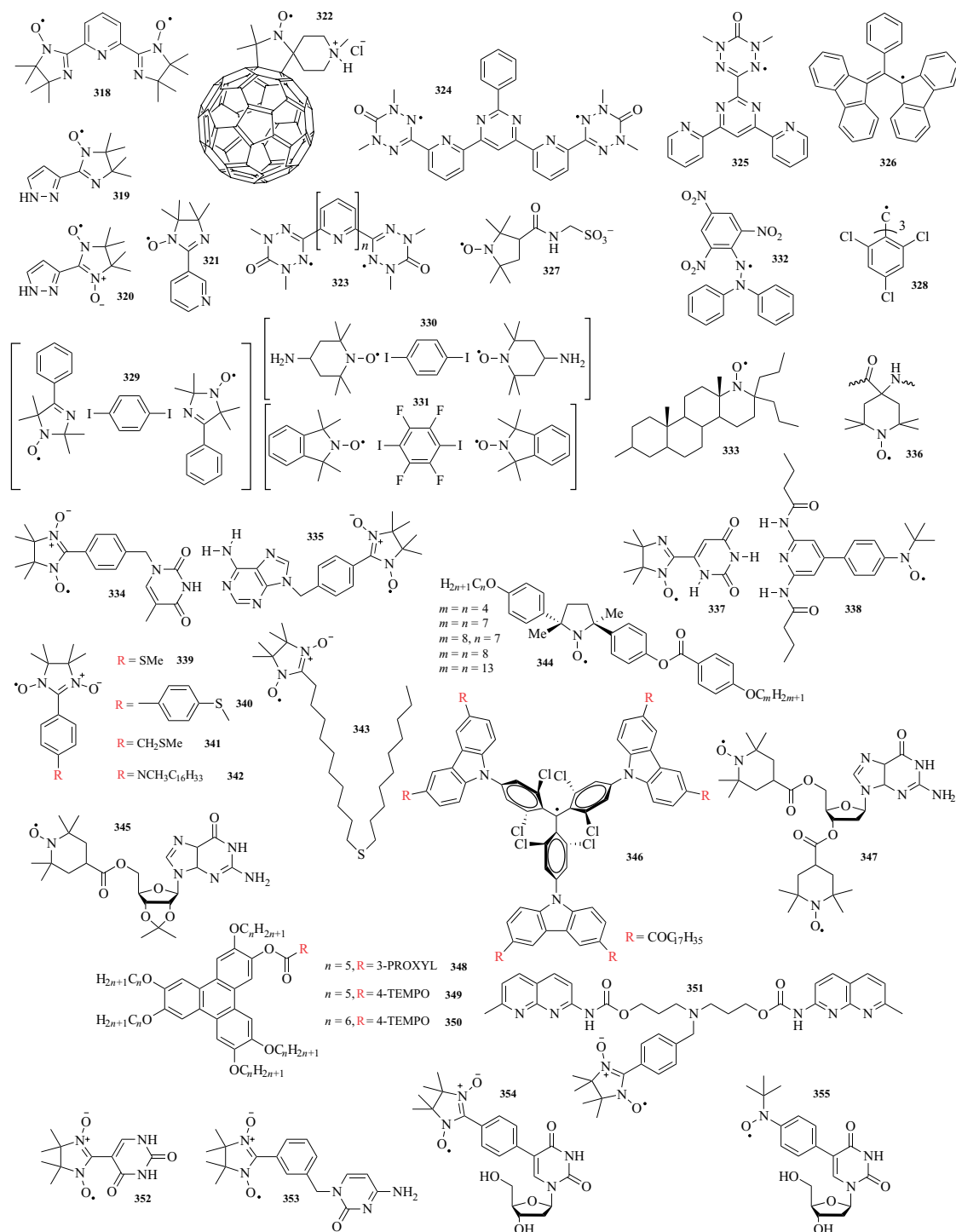


Figure 39 Self-assembling open-shell molecules.

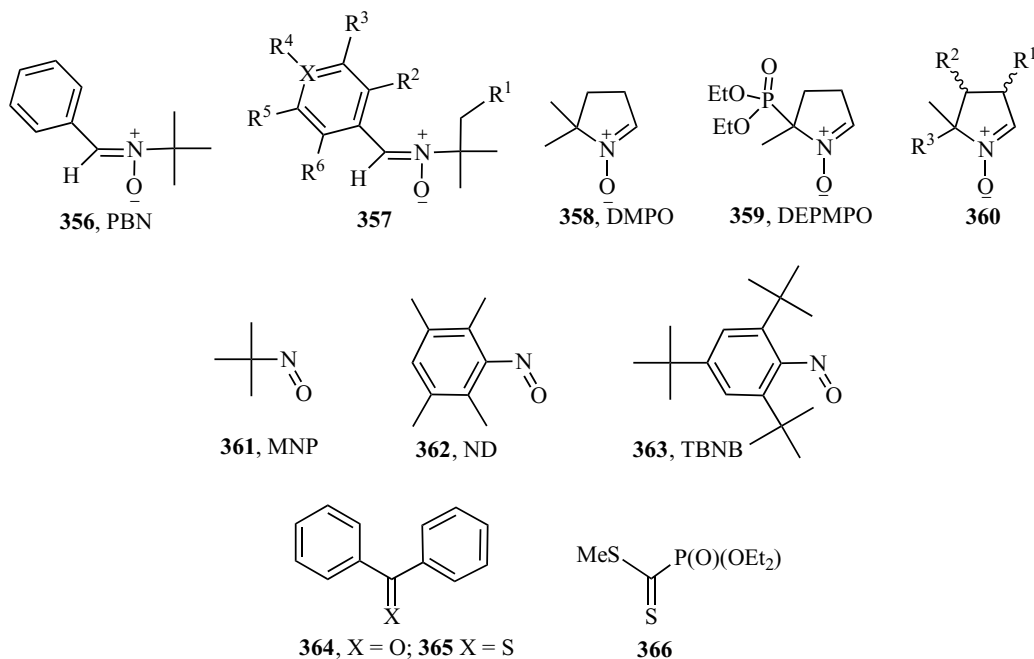


Figure 40 Main spin traps used in EPR/ST.

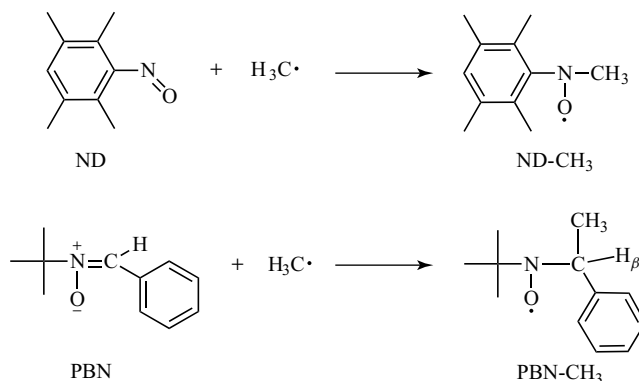


Figure 41 Trapping of methyl radical with phenyl *t*-butyl nitron (PBN) and nitrosodurene (ND).

have been assembled in Laponite films exhibiting 1D antiferromagnet properties.⁴³⁷ The probes CAT-16 **175** and 5-DSA **4** have been observed to aggregate mainly due to confinement and affinity (polar) effects in the large cavities of mesoporous micelle-templated silicas.⁴³⁸ Verdazyl radicals carrying pyridine or pyrimidine groups **323**, **324**, and **325** are believed to be useful building blocks for supramolecular assemblies.⁴³⁹ Nitroxides have also been assembled via directional nitroxide–halogen

interactions in the solid state (**329**, **330**, and **331**, Figure 39).^{440,441} Nitronyl nitroxides **334** and **335** have been assembled by means of Watson–Crick base pairing using adenine and thymine bases substituted with the corresponding radicals.⁴⁴² BDPA **326**,⁴⁴³ trityl **328**,⁴⁴⁴ and DPPH **332**^{445,446} radicals have been observed to aggregate under certain conditions as for the steroid radical STNO **333**,⁴⁴⁷ which self-assembles affording fibrillar networks correlated to its organogelation abilities.

Interestingly, transduction of the chirality from the molecular to the supramolecular level is quite efficient due to the strong chiral junction zones of the gelator. PROXYL-type nitroxide **327** was shown to cocrystallize with bis-(ethylenedithio) tetrathiafulvalene affording the first purely organic

paramagnetic metal.⁴⁴⁸ The iminylnitroxide **337** has shown interesting magnetic properties in the solid state (supramolecular dimer)⁴⁴⁹ and self-organizes with nitroxide **338** using complementary multipoint hydrogen bonding.⁴⁵⁰ Nitroxide labels carrying functional groups (**156**, **159**,⁴⁵¹ **339**, **340**,

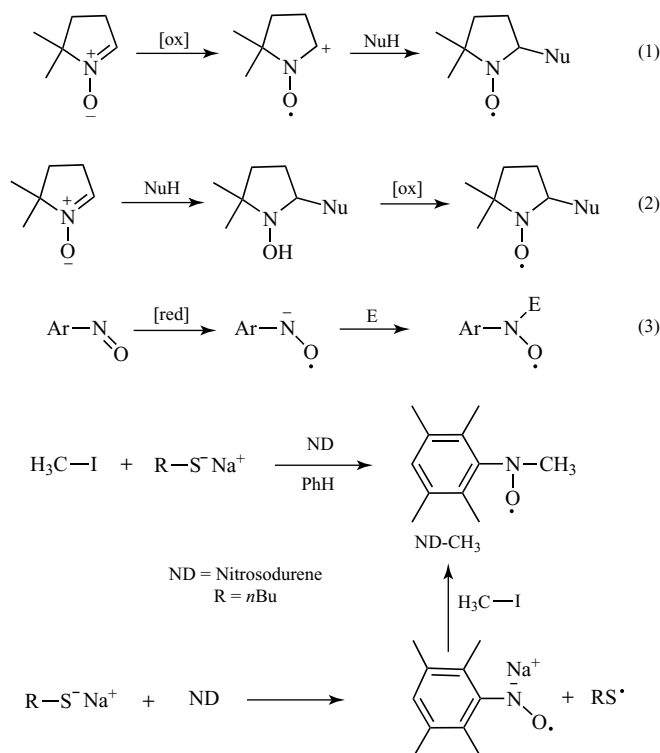


Figure 42 Main drawbacks encountered in EPR/ST experiments.

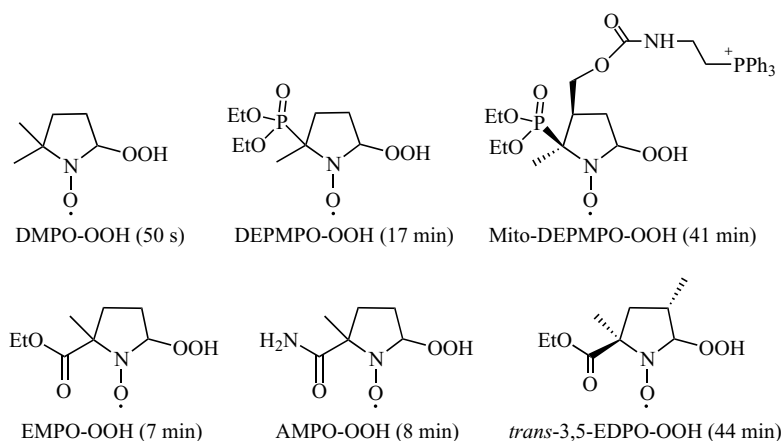


Figure 43 Half-life times of the superoxide spin adducts generated with various pyrroline-*N*-oxides.

341,^{452–454} **342**,⁴⁵⁵ and **343**)⁴⁵⁶ have been used to construct self-assembled monolayers on solid substrates^{457,458} for molecular-based spintronics devices. TEMPO **1**^{459,460} and the methyl ester of 16-DSA **7** radical⁴⁶¹ can be confined and clustered as small aggregates in the channels of the solid host compound TPP. A quite elegant approach at this interface between free radicals and supramolecular chemistry is the development of paramagnetic liquid crystals. A few approaches have been explored using nitroxides (**344** series^{462–465} and radicals **348**, **349**, and **350**)⁴⁶⁶ and trityl radical **346**.⁴⁶⁷ The nitroxide appended guanosine derivatives **345** and **347** have been observed to densely organize around potassium cations in aqueous solutions affording paramagnetic supramolecular octamers⁴⁶⁸ and hexadecamers,⁴⁶⁹ respectively. Eventually, a nitronyl nitroxide was grafted on a naphthyridine carbamate dimer (compound **351**) to target CGG/CGG triads as an addressable position in DNA duplexes.⁴⁷⁰ Nitroxides **352** and **353** have shown interesting magnetic properties in the liquid⁴⁷¹ and organized solid⁴⁷² phases, respectively.

Some ribonucleosides have been labeled by nitroxide spin labels with addition of a—N(O[•])—*t*Bu group on the base part of the structure but the recognition properties were not investigated.^{473,474} The spin-labeled nucleoside **354** has been synthesized and included in the sequence of oligodeoxynucleotides.⁴⁷⁵ The corresponding EPR spectra were sensitive to the degree of hybridization of the complementary strand and spin–spin interactions modulated by the distance between the spin centers. Molecule **355** with π -conjugated nitroxide spin label forms 1D ferromagnetic chains in the solid state.⁴⁷⁶ Finally, the water-soluble trityl radical Ox063 **3** has been reported to trigger the formation of polyelectrolyte networks in a structural manner reminiscent of a zip-like cooperative binding effect.⁴⁷⁷

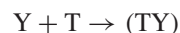
In conclusion, after the first advances in the use of spin probes/EPR to investigate the hollows of a variety of structures and materials, the rules of supramolecular chemistry started to add a predictive component in order to obtain structures of higher complexity and seek for advanced material applications. In this line, one growing fascinating field is that of paramagnetic, crystalline host compounds in which the building block of the supramolecular solid framework is carrying a free radical. Some crystals

have already appeared which hold great promises for the development of supramolecular solid-state recognition with paramagnetic compounds. Some emerging properties as, for example, modulation of the magnetic properties by the careful and subtle use of the (also emerging) rules of crystal engineering are likely to open new fields of development in the coming years.^{478–480} Paramagnetic open frameworks provide the opportunity to entrap functional guests to control bulk solid magnetic properties at will.

3 SPIN TRAPPING

3.1 Principle of Spin Trapping

The trapping of a transient free radical Y[•] with a diamagnetic spin trap T to generate a persistent spin adduct (TY)[•] which, under the actual reaction conditions, could be characterized by its EPR spectrum, constitutes the well-known spin trapping technique, hereafter abbreviated EPR/ST. The spin adduct radical (TY)[•] can be considered as reporting



on the radical chemistry occurring in the system under investigation.

EPR/ST was introduced in the late 1960s^{481–485} and since then it is commonly employed in various domains: organic chemistry, environmental chemistry, toxicology, biology, materials, food chemistry, and so on, and its advantages and drawbacks are largely debated.^{379,486–494} In spite of the enormous progress made in five decades, EPR/ST is still faced with limitations particularly for the investigation of *in vivo* free radical processes. The important literature on EPR/ST illustrates the wide scope of its applications and the continuing efforts to improve its efficiency and reliability.

3.2 Main Spin Traps

A large variety of trapping agents has been developed since the introduction of the spin trapping technique, some are depicted in Figure 40.

The most commonly used spin traps are open-chain (**356** and **357**) or five-membered ring

cyclic nitrones (358–360) and aliphatic or aromatic nitroso compounds (361–363). In both cases, the resulting spin adducts are nitroxides (Figure 41) whose half-life times depend strongly on the type of the trapped radical, the choice of the spin trap, and the experimental conditions. In spin adducts derived from nitroso derivatives (ND-CH₃, Figure 41), the trapped radical is directly bound to the nitrogen of the aminoxyl function, whereas in those from nitrones, it is bound to the carbon atom adjacent to it (PBN-CH₃, Figure 41). The EPR spectrum of ND-CH₃ is a triplet of quartet ($A_N = 1.370$ mT, $A_H(3\text{ H}) = 1.217$ mT, in benzene)⁴⁹⁵ and its formation in a chemical process investigated with EPR/ST can be considered as an evidence of the formation of methyl radicals. The spectrum of PBN-CH₃ is a triplet of doublet ($A_N = 1.496$ mT, $A_H(H_\beta) = 0.375$ mT, in benzene) that contains no direct information on the trapped methyl radical. However, for a PBN spin adduct, the magnitude of the β -hydrogen hyperfine coupling depends on the type of the trapped radical (PBN-OCH₂CH₃: $A_N = 1.415$ mT, $A_H(H_\beta) = 0.250$ mT, in ethanol; PBN-OSiPh₃: $A_N = 1.450$ mT, $A_H(H_\beta) = 0.560$ mT, in toluene), and it can be cautiously used for its identification.

Apart from nitrones and nitroso compounds, many other molecules undergo radical addition leading to more or less persistent adducts. These unconventional spin traps, such as 364, 365, and 366,⁴⁹⁶ can be specific for a particular family of radicals and should not be disregarded when designing an EPR/ST experiment.

It is worth mentioning that the results of an EPR/ST experiment must be interpreted with caution, since the EPR observation of a spin adduct does not necessarily imply the occurrence of a direct free radical trapping process (Figure 42).^{497–502} For example, the formation of the ND-Me spin adduct, observed when MeI is reacted with *n*BuS[−]Na⁺ in benzene in the presence of ND, does not result from the direct trapping of methyl radicals (Figure 42).⁵⁰¹ The chemical process corresponding to (2) (Figure 42) is called *inverted spin trapping*.⁴⁹⁹

Moreover, the failure to detect a spin adduct does not necessarily mean that radical species were not present in the investigated system. For example, nitroxide spin adducts can be rapidly reduced to EPR-silent hydroxylamines and that constitutes a main limitation of *in vivo* EPR/ST experiments.²³⁵

During the past three decades, EPR/ST has been extensively used to investigate the contribution of free radicals to various biological processes, and problems connected to oxidative stress have received a special attention.^{382, 487–493} The superoxide radical anion (O₂^{•−}) and the hydroxyl radical (HO[•]) play a major role in oxidative stress, and important efforts have been devoted to the search of spin traps especially suited to characterize these species (see **Oxidative Damage to Proteins**). Nitroso compounds are poorly water soluble and they yield short-lived spin adducts with oxygen-centered radicals, then, their use in biological EPR/ST is rare. Nitrones are reasonably water soluble, poorly toxic, and they usually generate more or less persistent spin adducts with oxygen-centered radicals. Although the half-life time of the spin adduct of superoxide with DMPO (DMPO-OOH, Figure 43) is only 1 minute in phosphate buffer at pH 7.2, this popular spin trap has been widely used in biological EPR/ST. In 1995, Tordo and coworkers⁵⁰³ showed that replacing one methyl group of DMPO with a diethoxyphosphoryl group (DEPMPO, Figure 40) leads to a significant increase (about 15 times) of the half-life time of the corresponding superoxide spin adduct (DEPMPO-OOH, Figures 43 and 44). Since then, a large number of pyrroline-*N*-oxides (360, Figure 40) bearing an electron-withdrawing group on C5 and various substituents on C3 and (or) C4 have been prepared,^{379, 493, 503–506} and for some of them, the half-life time ($\tau_{1/2}$) of the corresponding superoxide spin adduct is larger than 30 minutes.

The values of $\tau_{1/2}$, in phosphate buffer at physiological pH, for the superoxide spin adducts of DMPO, DEPMPO,⁵⁰³ Mito-DEPMPO,⁵⁰⁴ EMPO,⁵⁰⁵ AMPO,⁵⁰⁶ and *trans*-3,5-EDPO⁵⁰⁷ are shown in Figure 43, and the EPR spectrum of Mito-DEPMPO-OOH is shown in Figure 44.

4 CONCLUSION

The microenvironment and the motional dynamics of a free radical influence strongly the shape of its EPR signal; thus, nitroxides and to a lesser extent trityl radicals are routinely used for EPR probing of various chemical and biological systems. In this article, we have illustrated the strong potential of this approach in different domains: determination of the structure of biological membranes, proteins,

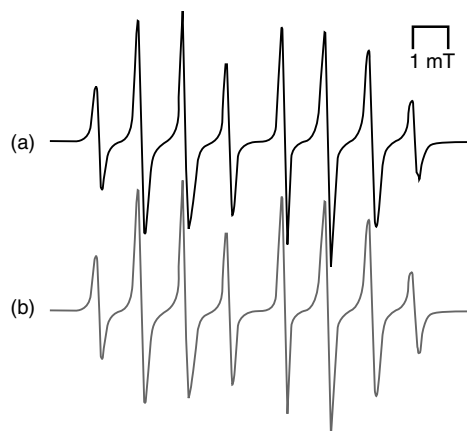


Figure 44 Experimental (a) and calculated (b) EPR spectra of Mito-DEPMPO-OOH spin adduct at rt in phosphate buffer, pH 7.3.⁵⁰⁴

DNA, RNA, and supramolecular assemblies and pH measurements, oxymetry, detection of transient radicals, and so on. In the next few years, we can expect that the design of new spin labels, spin probes, and spin traps and developing the use of pulsed and high-frequency EPR techniques will expand the frontiers of this research area.

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Radical Thiol–X Click Chemistry

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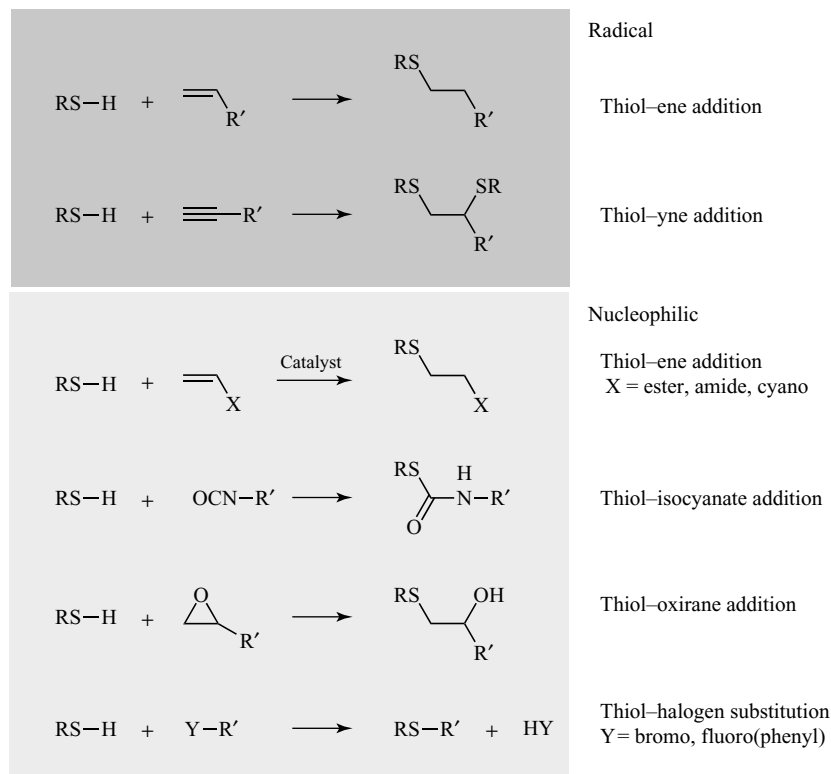
1 INTRODUCTION

The free-radical addition of thiols or mercaptans to unsaturated compounds (Scheme 1), which has been known for more than 100 years,¹ has become a well-established and versatile tool in organic synthesis² as well as in macromolecular and surface chemistry.^{3–9} Major reasons for the popularity and success of the hydrothiolation reaction are the ease and convenience of handling, its robustness, and its wide applicability. Owing to the often high reactivity and low selectivity of radical species, addition reactions may be accompanied by side reactions such as, for instance, radical–radical coupling, chain transfer, and polymerization as well as by *cis/trans* isomerization of olefins. For properly chosen reaction conditions, however, the radical additions of thiols to carbon–carbon double bonds (thiol–ene) and triple bonds (thiol–yne) can proceed smoothly in the absence of side reactions and even have “click” characteristics.^{10–15} The concept of “click” chemistry, as was introduced by Sharpless *et al.* 10 years ago,¹⁶ demands that a reaction be modular and wide in scope, gives quantitative yields, generates (if any) inoffensive by-products which can be removed by nonchromatographic methods, and is stereospecific (but not necessarily enantioselective). Practically, the process should be simple to perform and be accomplished with readily available reagents either in bulk or in environmentally benign solvents, and the products should be easily isolated. A click reaction ought to

be fast and be selective for a single product, and hence exhibit orthogonal reactivity. Polymer click chemistry further demands that reactants should be used in stoichiometric amounts, especially when it concerns polymer–polymer coupling, and that the products can be purified on a large scale.¹⁷

Most of these criteria can be readily fulfilled by radical thiol addition reactions, though quantitative yields can sometimes be achieved only when the thiol is used in (large) excess. Apart from radical reactions, thiols can react in a number of nucleophilic addition and substitution reactions. Nucleophilic thiol–X reactions, likewise classified as click reactions, include the base-catalyzed Michael-type thiol–ene addition to activated double bonds bearing electron-withdrawing groups,¹⁸ thiol–isocyanate addition,¹⁹ thiol–oxirane addition,²⁰ and thiol–halogen substitutions^{21,22} (Scheme 1). The chemical structures of reactants and reaction conditions are therefore crucial parameters deciding the orthogonality and click characteristics of a thiol–X reaction. For other reactions of the click family, such as the 1,3-dipolar Huisgen azide–alkyne cycloaddition which is regarded as the gold standard of click chemistry,¹⁶ orthogonality may not be an issue but the required usage of explosive compounds (azide) and potentially toxic transition-metal (copper) catalysts can be.

In the first part of this article, the mechanism of radical addition of thiols to carbon–carbon multiple bonds is briefly discussed. Description of the mechanism may not be all comprehensive but



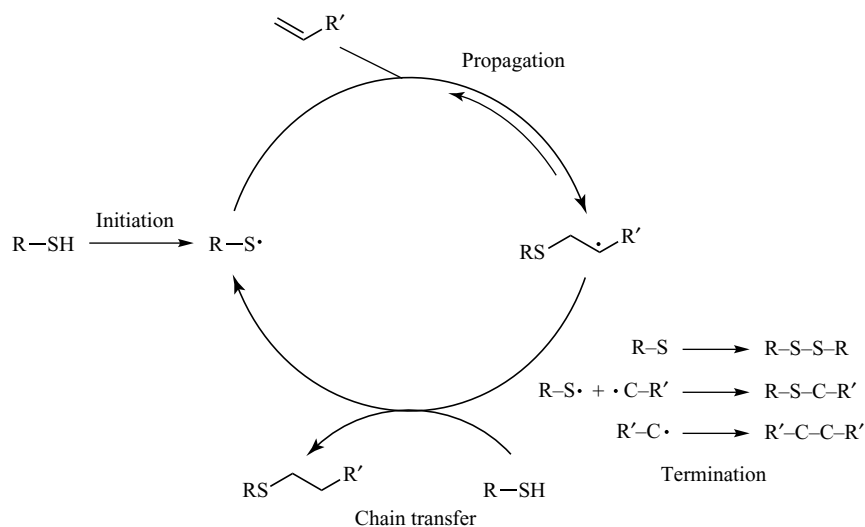
Scheme 1 Radical and nucleophilic thiol-X click reactions.

restricted to what is relevant for click chemistry. The following parts are devoted to the application of radical thiol-X chemistry in synthetic organic, macromolecular, and colloid/surface chemistry. Published work until December 2010 has been considered for this review.

2 MECHANISM OF RADICAL THIOL-X ADDITION

Radical thiol-X chemistry is the radical addition of thiols to unsaturated carbon-carbon bonds, either to alkenes or alkynes, proceeding via a chain process involving initiation, propagation and chain transfer, and termination steps.^{2-4,12,23} Mechanisms and possible side reactions of radical thiol-ene and thiol-yne addition reactions will be described first, followed by a discussion of different types of initiation systems that may influence the efficiency of the process.^{4,24}

The addition of a thiol to a carbon-carbon double bond is a three-step process (Scheme 2): generation of the thiyl radical, reversible addition of the thiyl radical to the double bond, preferentially in anti-Markownikoff orientation, and chain transfer of hydrogen to the intermediate carbon radical species. For radical thiol-ene chemistry, this hydrogen is ideally provided by another thiol group, thereby creating another thiyl radical. However, chain transfer may also occur via solvent molecules, especially halocarbons and aromatic hydrocarbons. The propagation/chain transfer cycle can turn several hundreds to thousands times before termination occurs by radical-radical recombination. Generally, the second step of chain transfer is the rate-limiting step. Therefore, the structure of the thiol (and solvent) strongly influences the kinetics of the reaction. For instance, aromatic thiols are far more efficient chain transfer agents than aliphatic thiols because of the possible stabilization of the radical species by resonance. Also, the thiyl radical addition to carbon-carbon double bonds is reversible, and the intermediate



Scheme 2 General mechanism of radical thiol–ene addition.¹³

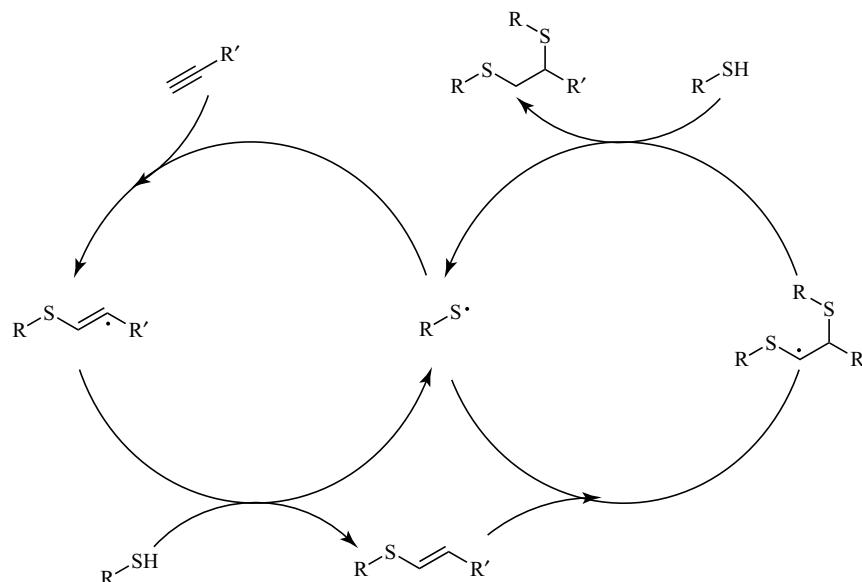
carbon radical may eliminate a thiyl radical with the formation of an alkene under cis/trans isomerization.²⁵ Stereochemistry can be maintained when the intermediate radical cannot disturb this stereochemistry as, for instance, for unsaturated rings, for which the product (mixture) can be determined by the relative rates of proton transfer to the carbon radical.

The rate of addition to alkenes is strongly dependent on the substituents. For aliphatic molecules, the addition rate decreases in the series from strained cycles (e.g., norbornene), to terminal alkenes, to cis double bonds, to trans double bonds.²⁶ If other neighboring groups are present, in vinylic as in an allylic position, the prediction of the reactivity becomes more complicated and in some cases also mixtures of products are obtained. The presence of halogens, heteroatoms, or groups containing heteroatoms results in the formation of products with the sulfide group on the vicinal position. Thioethers or halogens in allylic position can lead to a β -elimination upon thiyl radical addition to the double bond, yielding a new radical (either another thiyl or a halogen radical) and a new double bond (allyl sulfide). The radical addition to conjugated π systems affords a delocalization of the radical, so that chain transfer of a proton can occur on multiple positions, thereby yielding a mixture of products. When strained cycles, for example, cyclopropanes or oxiranes, are present as substituents, the carbon

radical formed after addition can also delocalize by a ring-opening mechanism, resulting in the formation of mixtures of isomeric structures after proton transfer.²

The mechanism of thiyl radical addition to carbon–carbon triple bonds (Scheme 3) is similar to the aforementioned chain process.²³ Addition of a thiyl radical to the alkyne moiety proceeds with anti-Markovnikoff orientation, again producing the more stable carbon radical. Proton transfer yields a vinyl thioether (sulfide) as intermediate product. Generally, the cis product of the first addition is found in higher abundance, which may be attributed to a preferential hydrogen transfer to the cis radical or the conformation of the intermediate radical. The intermediate alkene can participate in a thiol–ene addition, which usually yields the vicinal product (the geminal product is formed only when the neighboring group is aromatic; dithioacetals are formed in the course of nucleophilic thiol–yne additions).

The intermediate vinyl thioether is supposed to have a considerably higher reactivity toward thiyl radical addition than the alkyne.² This may hold true for thiol–yne photopolymerizations, for which the second addition was found to be about 3 times faster than the first,²³ but seemingly not for the thiyl radical addition to cyclooctyne²⁷ or alkynyl amino acids.²⁸ In contrast, the nucleophile-catalyzed



Scheme 3 General mechanism of radical thiol-yne addition.²³

addition of thiol to a vinyl thioether is about 1000 times slower than that to the triple bond.²⁹

The aforementioned mechanism of radical thiol additions indicates the possible occurrence of a number of side reactions. Radical thiol-X additions do not generally proceed as click reactions except for a limited number of cases (without severely losing the characteristics of being modular and wide in scope). Regarding the nature of the unsaturated group, terminal alkenes or alkynes and cyclic structures such as norbornene are preferred. In case of electron-deficient alkenes, for example, (meth)acrylates, special care should be taken to avoid (homo)polymerization of the alkene moieties. Furthermore, the presence of other species that can participate in radical reactions should be avoided, for instance, hydroquinones, anilines, or sulfoxides. On the other hand, thiol-ene single additions (but not polymerizations) can be performed in the presence of air or oxygen without severely affecting the kinetics but introducing an additional hydrogenperoxide moiety.⁴ It should also be considered that bases (amines) can deprotonate thiols ($pK_a \sim 10$) and inhibit the radical addition reaction.

Radicals can be generated in a variety of ways, the most straightforward ones involving the use of thermal or photochemical initiators (see **Overview of Radical Initiation**). Radical initiators can

be divided into two different classes, namely, initiators undergoing cleavage (type I) and initiators abstracting hydrogen (type II).²⁴ Examples of type I initiators include azo compounds (e.g., azobisisobutyronitrile (AIBN)) and peroxides (e.g., benzoyl peroxide (BPO)) and also photoinitiators (e.g., (2,4,6-trimethylbenzoyl)diphenylphosphine oxide (TMDPO) and 2,2-dimethoxy-2-phenyl acetophenone (DMPA)). These compounds undergo cleavage upon heating or irradiation with UV light with the formation of two radical species. Either one or both radicals can add to the unsaturated carbon-carbon bond directly or abstract hydrogen from a thiol to initiate the addition reaction. Type II photoinitiators, for instance benzophenone, react in their triplet excited state with a hydrogen donor, that is, thiol, to generate the thiyl radical and initiate the addition reaction.²⁴

Thiyl radicals can also be directly generated by either applying high temperature (typically far over 100 °C) or irradiation with UV light (typically using UV lamps with $\lambda_{\max}$ at 254 or 365 nm) or sunlight⁴ or exposure to a ⁶⁰Co radioactive source.² The direct generation of thiyl radicals is preferred for thiol-X click chemistry, as the formation of undesired by-products from chemical initiator fragments is avoided.

3 APPLICATIONS OF RADICAL THIOL-X CLICK CHEMISTRY

Radical thiol additions to unsaturated carbon–carbon bonds may have the characteristics of click reactions as discussed earlier. However, the intermediate radical species tend to undergo side reactions, thus reducing the yields as well as the functionality and purity of the crude products. Crucial parameters for obtaining click characteristics are not only the chemical structures of the reactants (e.g., substitution of the carbon–carbon multiple bond and reactivity of the thiol) but also the nature of the radical source and of the solvent. The relative amounts of the reactants should be chosen such that a quick addition and also hydrogen transfer are always assured. The thiol should therefore always be used in excess. For heterophase reactions, for example, inside micelles or on surfaces, the local concentration and accessibility of unsaturated groups need to be considered.

The following sections of this article discuss applications of radical thiol–X (X = ene and yne) click chemistry for the synthesis of functional materials. These sections comprise organic chemistry (synthesis of organic molecules, peptides, and dendrimers), macromolecular chemistry (synthesis and modifications of polymers and biomacromolecules, hyperbranched polymers, and polymer networks), and colloids and interfaces (modifications and functionalizations of organic and inorganic surfaces).

3.1 Organic Chemistry

Though radical thiol–X click chemistry has mostly been applied in macromolecular chemistry, the chemistry has been used earlier in the synthesis of especially bioorganic molecules. However, even when the conversion of reactants is quantitative, the products are often subjected to elaborate purification, for instance (flash) column chromatography. Such reactions, very strictly speaking, cannot be considered as click reactions. However, this does not mean that these reactions are less useful or not efficient. Especially, short reaction times and tolerance toward most functional groups make this synthetic pathway very attractive for the production of a palette of different compounds, including functional vegetable oils, saccharides, peptides, and dendrimers.

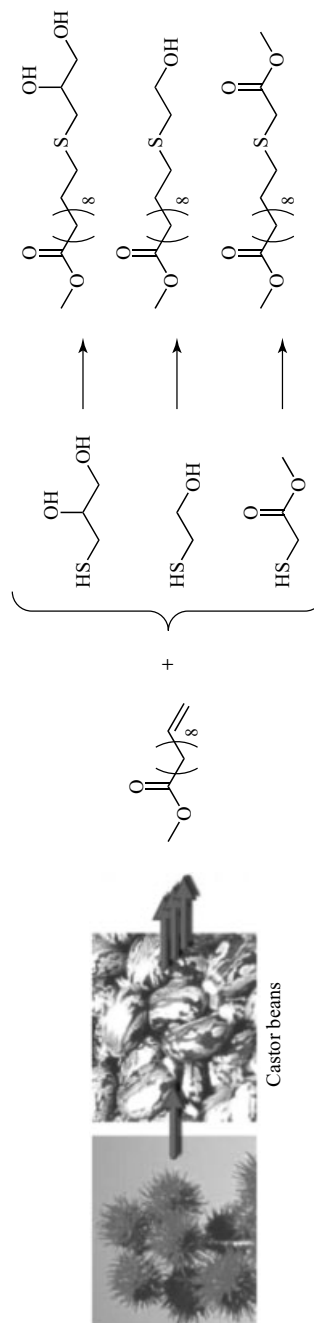
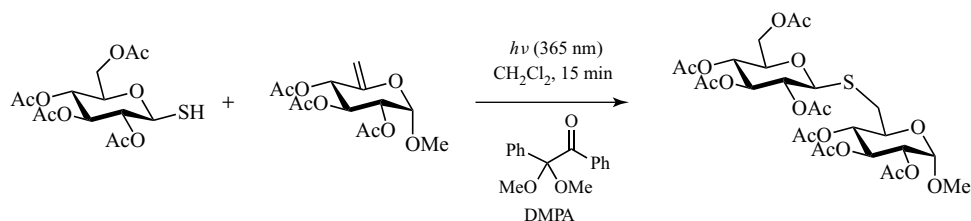


Figure 1 Synthesis of monomers for polyester by thiol–ene chemistry. [Redrawn from Ref. 31. © Wiley-VCH Verlag GmbH & Co. KGaA, 2010.]



Scheme 4 Photoinduced thiol–ene click coupling for the synthesis of thiodisaccharides. [Redrawn from Ref. 34. © American Chemical Society, 2009.]

3.1.1 Functional Vegetable Oils

Radical thiol–ene chemistry was used for the functionalization of unsaturated vegetable oils from renewable resources to make them more stable toward oxidation and better suitable for different applications such as lubrication or synthesis of polyesters.^{30,31} For the photoadditions of butanethiol to canola or corn oils (initiated by UV light, $\lambda < 325$ nm, $[\text{SH}]_0/[\text{C}=\text{C}]_0 = 6$), the conversion of the cis double bonds was $\sim 90\%$ or higher after 8 hours. However, the crude products consisted of mixtures of components, and the highest isolated yield of the purified product was about 61%.³⁰ Thiol additions to methyl-10-undecenoate and derivatives from castor oil, on the other hand, showed all the features of a click reaction (Figure 1).³¹ These examples highlight the importance of the degree of substitution at the double bond for click addition of thiols.

3.1.2 Saccharides and Glycoclusters

Thiol–ene chemistry is a well-established tool in carbohydrate synthesis. Lindhorst *et al.* applied the thermal addition of 2-mercaptoethanol to 3,6-diallyl-protected sugars (initiator: AIBN) as an intermediate step in the synthesis of glyco-dendrons.³² By irradiation of a methanolic suspension of perallylated D-glucose and cysteamine hydrochloride with UV 254-nm light, the pentavalent carbohydrate structure was produced in virtually quantitative yield. Likewise, Klaffke *et al.* applied the same procedure for the synthesis of a series of amine-functional mono- to trisaccharides in 70–80% yield.³³

Dondoni *et al.* described the photoinduced click coupling (irradiation at 365 nm in the

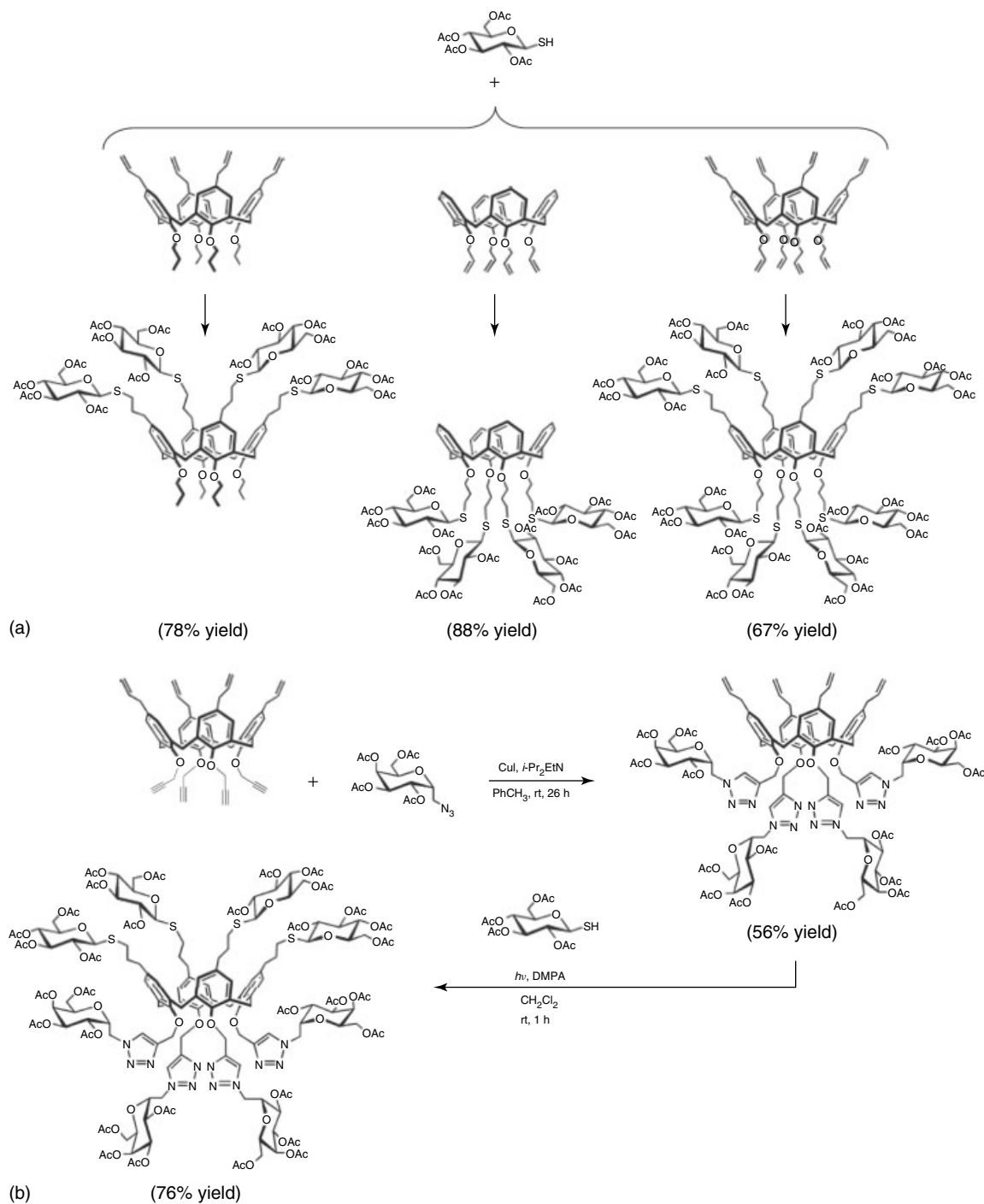
presence of DMPA as sensitizer) of anomeric sugar thiols with sugar alkenes.³⁴ The 1,6-linked *S*-disaccharides were obtained in good to excellent yields ($>75\%$) and high diastereoselectivities (up to 99%) (Scheme 4).

The same group also described the modification of calix[4]arenes with thiosugars to yield glycoclusters.³⁵ The reactions were performed in dichloromethane solution in air with irradiation at 365 nm in the presence of DMPA. The positions (above and/or below the rim of the macrocycle) and nature of the unsaturated groups (double or triple carbon–carbon bond) could be changed, thereby obtaining a number of different molecules with a predefined number of sugar moieties (Scheme 5a). Furthermore, by orthogonal combination of the Huisgen azide–alkyne cycloaddition and radical thiol–ene addition, different types of sugar moieties could be incorporated regioselectively to yield Janus-type glycoclusters (Scheme 5b).

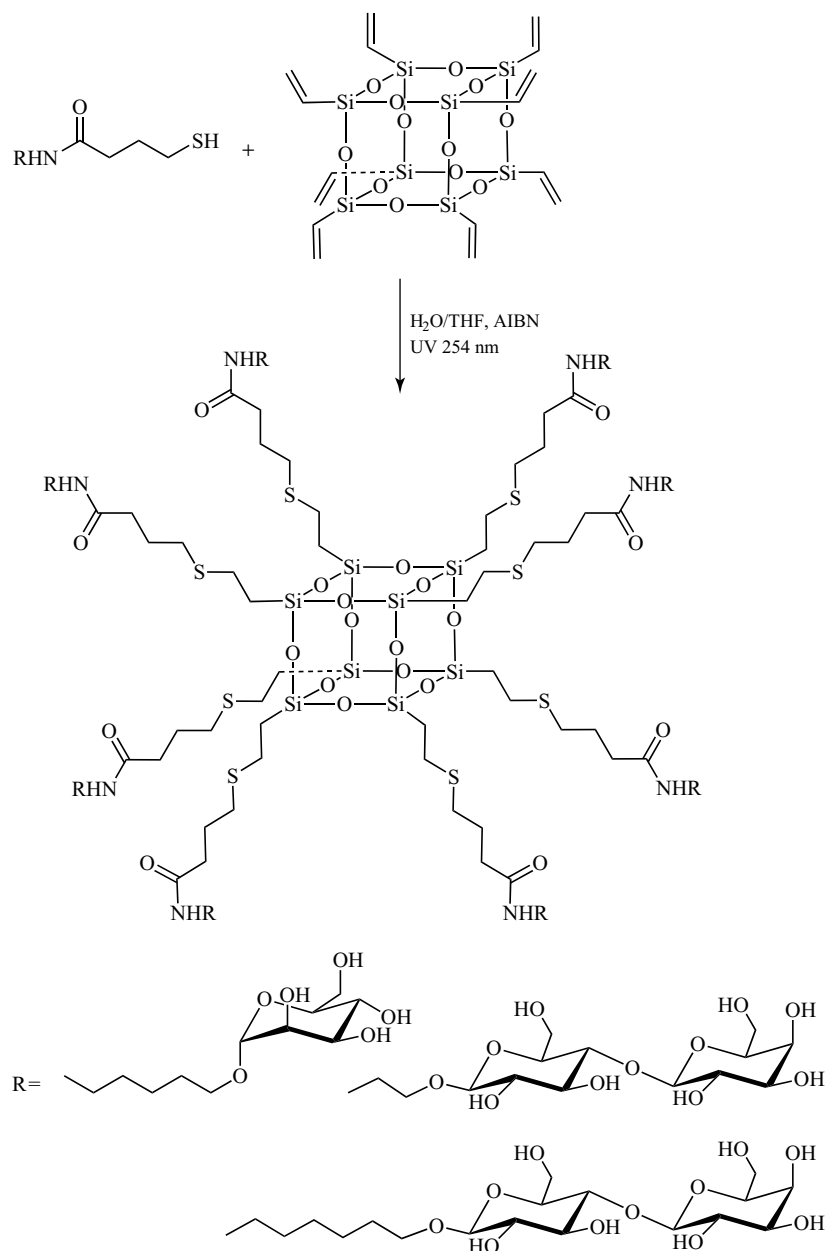
Likewise, glycoclusters based on polyhedral oligosilsesquioxanes (POSS) were prepared (Scheme 6).³⁶ Octavinyl POSS, which is a commercially available compound, was reacted with sugar thiols ($[\text{SH}]_0/[\text{C}=\text{C}]_0 \sim 4$) in a 1:1 mixture of water/tetrahydrofuran through irradiation with UV light (254 nm) in the presence of catalytic amounts of AIBN. Purification of the crude products by gel filtration afforded the pure glycoclusters in $\sim 70\%$ yield; unreacted sugar could be recovered in pure form.

3.1.3 Functional Amino Acids and Peptides

The modification of cysteine units is commonly done via nucleophilic Michael addition to maleimides or (meth)acrylates,⁷ but recently also different thermal and photochemical



Scheme 5 (a) Photoinduced multiple thiol-ene click coupling for the synthesis of calix[4]arene-based *S*-glycoclusters. (b) Orthogonal glycosylation of calix[4]arene applying sequential Huisgen azide-alkyne cycloaddition (first step) and radical thiol-ene addition (second step). [Reproduced and adapted from Ref. 35. © Royal Society of Chemistry, 2009.]



Scheme 6 Preparation of polyhedral oligosilsesquioxane (POSS) based glycoclusters. [Redrawn from Ref. 36. © American Chemical Society, 2004.]

routes of radical thiol–ene additions have been described.

Differently protected and unprotected cysteines were treated with 1-alkenes in the presence of AIBN as radical source at 90 °C in organic solvents.³⁷ Importantly, the S-alkylated cysteines

could be obtained in high yields and without racemization.

Short peptides (4–16 amino acids) with an alternating sequence of L-leucine and L-allylglycine were reacted with hydrophilic thiols, namely, cysteamine hydrochloride, thioglycolic acid, and

2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranose.³⁸ The radical additions were initiated by AIBN at 70 °C and run in either dimethylformamide (DMF) or toluene solution depending on the solubility of the thiol. For all cases, the conversions of allyl groups were quantitative within 20 hours. The shorter peptides, but not the 16-mer one, could be isolated in good to excellent yields.

Dondoni and Massi *et al.* used the hydrothiolation reaction for the coupling of allyl *C*-glycosides with cysteine and glutathione.³⁹ Best yields, that is 90% or higher, were achieved when reactions were performed in 0.5 M DMF solution with irradiation at 365 nm and DMPA as sensitizer; the thiol was used in threefold excess with respect to double bonds. This procedure was also successfully applied for the photoinduced glycosylation of a synthetic nonapeptide carrying a single cysteine unit and of native globular bovine serum albumin (BSA) (Scheme 7), as confirmed by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. Reactions were conducted in dimethylsulfoxide (DMSO), though sulfoxides can act as a radical scavenger and thiol oxidation agent,⁴⁰ and phosphate buffer under argon atmosphere.

The photochemical coupling of protected cysteine derivatives to 1-alkenes was studied by Kunz *et al.* as model reactions for the conjugation of amino acids and peptides to make BSA-glycopeptide vaccines.⁴¹ Reactions were performed either with irradiation at 254 nm or thermal initiation with radical starter in aqueous or alcoholic solutions; the yields of purified compounds were between 31% and 88%. The coupling of thiol-terminated glycopeptide antigen to allylether-modified BSA, as exemplarily shown in Scheme 8, was performed with UV 254-nm irradiation in aqueous phosphate buffer solution under argon. The antigen-BSA conjugate contained on average eight glycopeptides per molecules BSA, as indicated by MALDI-TOF mass spectrometry, corresponding to a degree of functionalization of 32%. This procedure cannot, contrary to the previous example described by Dondoni and Massi, be considered as a click reaction even though a larger number of glycopeptide chains could be attached to BSA.

Recently, Dondoni *et al.* also reported the nucleophilic functionalization of cysteine derivatives with propargyl bromide and subsequent thiol-yne addition of sugar thiols, that are thioglucose,

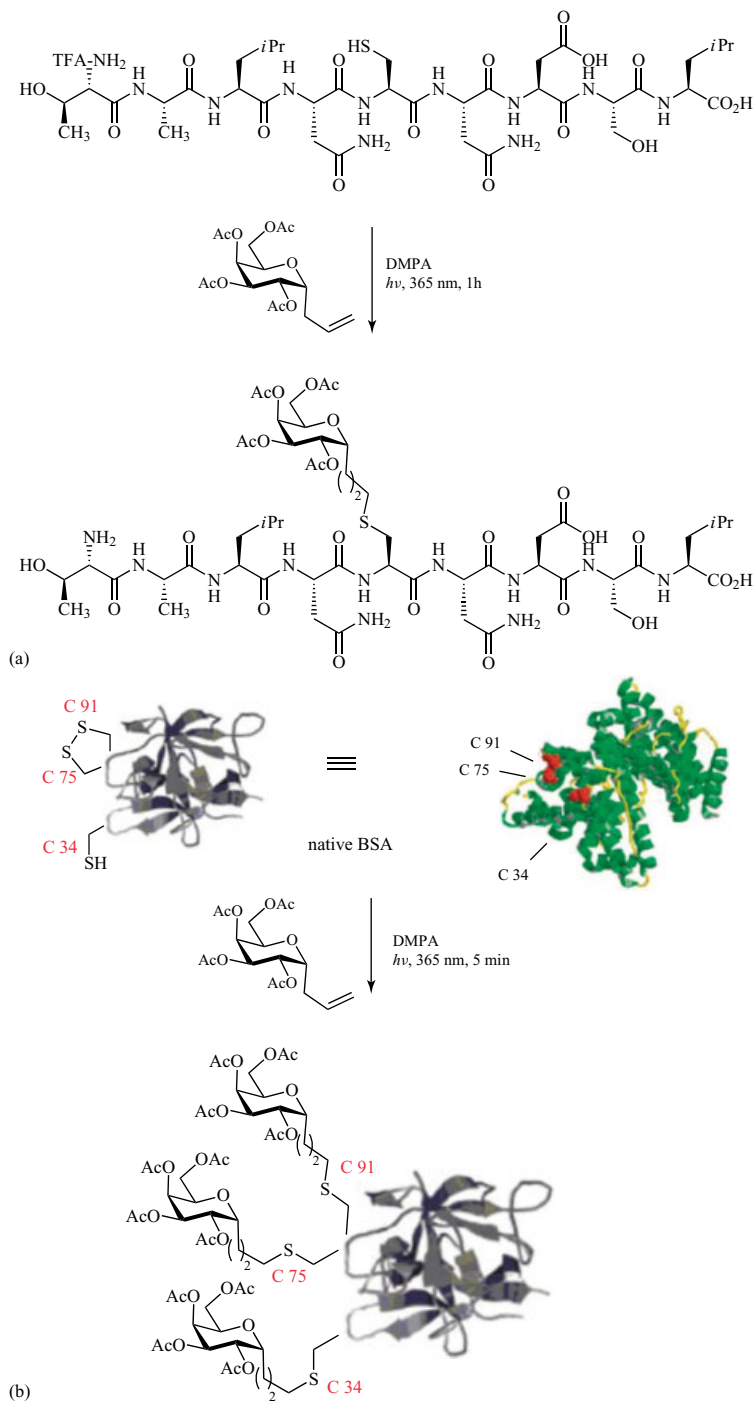
galactose, and lactose, and thiol-functionalized biotin (Scheme 9).²⁸ The photoinduced double addition of thiosugar to alkynyl amino acids and peptides was found to proceed, under the experimental conditions noted in Scheme 9a, smoothly in quantitative yield (>95%). Making use of the fact that the radical addition to the internal vinyl thioether was slow as compared to the terminal alkyne, it was also possible to perform a one-pot sequential addition of two thiol radicals generated by different thiols, that is, sugar thiol and biotin thiol (Scheme 9b). However, the mixed addition product could only be isolated in a low yield of 34%.

Similarly, Anseth *et al.* studied oligopeptides containing 1–3 lysine units and coupled 4-pentynoic acid to the ϵ -amino groups to introduce alkyne groups in the side chains.⁴² Thiol-yne photochemistry was then applied to achieve clustered peptides in purified yields of 77–87%.

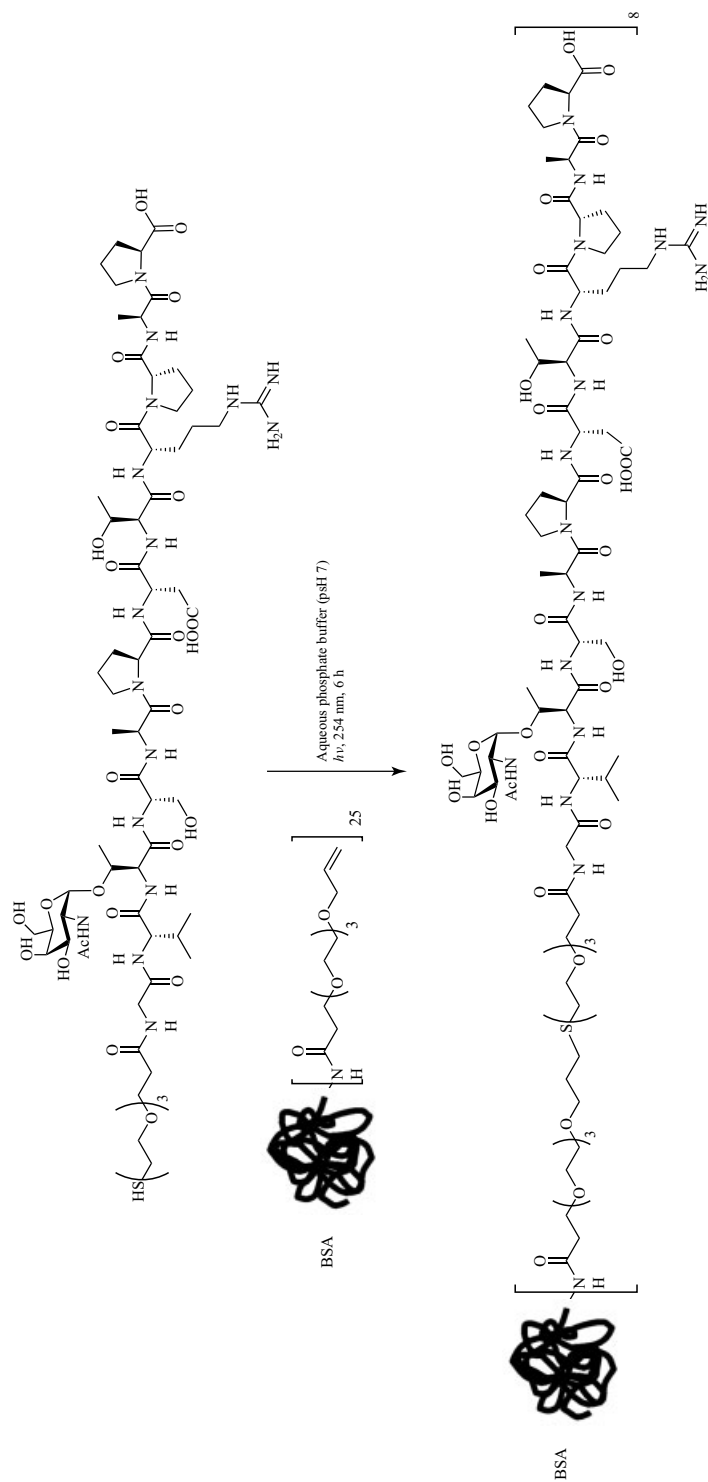
The photochemical click functionalization of propargyl esters with various thiols, including a derivative of proline (captopril), has also been described.⁴³

3.1.4 Cyclic Oligopeptides and Macrocycles

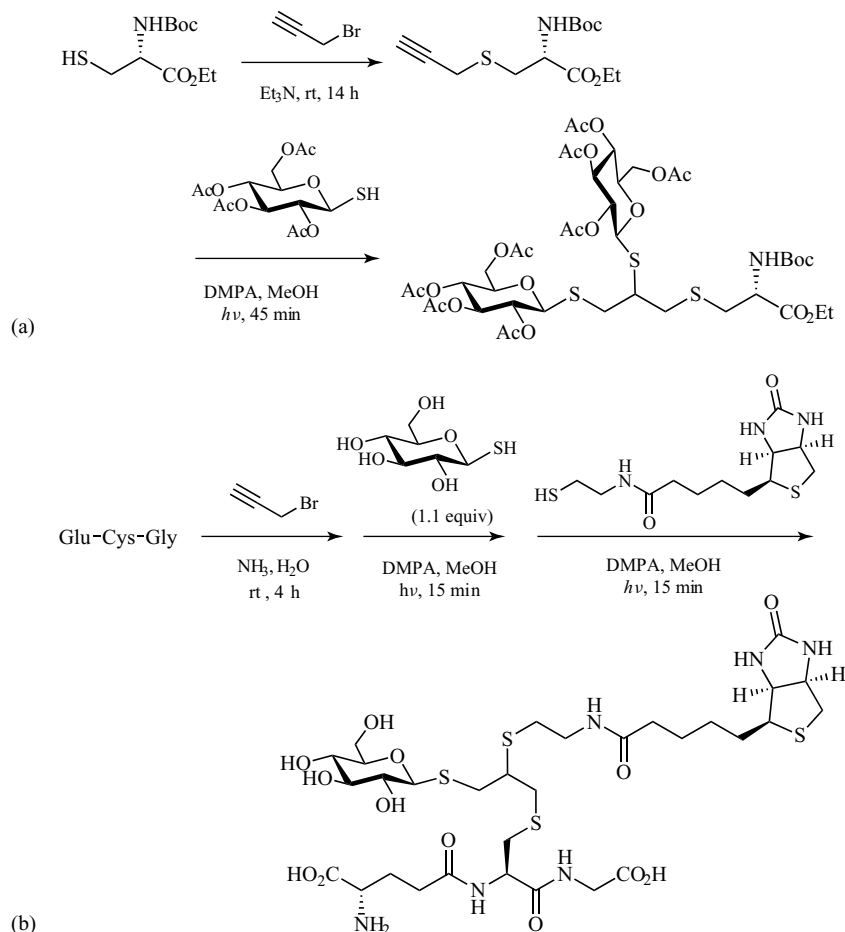
Anseth *et al.* applied the radical thiol-ene coupling for the synthesis of cyclic peptides.⁴⁴ A peptide sequence bearing an alkene group, either allyl or norbornene, in the first amino acid and a protected thiol residue in the last (cysteine) was prepared using solid-phase synthesis. While still attached to the resin, the cysteine was deprotected and the sample was irradiated with UV light (365 nm) in the presence of DMPA. The radical thiol-ene reaction between the two reactive groups in the peptide sequence led to a cyclization of the peptide as shown in Scheme 10a. Building on this work, the same group used sequential thiol-ene and thiol-yne photochemical reactions for the synthesis of cyclic multivalent peptides.⁴² The aforementioned cyclic peptide was extended by two glycines and a cysteine (isolated yield: 15%). This cyclic peptide was then attached to linear oligopeptides bearing up to three side-chain triple bonds via thiol-yne addition (Scheme 10b). The cyclic dimer and tetramer were isolated in 48% and 11% yield, respectively, but the cyclic hexamer could not be



Scheme 7 Photochemical glycosylation of cysteine units in (a) a synthetic nonapeptide and (b) native bovine serum albumin (BSA). [Reproduced from Ref. 39. © Wiley-VCH Verlag GmbH & Co. KGaA, 2009.]



Scheme 8 Photochemical coupling of a thiol-terminated glycopeptide antigen to olefin-modified bovine serum albumin (BSA). [Redrawn from Ref. 41. © Wiley-VCH Verlag GmbH & Co. KGaA, 2007.]



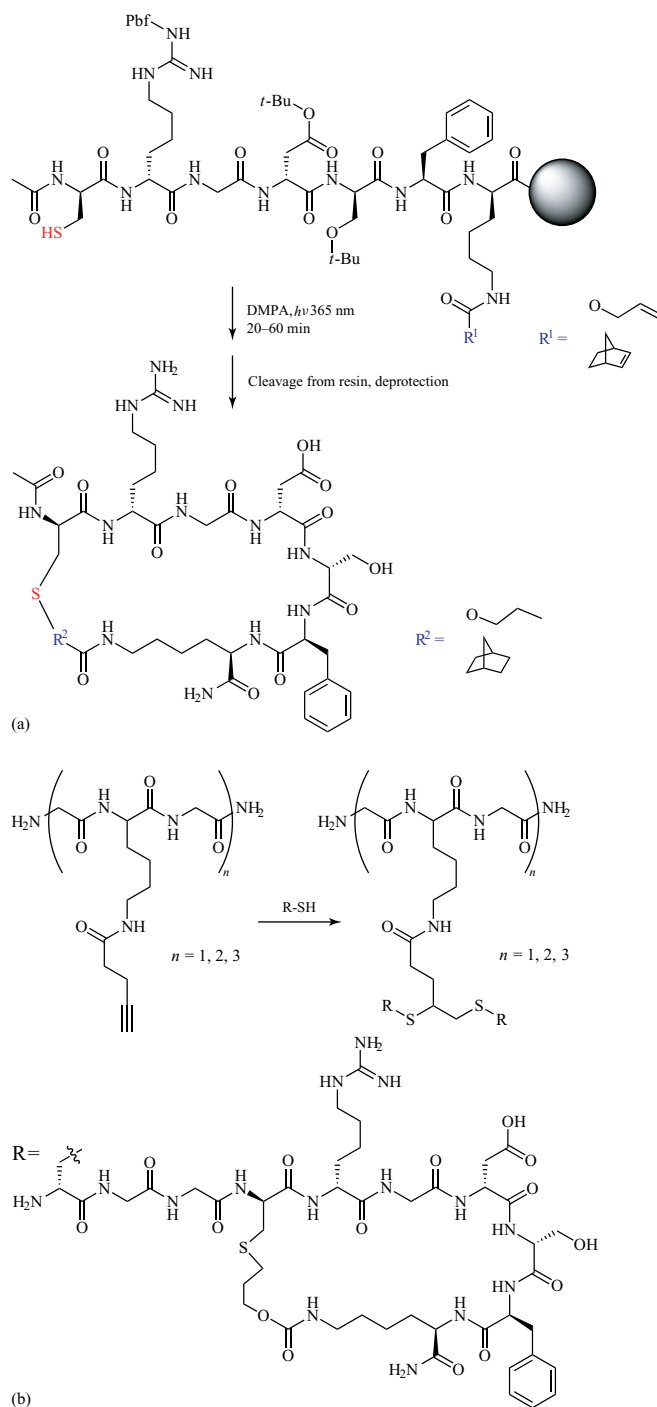
Scheme 9 Photoinduced thiol–yne modification of cysteine-based alkynyl peptides: (a) double addition of sugar thiols and (b) sequential addition of sugar thiol and biotin thiol. [Redrawn from Ref. 28. © American Chemical Society, 2010.]

observed. The decreasing yields of clusters with increasing number of cycles were attributed to steric hindrance.

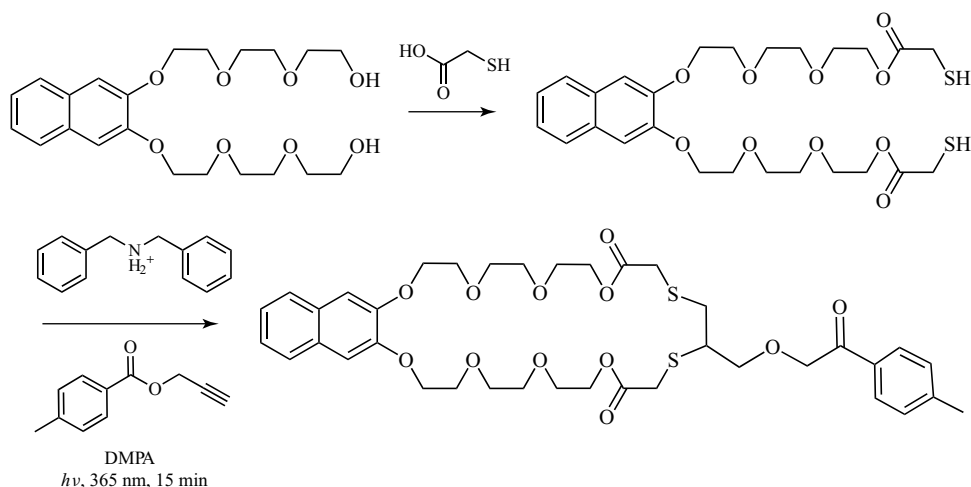
Li *et al.* were able to prepare macrocycles and rotaxanes via disulfide coupling and thiol–yne photochemistry (Scheme 11).⁴⁵ A bis(triethylene glycol)-naphthalene was thiolated by esterification with thioglycolic acid and then assembled into a cycle with secondary dibenzylammonium ions at high concentration. The cycle was closed by addition of prop-2-ynyl benzoate under irradiation at 365 nm in the presence of DMPA. The desired macrocycle was obtained in 80% yield. The use of a dumbbell-shaped dibenzylammonium salt template resulted in the formation of a rotaxane.

3.1.5 Dendrimers

Dendrimers are repeatedly branched, monodisperse molecules having rather spherical shape (see the structure in Scheme 12) and are classified by generations G1, G2, G3, ..., referring to the number of repeated branching cycles during the synthesis. Dendrimers are synthesized by either convergent or divergent processes. Thiol–X chemistry has exclusively been applied in divergent reaction processes: that is, starting from a multifunctional core, which is then extended to the outward using AB₂ monomers. Importantly, in order to obtain the desired perfect dendrimer structure, which is usually confirmed by nuclear magnetic resonance (NMR) spectroscopy and MALDI-TOF mass spectrometry,



Scheme 10 (a) On-resin cyclization of oligopeptides⁴⁴ and (b) synthesis of clustered peptides⁴² using thiol–ene/thiol–yne photochemistry. [Redrawn from Refs 42 and 44. © Royal Society of Chemistry, 2010.]



Scheme 11 Synthesis of sulfuric macrocycle by thiol-yne photochemistry. [Redrawn from Ref. 45. © American Chemical Society, 2010.]

every reaction step must click and come to full completion.⁹

Hawker *et al.* applied nucleophilic epoxy-amine and radical thiol-ene additions for the synthesis of dendrimers.⁴⁷ The core molecule 1,4-bis(aminomethyl)benzene was first reacted with allyl glycidyl ether (AB₂ monomer), and subsequently the allyl groups were modified with 2-mercaptoethylamine hydrochloride. The final G3 dendrimer could be further functionalized with monomethyl(triethylene glycol)mercaptane.

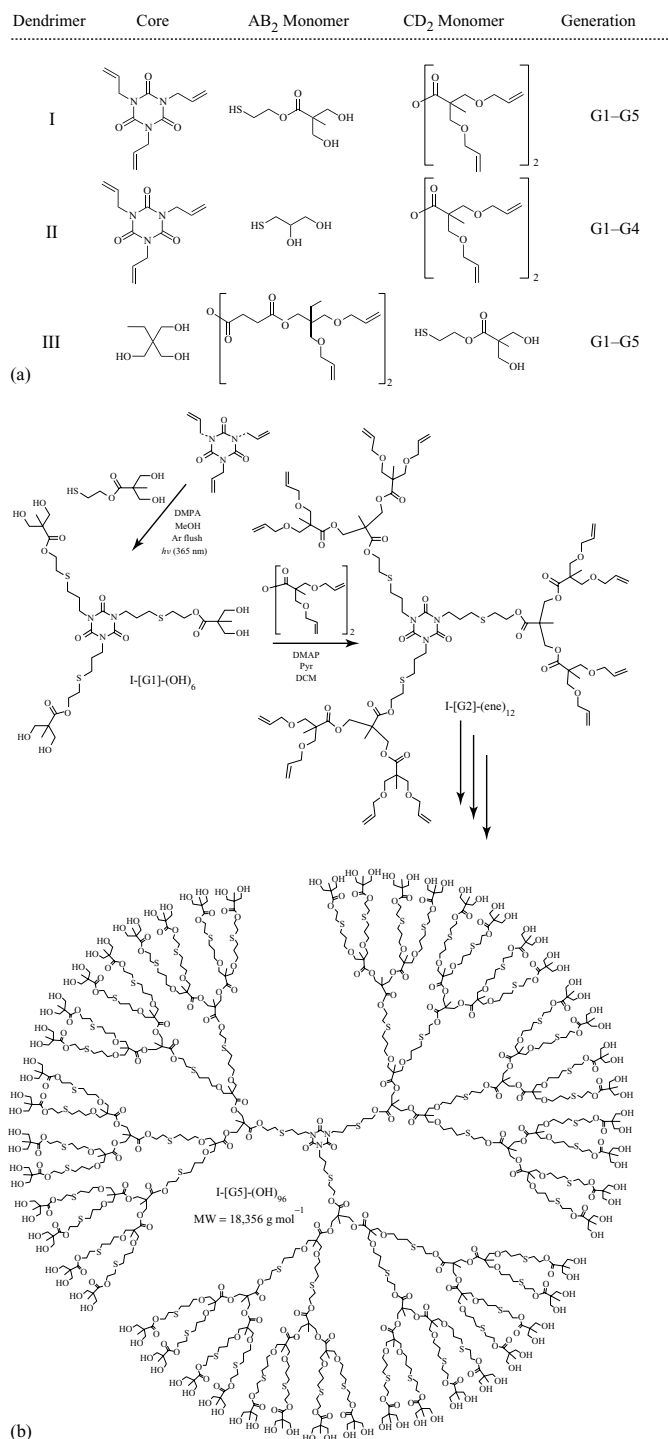
The synthesis of a G4 dendrimer starting from 2,4,6-triallyloxy-1,3,5-triazine as tris-alkene core has also been described.⁴⁸ The AB₂ monomer 1-thioglycerol was added to the core by irradiation at 365 nm in the presence of trace amounts of DMPA. The reaction was performed in air and came to completion within 30 min when at least 1.5 equiv of AB₂ monomer were used. The OH functionalities were subsequently converted into ene functionalities by esterification with 4-pentenoic anhydride to yield [G1]-ene₆. Repetition of this procedure afforded the fourth-generation dendrimer [G4]-ene₄₈. Dendrimers were purified by simple precipitation into diethyl ether and recovered in 90+ % yield. Additionally, the double bonds on the surface of the dendrimers could be click-modified with functional thiols.

The combination of thiol-ene chemistry and esterification reactions was further applied for the generation of a dendritic library from different

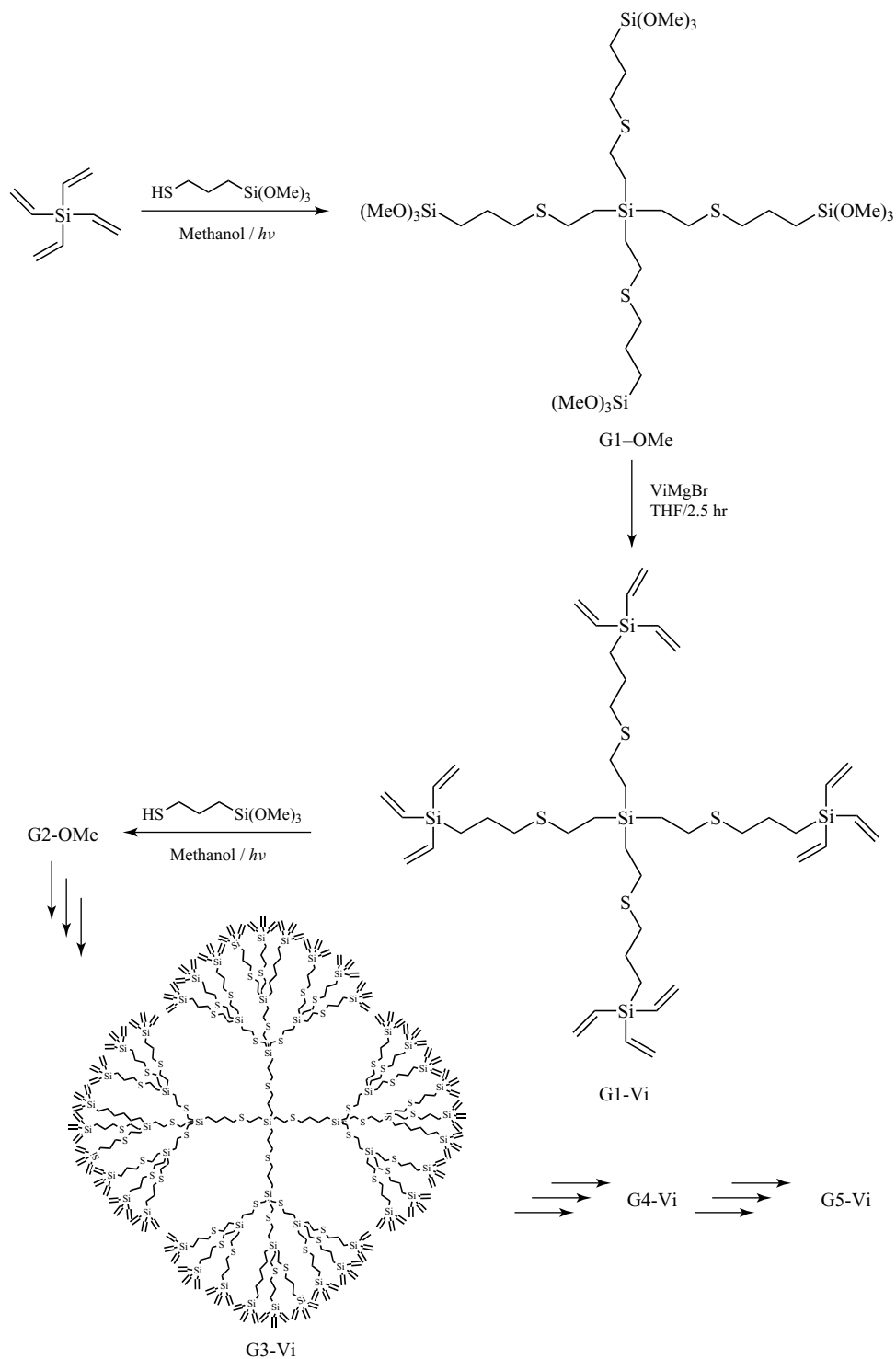
core molecules and AB₂ and CD₂ monomers (Scheme 12a).⁴⁶ For instance, a fifth-generation dendrimer [G5]-OH₉₆ could be obtained starting from a triallyl isocyanurate core (Scheme 12b). Importantly, these coupling chemistries eliminate the traditional need for protection/deprotection steps and afford dendrimers in high yield and purity.

Stenzel *et al.* applied a thiol-yne and esterification process to obtain the third-generation dendrimer having as much as 192 hydroxy groups, [G3]-OH₁₉₂.⁴⁹ The core molecule employed was a trifunctional alkyne and the AB₂ monomer was 1-thioglycerol; esterification was achieved with acetylene anhydride. Dendrimers were obtained in high purity, though yields were not given. Furthermore, [G1]-yne₁₂ was successfully reacted with thioglycolic acid to give a carboxylated [G1]-COOH₂₄.

Multifunctional branched structures and dendrimers based on organosilanes were synthesized by Rissing and Son (Scheme 13).^{50–52} Tetravinylsilane was functionalized with 3-mercaptopropyl-trimethoxysilane (MPTMS) by thiol-ene photoaddition with irradiation at $\lambda_{\text{max}} = 365$ nm (broadband emission of a sunlight bulb) in the absence of a photoinitiator. The methoxy groups were exchanged for vinyl groups in a Grignard reaction using vinyl magnesium bromide. Repetition of the procedure gave the G3 dendrimer in quantitative yield. The synthesis of the higher generation dendrimers required the use



Scheme 12 (a) Core molecules and monomers employed for the synthesis of dendritic libraries. (b) Synthesis of fifth-generation dendrimer using thiol-ene/esterification chemistries. [Reproduced from Ref. 46. © American Chemical Society, 2010.]



Scheme 13 Synthesis of carbosilane-thioether dendrimers by thiol-ene and Grignard reactions (Vi = vinyl). [Reproduced from Ref. 52. © American Chemical Society, 2009.]

of a photoinitiator in the thiol–ene reaction step. The production of a G6 dendrimer failed, likely because of the extremely high concentration of vinyl groups.

Radical thiol–ene photochemistry has also been applied in combination with the Huisgen azide–alkyne click reaction by Hawker *et al.* (Scheme 14).⁵³ The highly orthogonal and time-efficient protocol of radical thiol–ene chemistry and copper-catalyzed azide–alkyne cycloaddition allowed the synthesis of a G6 dendrimer within a single day. The core containing three alkene groups was functionalized with a thiol containing two azide groups, which were in turn functionalized in an azide–alkyne cycloaddition, and so on. The reaction cycles proceeded smoothly to the generation four dendrimers. Some dendrimer–dendrimer cross-coupling through radical recombination occurred in the fifth-generation growth step.

3.2 Macromolecular Chemistry

Especially in macromolecular chemistry, the radical thiol–ene reaction has found widespread acceptance and application. Early examples of thiol–ene reactions, such as for instance the step-growth polymerization and the modification of diene rubbers, may not be classified as true click reactions, as discussed below; nevertheless, the chemistry was very convenient and often highly effective.

3.2.1 Functional Polymers

Even though this chemistry was known since the beginning of the last century,¹ there were just a few reports published until 2003 (most of them dated 1990 or later) dealing with the use of radical thiol additions for the modification of diene rubbers, polybutadienes (Boutevin *et al.* and others),^{54–66} and polysiloxanes (Boileau *et al.*)^{67,68} and for polymer end functionalization (Kataoka *et al.*).⁶⁹ Since 2004, the radical thiol–(1,2-)polybutadiene modification has been explored extensively for the generation of functional homopolymers and block copolymers, including polyelectrolytes and biohybrid polymers (Schlaad *et al.*^{70–77} and others^{78–81}) and for the thiolation of polyurethanes.⁸² The reaction was

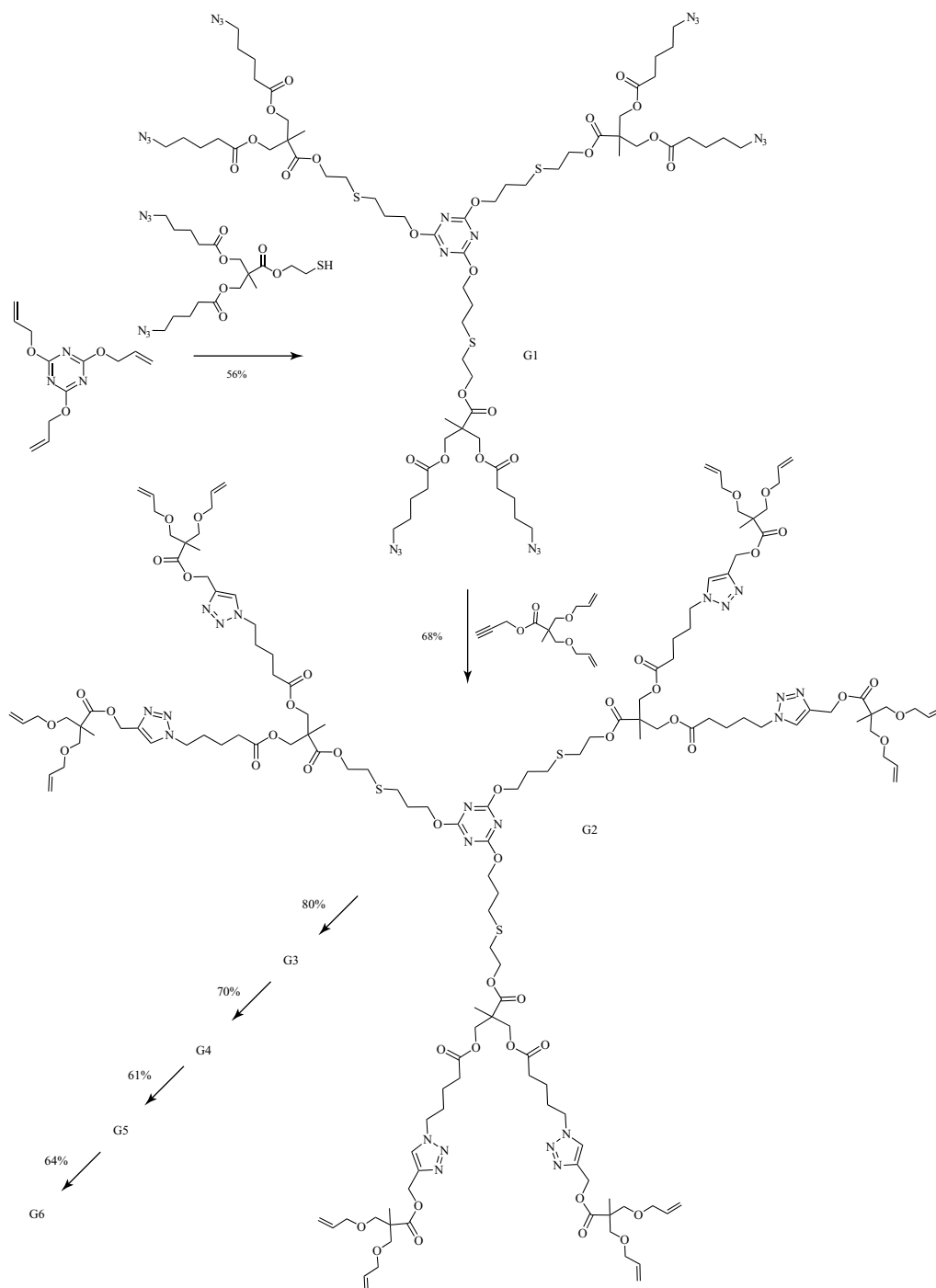
demonstrated to be modular and wide in scope, but is plagued by some side reactions, especially intramolecular cyclization on the polymer backbone through addition of the intermediate carbon radical to a neighboring double bond (Scheme 15).^{71,76,78,80} Degrees of functionalization of up to 80% at full conversion of double bonds could be achieved. Nevertheless, thiol–polybutadiene addition does not qualify as a polymer click reaction. Thiol–ene photoaddition to polyisoprenes was found to occur preferentially on the 1,2-units but not on 1,4- and 3,4-units, thus in a non-click fashion.⁸³

From the insight and experience gained from these examples, radical thiol–ene chemistry was developed in a way that it proceeds as a click reaction.

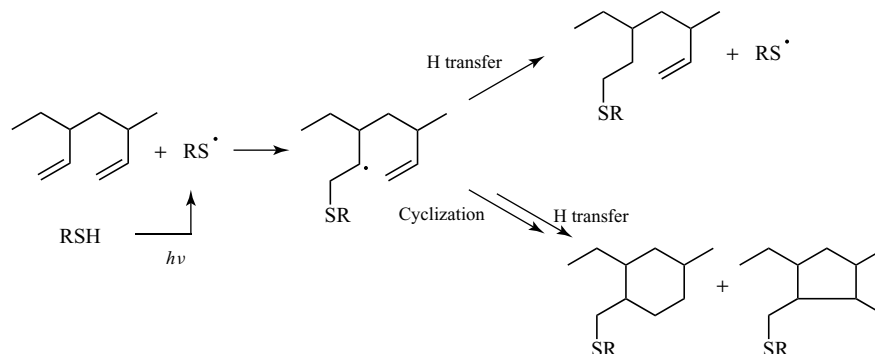
Main-/Side-Chain Functional Polymers

Schlaad *et al.* were the first to use the term “thio-click” for a radical thiol–ene reaction system, namely for the photochemical thiolation of poly[2-(3-butenyl)-2-oxazoline] homopolymers and copolymers with a series of different thiols (Scheme 16).⁸⁴ The increased distance between intermediate radical and neighboring double bond, as compared to 1,2-polybutadiene, disfavors any intramolecular cyclization reaction, thus promoting a side-reaction-free thiol click addition. In order to minimize radiation damage to the polymer and to keep radical concentration low (to avoid radical–radical coupling), thiyl radicals were generated directly by irradiation with UVA light ($\lambda > 300$ nm) in the absence of a photoinitiator.

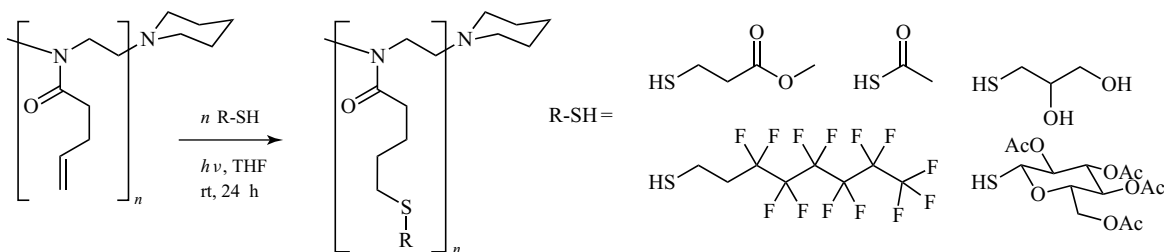
Since then, several other groups (Hawker *et al.* and others) have shown that the same click character can be obtained for other types of ene polymers (Figure 2) and thiols.^{85–89} Thiol–ene “clickable” copolymers include poly[(4-(3-butenyloxymethyl)-styrene)-*co*-styrene] and poly[(3-butenyl methacrylate)-*co*-(methyl methacrylate)],⁸⁵ which were synthesized by controlled radical polymerization techniques (RAFT (Reversible Addition Fragmentation chain Transfer) and ATRP (Atom Transfer Radical Polymerization), respectively), poly(ethylene oxide)-*block*-poly[(6-allyl- ϵ -caprolactone)-*co*-(ϵ -caprolactone)],⁸⁵ poly(ethylene oxide)-*block*-poly(DL-allylglycine),⁸⁶ poly(allyl glycidyl ether)-*block*-poly(ethylene oxide)-*block*-poly(allyl glycidyl ether),⁸⁷ poly[(methyl-2-allyloxycarbonyl-propylene carbonate)-*co*-(L-lactide)]⁸⁸ synthesized by ring-opening polymerization



Scheme 14 Synthesis of a sixth-generation dendrimer by thiol-ene (steps 1, 3, and 5) and Huisgen alkyne-azide (steps 2, 4, and 6) click reactions. [Adapted and redrawn from Ref. 53. © American Chemical Society, 2010.]



Scheme 15 Thiol–ene modification of 1,2-polybutadiene: regular addition step and intramolecular cyclization. [Redrawn from Ref. 76. © American Chemical Society, 2008.]



Scheme 16 Thiol–ene click modification of poly[2-(3-butenyl)-2-oxazoline]. [Redrawn from Ref. 84. © American Chemical Society, 2007.]

techniques, poly(octylallene-*co*-styrene) by coordination polymerization,⁸⁹ and commercial poly[2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylene vinylene].⁹⁰

All these polymer structures have in common that the distances between double bonds are too large or backbones are too stiff to form intramolecular cycles during the radical addition process, as for poly[2-(3-butenyl)-2-oxazoline]. Evidently, the design of the polymer structure decides on the click characteristics of the thiol–ene reaction rather than the nature of the thiol or the initiation process. However, Hawker *et al.* reported that photochemical reactions yielded higher efficiencies, required shorter reaction times, and were more tolerant to functional groups and backbones than their thermal counterparts.⁸⁵

It is especially worth mentioning that the thermal addition of 2-mercaptoethanol to poly(styrene-*co*-octylallene), as described by Ni and Shen *et al.*,⁸⁹ proceeded smoothly to quantitative yield, despite the fact that the backbone contained both terminal and internal double bonds with

different reactivities. The reaction was performed in toluene solution at 70 °C (initiator: AIBN) with a 40-fold excess of thiol with respect to double bonds. Conjugated internal double bonds as in poly[2-methoxy-5-(2-ethylhexyloxy)-1,4-phenylene vinylene] were photochemically reacted readily with dodecanethiol in bulk ($[SH]_0/[C=C]_0 = 4$), reaching quantitative conversion within 40 s.⁹⁰

Also, poly(ethylene oxide)-*block*-poly(DL-alanyl-glycine) could be click-modified with 1-thio- β -D-glucopyranose to yield a well-defined glycopolymer without the need for protecting groups.⁸⁶ The photoaddition reaction was performed in trifluoroacetic acid as (however, not truly environmentally benign) solvent with a twofold excess of the thiosugar. Full functionalization was achieved within 2 days.

Another route toward thiol–ene “clickable” polymers is based on polymer-analog reactions, often (trans-)esterification reactions. As an example, poly(2-hydroxyethyl methacrylate)s were first reacted with 4-pentenoic acid before the addition of glucithiose (irradiation with UV light, initiator:

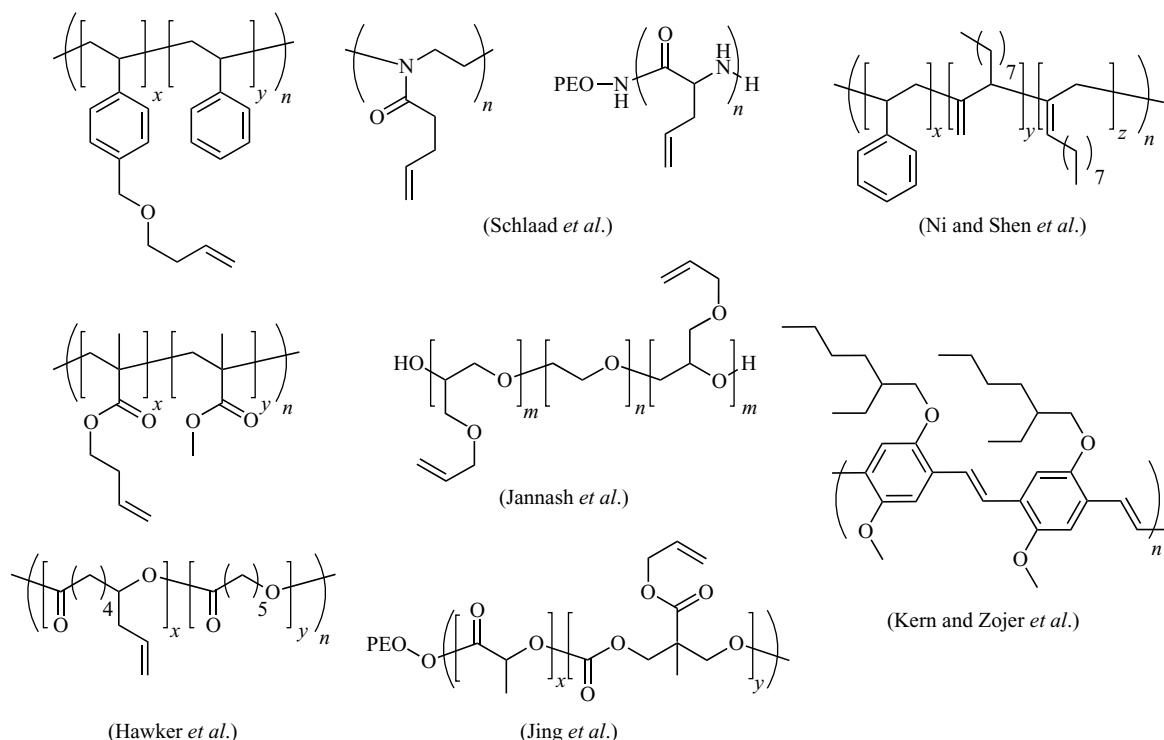


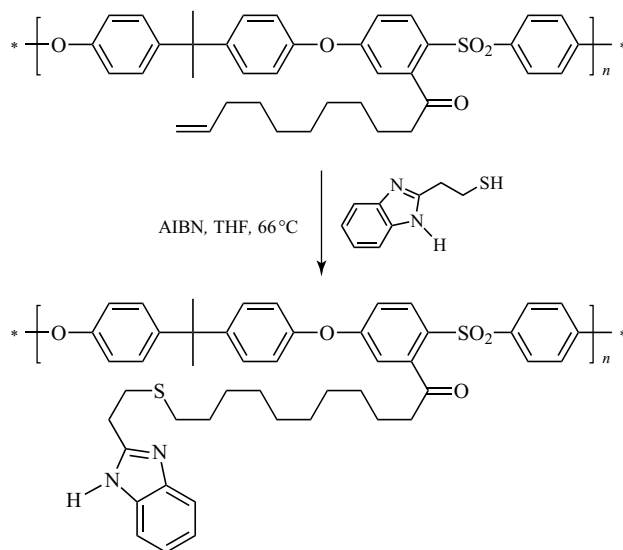
Figure 2 Examples of thiol-ene clickable ene polymer backbones.^{84–89}

DMPA) to yield neoglycopolymers.⁹¹ Hafrén and Córdova *et al.* modified cellulose, that is, filter paper, by tartaric acid-catalyzed reaction with either 2-(oct-7-enyl)oxirane or 9-decenoic acid to yield ene-functionalized cellulose, onto which hydrophobic thiols, for example, benzylthiol, were added in a photochemical reaction. The attachment of the thiol to cellulose could be confirmed, but not the quantitative conversion of double bonds.⁹² Huang *et al.* submitted poly(γ -benzyl-L-glutamate) to a partial transesterification reaction with allyl alcohol to obtain a poly[γ -(benzyl/allyl)-L-glutamate] copolymer.⁹³ The addition of thioglycerol to the allyl side chains ($[\text{SH}]_0/[\text{C}=\text{C}]_0/[\text{AIBN}]_0 = 40:1:2$, toluene, 80 °C, 24 hours), however, was not quantitative, which was attributed to steric hindrance and decreased reactivity of allyl groups.

Jannasch *et al.* grafted 10-undecenoyl chloride onto lithiated polysulfone followed by the thermal addition of 2-(2-benzimidazolyl)ethanethiol (Scheme 17).⁹⁴ In order to convert all double bonds into thioether links, 10 days of reaction was

required and additional amounts of AIBN were charged every 24 hours.

Thiol-ene clickable polymers may also contain thiol instead of ene groups, for instance cysteine-containing peptides (see Sections 3.1.3 and 3.1.4), poly(L-cysteine),⁹⁵ and poly[2-(2-mercaptoethyl)-2-oxazoline] copolymers,⁹⁶ as synthesized by ring-opening polymerization, and poly(pyridyl disulfide ethyl methacrylate), as synthesized by RAFT polymerization (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**) (Figure 3).^{97,98} Bulmus and Davis *et al.* investigated the exchange of the pyridyl disulfide side chain with various thiols and also glutathione; reactions were carried out at room temperature under nitrogen atmosphere to minimize the oxidation of free thiols.⁹⁷ Alternatively, but turning out to be less effective than the exchange reaction, poly(pyridyl disulfide ethyl methacrylate) was submitted to concurrent deprotection (catalyst: tris(2-carboxyethyl)phosphine) and photoaddition



Scheme 17 Thermal addition of 2-(2-benzimidazolyl)ethanethiol to undecenoyl-grafted polysulfone. [Redrawn from Ref. 94. © Elsevier, 2006.]

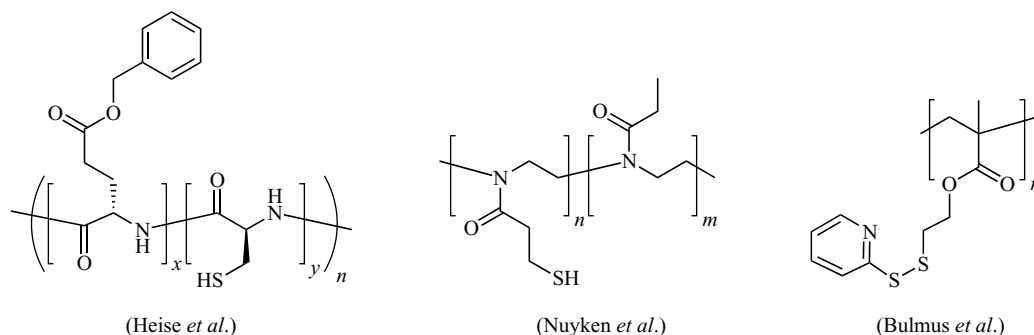


Figure 3 Examples of thiol–ene clickable thiol polymer backbones.^{95–97}

(UV 365 nm, DMPA) of allyl-poly(ethylene oxide) (PEO, 2 kDa) with a yield of about 60%.⁹⁸

Heise *et al.* applied radical/nucleophilic 1 : 1 additions of poly(ethylene oxide) methyl ether acrylate or fluorescein *O*-acrylate to a poly(L-cysteine) copolymer.⁹⁵ Reactions were carried out with AIBN as the initiator at 70 °C in DMF solution, in the presence of pyridine as a base, and came to completion within 1 hour.

Poly[2-(2-mercaptoethyl)-2-oxazoline] copolymers, however, have only been modified by nucleophilic but not radical thiol–ene addition.⁹⁶

It is noteworthy that free thiols on the backbone are prone to intra- and interchain thiol–disulfide exchange reactions, resulting in

nonquantitative grafting and cross-linking.^{98–100} The cysteine-containing copolymer underwent slow oxidative cross-linking under atmospheric conditions.⁹⁵ Hence, thiolated polymers are less suited for click chemistry applications than unsaturated ene polymers.

Polymers carrying carbon–carbon triple bonds in the side (or main) chains have been click-functionalized with azides, applying Huisgen [3 + 2] cycloaddition reaction, but not with thiols.

End-Functional Polymers

Polymers for thiol–ene click end-functionalization carry alkene/alkyne or thiol groups at their chain ends, which can be synthesized by living/controlled

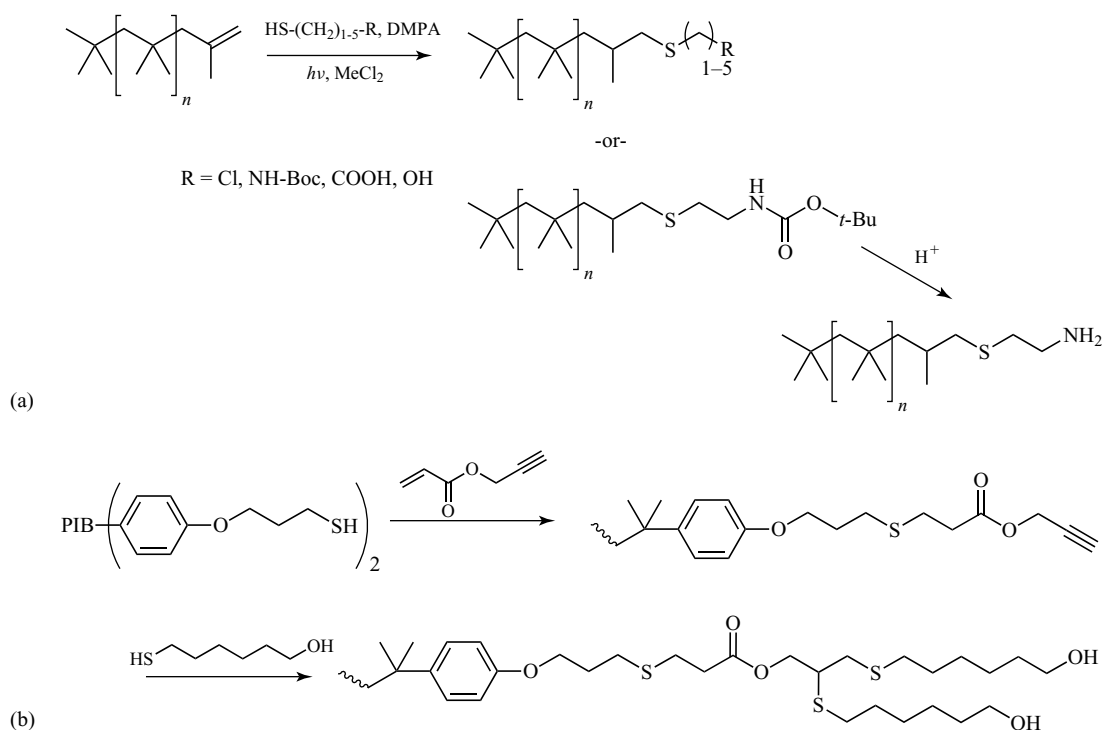
polymerization techniques using functional initiators and/or quenching agents.^{3,101,102} Alkene/alkyne groups may and thiol groups must be appropriately protected, depending on the applied polymerization technique. Polyisobutylenes, for instance, which are available through cationic polymerization, can be readily prepared with alkene end groups. Terminal dithioester or trithiocarbonate, etc. groups of RAFT polymers can be converted into a thiol by reduction or aminolysis.¹⁰³

Poly(ethylene oxide) with terminal allyl groups (4.9 kDa)⁶⁹ or methyl(*n*)vinyl(3-*n*)silyl groups (2.8–2.9 kDa)¹⁰⁴ were quantitatively modified by thermal addition of cysteamine hydrochloride (AIBN, 15 equiv thiol, DMF, 70 °C, 24 hours) or thioglycolic acid (AIBN, 3 equiv thiol, toluene, 80 °C, 2 hours), respectively. Hawker *et al.* modified allyl-poly(ethylene oxide) (5 kDa) with various thiols (thioglycolic acid, MPTMS, thio-adamantane, Fmoc-protected cysteine, and thioglycerol) applying both thermal and photochemical procedures, the latter being the more efficient one to give quantitative

or near-quantitative (94%, thio-adamantane) conversion within 1 hour.⁸⁵ Allyl-terminated poly(ethylene oxide)-*block*-poly(L-lactide) was reacted with three model thiols, that is, 3-mercaptopropionic acid, thioglycerol, and *N*-Boc-cysteamine, in THF solution at room temperature; radicals were generated by irradiation with UV light (254 nm).⁸⁸ Reactions came to completion within 1–2 hours. Thiocholesterol could be quantitatively added to allyl-terminated poly(2-isopropyl-2-oxazoline) by irradiation with UV light.¹⁰⁵

The peroxide-initiated addition of MPTMS to the terminal methylvinylidene group of isotactic polypropylene (*i*-PP, 50 kDa) in the melt, on the other hand, failed and could only be observed in the presence of a coagent like triallyl trimellitate.¹⁰⁶ The low unsaturation content of polypropylene and the high temperature (170 °C) were shown to disfavor product formation because of the reversibility of thiyl radical attack on the olefin.¹⁰⁷

Polyisobutylene (PIB, 1.3–3.6 kDa) with one or two (α,ω -) terminal methylvinylidene groups, on the other hand, could be quantitatively



Scheme 18 Thiol–X click functionalization of polyisobutylene (PIB) carrying terminal (a) alkene. [Redrawn from Ref. 108. © Royal Society of Chemistry, 2010.] (b) Thiol → alkyne groups.¹⁰⁹

functionalized with a series of different thiols (Scheme 18a).¹⁰⁸ The thiol reactant was used at 1.5 equiv with respect to double bonds, and the reaction times were in the order of a few minutes. Also, thiol-terminated polyisobutylene (PIB) was subjected to a one-pot sequential nucleophilic thiol–ene addition of propargyl acrylate and photochemical thiol–yne addition of 6-mercaptohexanol (Scheme 18b).¹⁰⁹ Both reaction steps were confirmed by ¹H NMR spectroscopic analyses to proceed in quantitative yield.

The dithiophenyl end group of poly(*N*-isopropylacrylamide) PNIPAM (5.9 kDa), as synthesized by RAFT polymerization, was reacted with octylamine and either allyl methacrylate or propargyl acrylate in the presence of dimethylphenylphosphine, that is, *in situ* aminolysis of dithiophenyl to thiol and subsequent thiol–ene Michael addition, by Lowe *et al.*¹¹⁰ The obtained PNIPAM-alkene and PNIPAM-alkyne were then reacted with three different thiols (hexanethiol, 6-mercaptohexanol, and 3-mercaptopropyl-POSS) applying UV 365 nm light in the presence of benzil dimethyl ketal (Irgacure 651) photoinitiator, to reach quantitative conversion within 2 hours.

Termination of polystyryl lithium (2.8 kDa) with chlorodimethylsilylhydride and subsequent hydrosilylation with octavinyl-POSS yielded a PS-POSS-(vinyl)₇ (after purification by fractional precipitation).¹¹¹ After photoaddition of thioglycolic acid (DMPA, UV 365 nm, THF), the hepta carboxylated polymer was obtained in 52% yield.

Combinations of different “click” reactions have been used for the orthogonal functionalization of heterobifunctional (telechelic) polymers, for instance, α -alkene- ω -azido-polystyrene (Scheme 19a)⁸⁵ or α -alkene- ω -alkyne-poly(ϵ -caprolactone) (Scheme 19b).¹¹² In case of functionalization of alkene/azide end groups, the sequence of thiol–ene and azide–alkyne cycloaddition could be chosen arbitrarily; both pathways yielded the same product in high purity. For alkene/alkyne, the azide had to be added before the thiol because the thiol would have reacted with either end group, thereby either creating a mixture of end groups or a polymer with two functional end groups on one side and one on the other (depending on the amount of thiol employed).

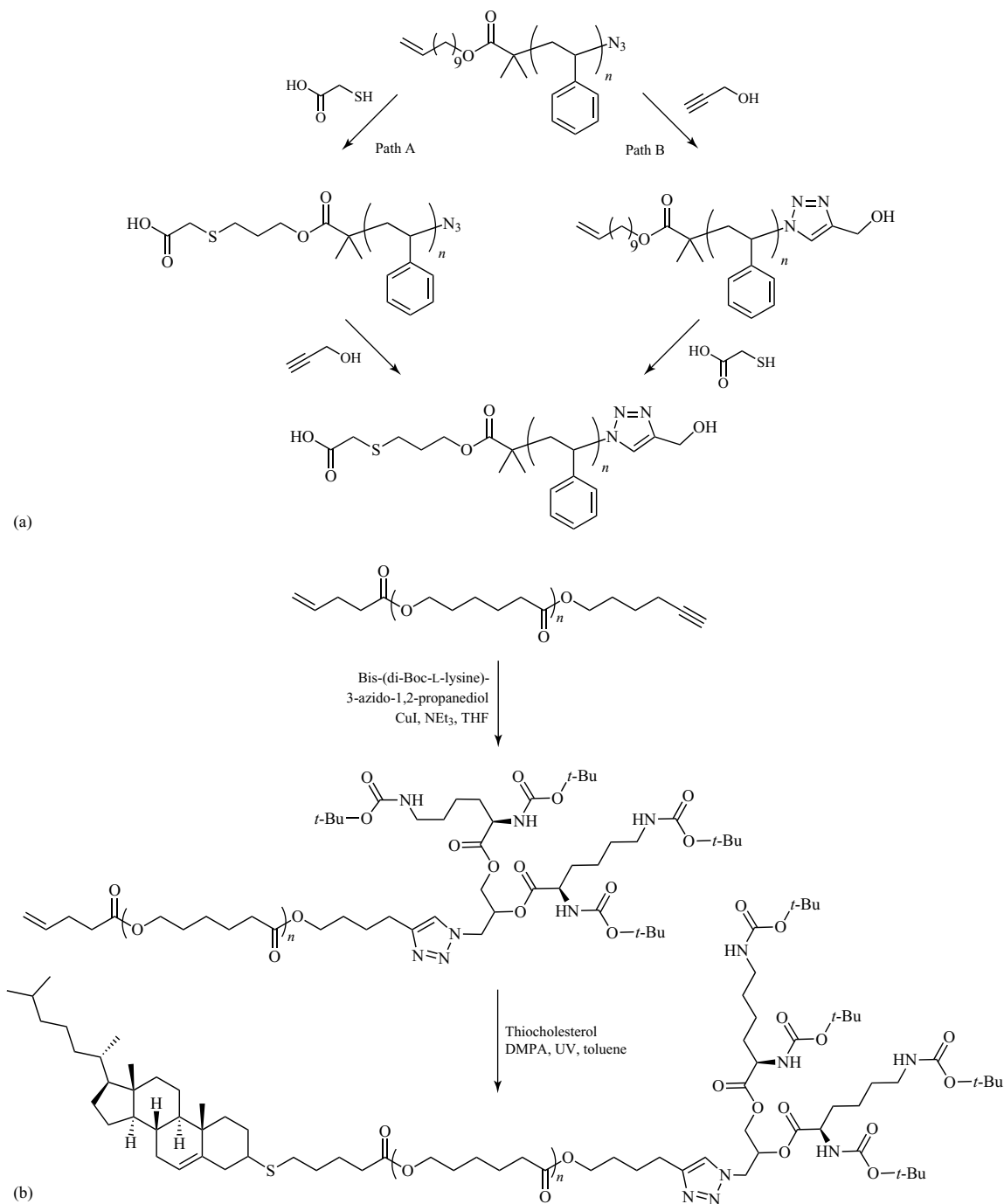
It is worth noting that the click coupling or conjugation of polymer chains via radical thiol–X chemistry has been attempted, applying

both thermal and photochemical routes, but failed, especially when the reactants were employed in exact or near-equimolar ratio.¹¹³ The major side reaction causing interruption of the thiol–ene propagation circle is supposed to be the head-to-head coupling of radical leading to the formation of polymer–polymer disulfides.

3.2.2 Branched Polymers and Networks

Step-growth polymerization can be used for the creation of different architectures: linear polymers, branched polymers, and networks. First indications of the step-growth polymerization by radical thiol–ene chemistry were obtained by Braun *et al.*, who observed the formation of an extremely high-boiling material for alkene-thiols due to polymerization.^{114,115} Some time later, also the polymerization of dienes with hydrogen sulfide¹¹⁶ and dithiols were reported.^{117–120} After this initial work, especially by the group of Marvel, mostly chemical industry picked up on the thiol–ene polymerization, yielding numerous patents.¹²¹ Since the mid-1990s, thiol–ene polymerization came back into focus,^{122–132} also promoted by the works of Hoyle and Bowman.^{4,12}

Linear polymers are produced by the reaction of difunctional thiol monomers with difunctional alkene monomers or by reaction of heterofunctional thiol–alkene monomers, the latter mainly having been used in the first works because of problems with the synthesis of these monomers.¹¹⁵ The synthesis of difunctional (or multifunctional) monomers does not suffer from this disadvantage and has therefore been applied far more widely. Not only dithiols but also hydrogen sulfide can be used as difunctional monomers.¹¹⁶ By using off-stoichiometric ratios of the different monomers, the average length of the polymers can be controlled to some degree, as well as the end groups (an excess of one monomer yields polymers with such end groups). Besides purely synthetic monomers,^{117–120,133} also diene biomolecules (fatty acid-based monomers) have been used (UV, photoinitiator).^{134,135} The functional end groups can in turn be used for end-group modification (e.g., with alcohol, carboxylic acid, and silanes).^{134,135} Mostly, polymers with relatively low molecular weights up to a few kilodaltons are obtained.



Scheme 19 Orthogonal click strategy for combined radical thiol-ene addition and azide-alkyne cycloaddition: (a) alkene-polystyrene-azide. [Redrawn from Ref. 85. © American Chemical Society, 2008.] (b) Alkene-poly(ϵ -caprolactone)-alkyne. [Redrawn from Ref. 112. © Royal Society of Chemistry, 2010.]

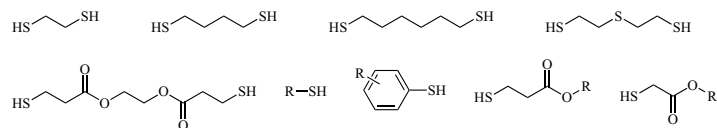
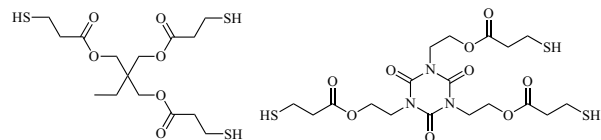
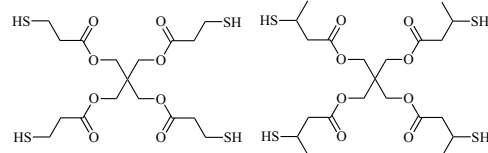
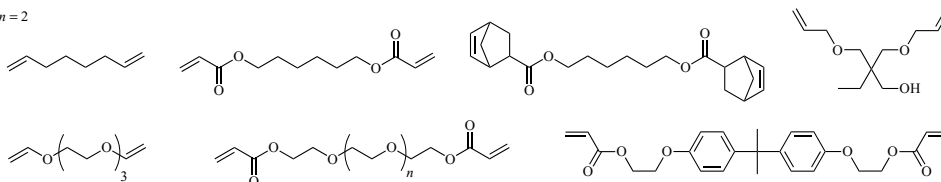
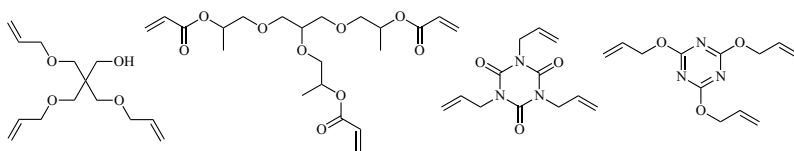
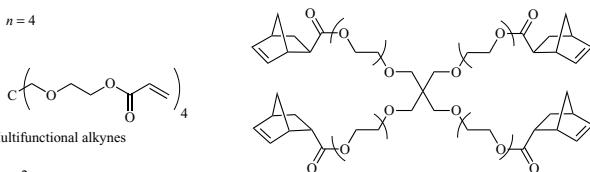
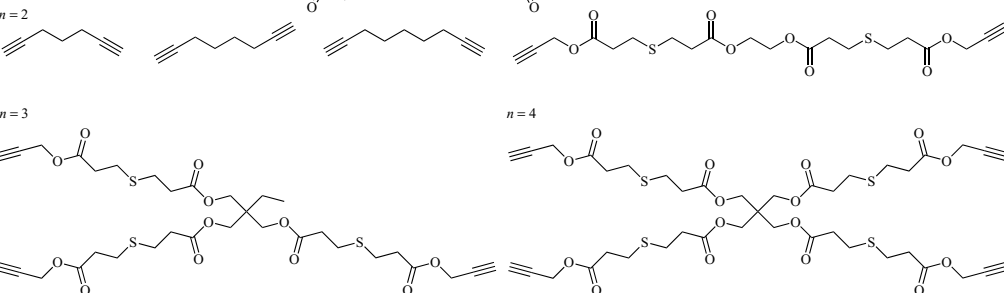


Hyperbranched Polymers

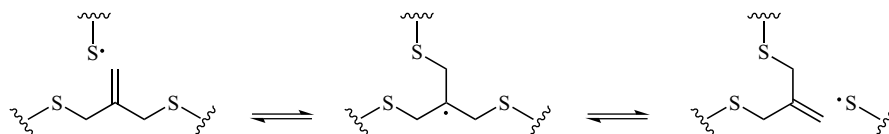
The post-polymerization functionalization of branched polymers by radical thiol-X chemistry has also been shown. The polymers were synthesized using, for example, RAFT polymerization

Polymer Networks

Polymerization is usually initiated photo-chemically in the presence or absence of the photoinitiator. It was demonstrated that UV light with wavelengths of 254 and 365 nm can

$n = 2$  $n = 3$  $n = 4$  $n=2$  $n = 3$  $n = 4$  $n = 2$ 

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DOI: 10.1002/9780470971253.rad082



Scheme 21 Reversible addition fragmentation for stress relieving in thiol–ene polymer networks. [Reproduced from Ref. 147. © American Chemical Society, 2009.]

initiate polymerization, though the initiation with the shorter wavelength was shown to be far more efficient.^{146,149}

The thiol–X radical addition proceeds exothermally, generating heat, which leads to the formation of stress in the material. It has been suggested to use the reversible addition fragmentation process to relieve this stress (Scheme 21). After polymerization, radical species are generated yielding thiyl radicals, which add to a double bond of an allyl sulfide group. The fragmentation (β -elimination) of the resulting species will favor the elimination of a strained group, thereby relieving stress.^{147,148}

The properties of the networks that are formed are strongly dependent on numerous parameters. Firstly, the nature of the monomers is highly important. The cross-linking needed for stabilization of the networks is more effective using monomers with more functional groups.¹²⁹ The resulting higher cross-linking density also results in an increase of the glass-point temperature of the materials.¹⁵⁰ Similarly, the molecular weight or size of the monomers influences the cross-linking density and thereby the glass-point temperature; lower molecular weight monomers shift the glass-point temperature to higher values. With the cross-linking density, the heat capacity of the materials also increases.¹⁵¹ The cross-linking density can also be influenced by changing the reaction conditions such as temperature and the radical concentration.¹⁵² Spacer lengths further influence properties such as the density and the free volume of the network; the use of longer spacers decreases the density of the networks and increases the free volume.¹⁵³

Since step-growth polymerization is a radical process, the free-radical polymerization of alkenes can occur, especially for (meth)acrylate monomers. At 1:1 ratio of (meth)acrylate and thiol functional groups, the degree of free-radical polymerization is minimized, though still present since the homopolymerization is faster than the thiol–ene addition.¹⁵⁴ This so-called mixed mode process allows the tuning of different properties: for instance, the

glass transition point by using an excess of alkene groups.^{150,155,156} As a side effect, phase separation can occur in the system, yielding inhomogeneous materials. The nature of the thiol hardly influences the materials properties, contrary to the alkene, though materials prepared with secondary thiols were found to be more stable upon storage.¹⁵¹

The addition of functional groups can also be used to influence the properties of the network. The addition of 3-mercaptopropionic acid to a mixture of multifunctional thiols and alkenes, for instance, yielded networks with an increased stability as a result of hydrogen-bonding interaction.¹⁵⁷

Thiol–yne chemistry, just as well as thiol–ene chemistry, can be applied to prepare networks, using multifunctional thiols and molecules with more than one triple bond. If a dithiol was to be used in combination with a monoalkyne, linear polymers should be formed, though this has not been reported yet. Radical thiol–yne chemistry yields materials with higher amounts of sulfur, thereby achieving superior refractive indices,¹⁵⁸ which makes such materials more suitable for optical applications.^{23,159} Additionally, the cross-linking density of the networks is higher.

Networks can also be prepared using a combination of methods, for example, radical thiol–X chemistry with reactions such as the nucleophilic addition of thiols to different groups (e.g., to isocyanate or epoxy groups).^{160–162} The different types of chemistry can be performed sequentially, since the nucleophilic addition requires a catalyst, whereas the radical thiol–ene addition is started upon the generation of radicals (typically by irradiation with UV light). The different reactions can also be performed simultaneously. By adjusting the reaction parameters, the properties of the final network can be controlled.

The polymer networks prepared using radical thiol–ene photopolymerization are interesting not only academically but also for applications, such as in adhesives (first commercial products are already available); as high-refractive-index,

high-energy-absorbing, and high- T_g materials; as dental restorative materials;¹⁶³ or to stabilize bone fractures.¹⁶⁴ The quick cross-linking of the monomer mixture upon irradiation with UV light as well as the tolerance of the curing toward water, oxygen, and other functional groups makes it a promising chemistry for numerous applications.

The network formation using radical thiol–X chemistry is not limited to the cross-linking of small molecular monomers, but also (end-)functionalized polymers can be used to create networks, as for instance shown for allyl end-functionalized polyurethane polymers which could be cross-linked in combination with a trifunctional thiol monomer.¹⁶⁵ Water-soluble polymers have been used in a similar way. The resulting materials can, for example, be used as hydrogels and will be discussed in the next paragraph. Besides bulk materials, also beads¹⁶⁶ (porous or nonporous, prepared using microfluidic devices) or thin layers (patterned or not) on surfaces can be prepared. The patterning of surfaces with 3D features will be discussed in Section 3.3.2.

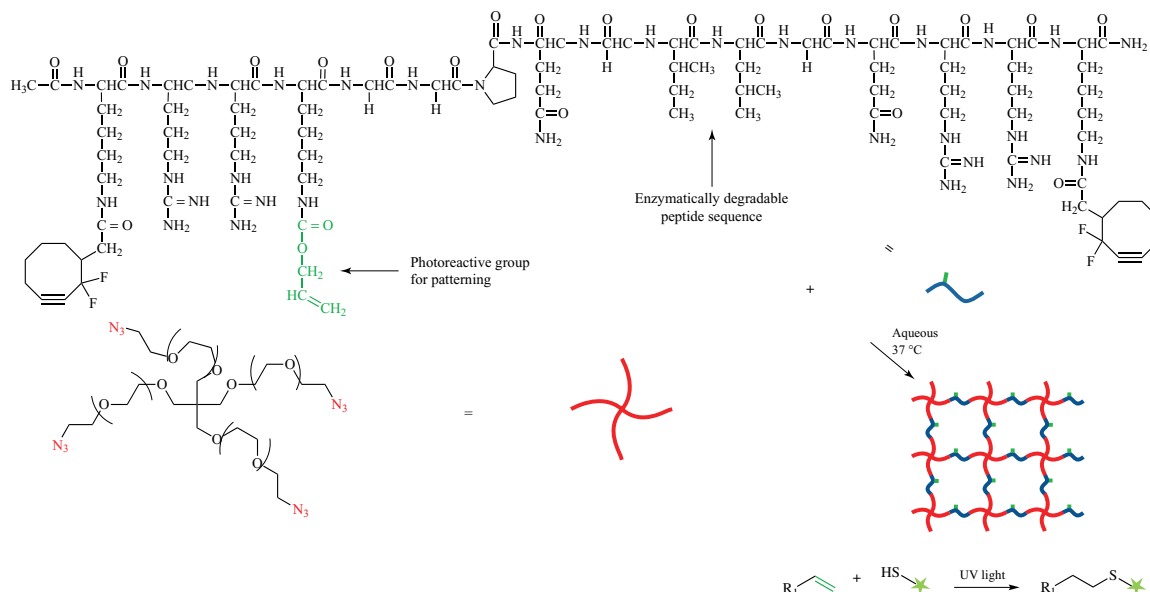
Hydrogels

Hydrogels can be prepared using the same methods that are used to prepare thiol–ene networks. Linear, star-shaped, or branched polymers based on PEO

or PMAA with multiple functional groups, thiol, or allyl are incorporated in the network.¹⁶⁷ The reactions could be performed in bulk or in solution with solid contents ranging from 50 to 3 wt%.

Hult *et al.* prepared hydrogels based on α,ω -alkene-functionalized linear PEO in combination with three-arm star-shaped PEO–SH-bearing terminal thiol groups.¹⁶⁸ Also, the hydrogel could be covalently bound to a thiol-functionalized surface. Bowman *et al.* described the synthesis of a similar type of thiol-allyl ether photopolymers employing di- and tetrafunctional thiols and diallyl-poly(ethylene oxide).¹⁶⁹

Anseth *et al.* synthesized a series of biodegradable hydrogels based on PEO and poly(L-lactide) (PLLA) polyesters using multifunctional thiols ($n = 2, 3$, and 4) and an α,ω -diacryloyl-functionalized PLLA–PEO–PLLA triblock copolymer.^{170–172} The radical polymerization occurred in a mixed mode via chain-growth (acrylate) and step-growth mechanisms (thiol–ene), transitioning from more chain-like to more step-like with increasing thiol to acrylate ratio, thereby controlling the microstructure and degradation characteristics of the network. The conversion of the acrylate was found to be virtually quantitative, though a large number of thiol groups remained unreacted, demonstrating that thiol–ene



Scheme 22 Synthesis of peptide-based hydrogel by sequential click reactions: (a) azide-alkyne step-growth polymerization to form hydrogel and (b) thiol-ene functionalization. [Reproduced from Ref. 178. © Nature Publishing Group, 2009.]

polymerization may be efficient but is not a click reaction. It should be highlighted that the polymerization was initiated by exposure to UV light, with or without a photoinitiator, and allowed the production of centimeter-thick samples.¹⁷⁰

PEO–peptide hydrogels have also been studied by Anseth *et al.* aiming to enhance the biodegradability and to improve the binding and viability of living cells. Reactants were either a star-shaped PEO with four norbornyl end groups and a short peptide sequence bearing two cysteine moieties^{173–175} or a linear α, ω -diacryloyl–PEO and a peptide containing four cysteine residues.¹⁷⁶ It could be shown that, when proteins are encapsulated in the matrix, their activity is nearly fully maintained, showing the biocompatibility of radical thiol–ene chemistry. Another route to incorporate cysteine-containing peptide sequences into PEO hydrogels involved the mixed mode photopolymerization of PEO-diacrylate and cysteine peptide. Incorporation of about 95% peptide could be achieved at an acrylate : cysteine ratio of 4 : 1 within 10 minutes of irradiation with 365 nm light ($\sim 5 \text{ mW/cm}^{-2}$).¹⁷⁷

Anseth *et al.* have described the synthesis of a peptide-based hydrogel by Huisgen azide–alkyne [3 + 2] cycloaddition, as shown in Scheme 22.^{178,179} The pendant double bonds in the peptide sequences were then click-functionalized with thiolated dye molecules. Because the thiol–ene reaction is light-driven and the degree of modification is directly related to the dosage of light delivered to the system, it was possible to create biochemical gradients of multiple peptides with well-defined magnitude and slope throughout the 3D network.

3.3 Colloid and Surface Chemistry

Surfaces that can be functionalized with unsaturated or thiol moieties can also be used in the functionalization by radical thiol–X chemistry, though the restricted accessibility of functional groups on surfaces makes it difficult to reach quantitative conversion, as required for click chemistry. Moreover, characterization of the surface may not be easy, making it hard to prove that a certain reaction proceeded as a click reaction.

Nevertheless, any reaction that in solution is a click reaction is potentially interesting for the modification of surfaces in heterophase, where

highly efficient methodologies are needed to obtain optimal degrees of functionalization. The following part on application of radical thiol–X chemistry to surfaces is divided into the functionalization colloidal particles and of planar surfaces.

3.3.1 Modification of Colloidal Particles

Different ways to introduce unsaturated groups or thiol groups can be applied, the chemistry depending on the nature and type of the particle. For silica nanoparticles, the use of silanes is most straightforward. Acrylate-functionalized silica nanoparticles, as described by Bowman *et al.*, can be obtained using 3-acryloxypropyl trichlorosilane,¹⁸⁰ which can be converted into a thiol-terminated surface by reaction with 1,3-propanedithiol. Subsequently, 1,6-hexanedithiol and triethyleneglycol divinyl ether were photopolymerized (DMPA, UV 365 nm) to yield polymer-coated particles.

Similarly, Kang *et al.* prepared silica particles bearing methacrylate groups, which were copolymerized with *N*-vinylcarbazole in the presence of divinylbenzene.¹⁸¹ Thiol-terminated PNIPAM (prepared by RAFT, see Section 3.2.1) was added to the double bonds on the surface of particles with a grafting density of 0.1 chains/nm². The silica template was then removed by HF etching to obtain hollow polymer capsules.

Caruso *et al.* used radical thiol–ene chemistry to stabilize hydrogen-bonded multilayers of poly(*N*-vinylpyrrolidone) (PVP) and poly(methacrylic acid) bearing side chains with either thiol or acrylate groups, as prepared by layer-by-layer (LbL) deposition onto a silica particle template (Figure 5).¹⁸² After the photochemical cross-linking of the PMAA layers (256 nm, 2 hours), the silica template was removed by etching with hydrogen fluoride followed by incubation in neutral water to remove the hydrogen-bonded PVP. The obtained polymer capsules could be further functionalized by thiol–ene addition of PEO–acrylate or PEO–maleimide.

Iron oxide nanoparticles stabilized with mercaptopropionic acid¹⁸³ or 3-allylacetylacetonate¹⁸⁴ could be functionalized with charged groups, for example, but-3-ene-1,1-diylidiphosphonic acid or its ester or with cysteine. Besides inorganic nanoparticles, also fullerenes¹⁸⁵ and carbon nanotubes¹⁸⁶

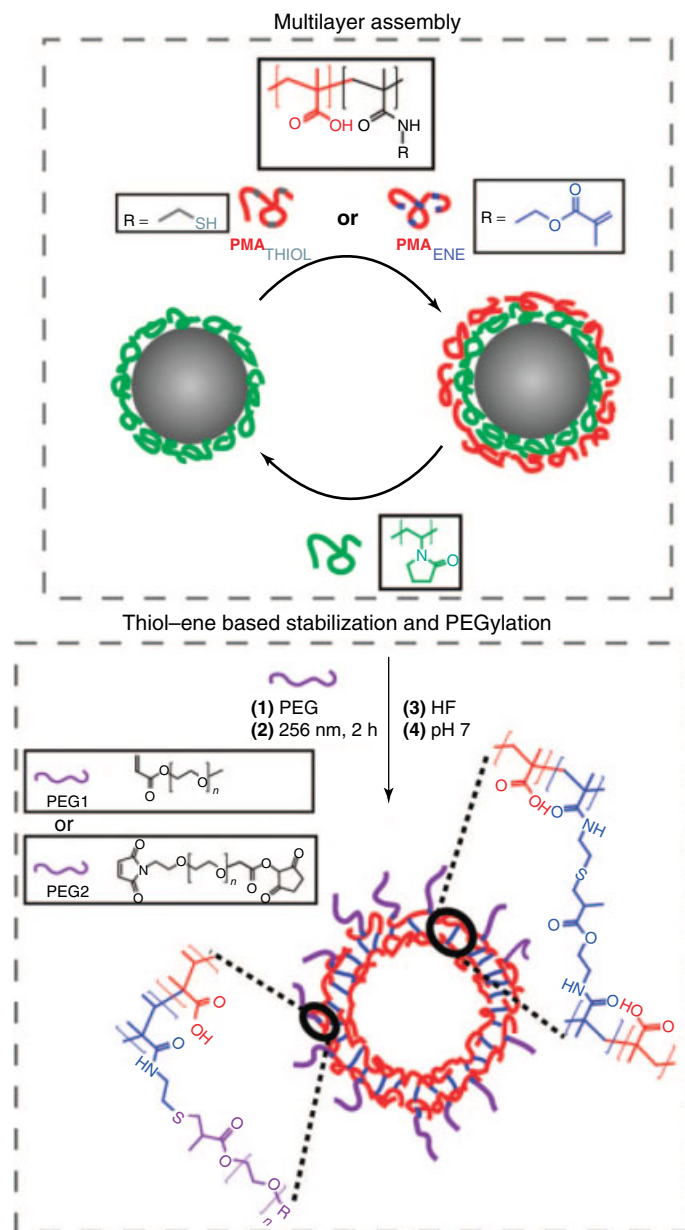
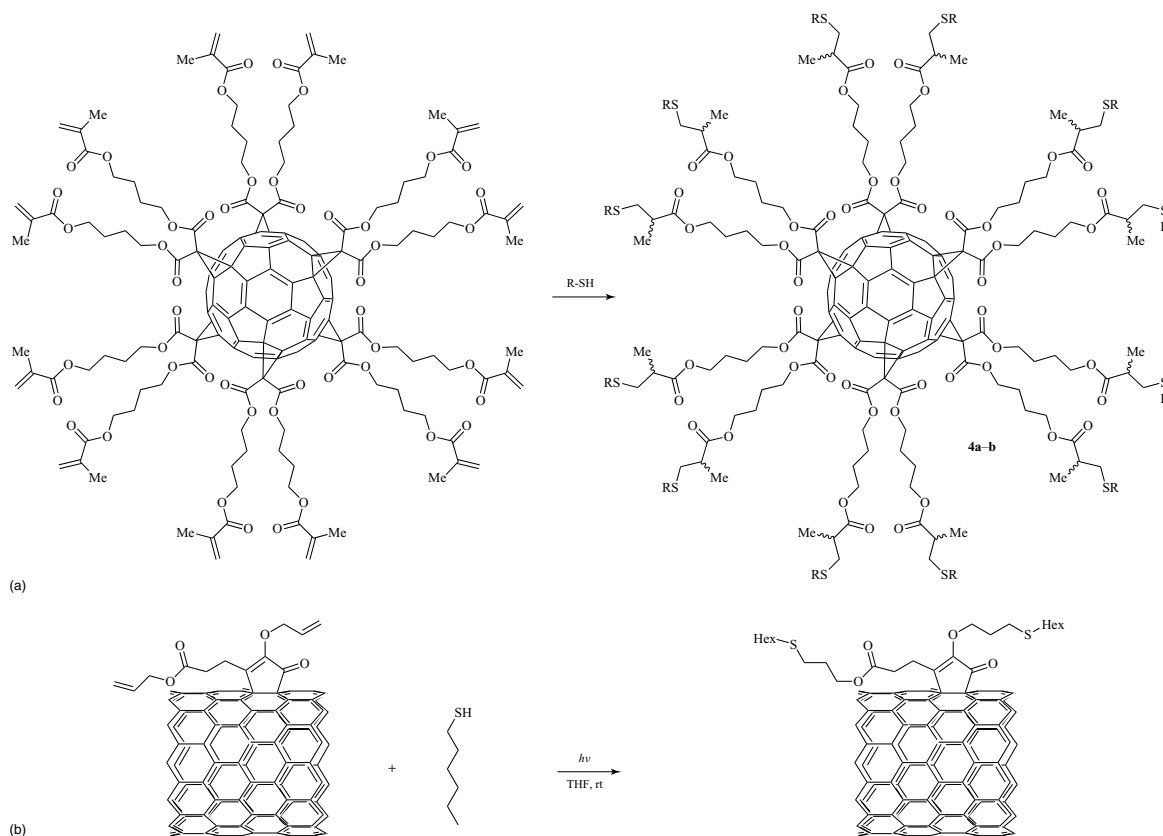


Figure 5 Preparation of polymer multilayer-coated silica particles and subsequent stabilization and functionalization via thiol-ene photochemistry. [Reproduced from Ref. 182. © American Chemical Society, 2009.]

have been functionalized with aliphatic thiols by radical thiol-ene chemistry (Scheme 23).

Polymeric particles carrying double bonds were produced by emulsion polymerization of divinylbenzene.^{187,188} The functionalization of the particles with polymer chains was

performed by thermal addition of either thiol end-functionalized PNIPAM¹⁸⁷ or PEO¹⁸⁸ or by addition of 1-azidoundecan-11-thiol, which then were reacted with alkyne end-functionalized poly(2-hydroxyethyl methacrylate) (PHEMA) by azide-alkyne cycloaddition.¹⁸⁷



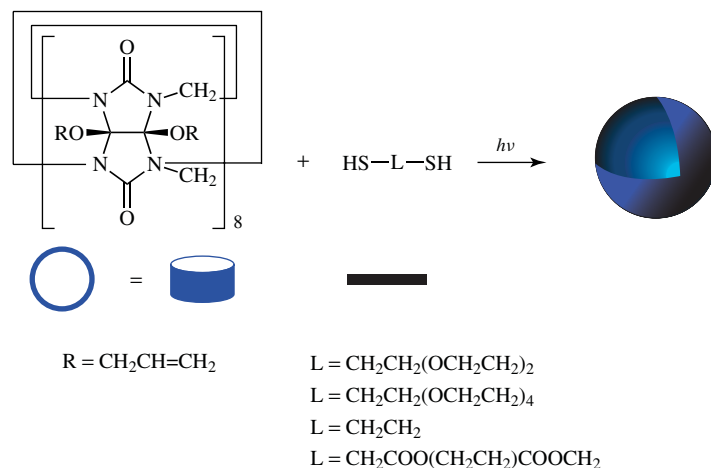
Scheme 23 Thiol–ene functionalization of (a) fullerenes. [Reproduced from Ref. 185. © Royal Society of Chemistry, 2010.] (b) carbon nanotubes. [Reproduced from Ref. 186. © American Chemical Society, 2009.]

Harth *et al.* showed the cross-linking of copolymers of α -allyl- δ -valerolactone and δ -valerolactone, the allyl groups of which were partially oxidized to epoxy groups with diamines.^{189,190} Cross-linking could also be performed using dithiols instead of diamines, eliminating the need for oxidation.¹⁹¹ The remaining double bonds could be functionalized with numerous different thiols, such as short peptide sequences, taxol, and dendrimers.

Schlaad *et al.* obtained porous microparticles bearing double bonds by crystallization of a statistical copolymer of poly(2-isopropyl-2-oxazoline) and poly[2-(3-butenyl)-2-oxazoline] in hot water.¹⁹² The polymer particles were functionalized in aqueous dispersion with 1-thiosugars, the conversion of double bonds reaching $\sim 60\%$. The nonquantitative addition of thiol was explained by a restricted accessibility of double bonds rather than side reactions.

Although very poorly soluble, syndiotactic 1,2-polybutadiene (PB) could be functionalized by thiol–ene chemistry either in the melt⁶¹ or in an aqueous dispersion.⁸⁰ In the latter case, the additions of 3-mercaptopropionic acid and methyl 3-mercaptopropionate proceeded to 85% yield. Using strongly hydrophilic thiols, only surface functionalization was achieved, that is, degrees of functionalization of up to 15%, nevertheless eliminating the need for surfactants in order to stabilize the dispersion.⁸⁰

Finally, Kim *et al.* synthesized nanocapsules using thiol–ene click photopolymerization of (allyloxy)₁₂cucurbit[6]uril, which is a rigid disk-shaped molecule with a cavity and 12 allyl groups at the periphery, and oligoethylene oxide or alkyl-based dithiols (Scheme 24).¹⁹³ The reaction was performed with UV radiation (254 and 300 nm) of a mixture of reactants at a ratio



Scheme 24 Template-free synthesis of polymer capsules through photopolymerization of (allyloxy)₁₂cucurbit[6]uril and dithiols. [Reproduced from Ref. 193. © American Chemical Society, 2010.]

allyloxy:thiol = 1 : 8 in methanol for 20 hours. The product was isolated in 87% yield after dialysis and contained no residual double bonds.

3.3.2 Modification of Surfaces

Polymerization on Surfaces

The formation of networks, as has been described earlier, can also be performed on surfaces. The curing of the thiol–ene mixtures can be used to make simple layers, but also to create 3D structures, using either a template (stamp) in a (nano)contact-molding imprint lithography approach^{194–199} or photomasks (Figure 6).^{200–204}

In contact-molding lithography, the material was cross-linked upon irradiation with UV light, so that the form was maintained upon removal of the template. This procedure allowed the preparation of structures with features below 100 nm. This chemistry was performed either on surfaces with functional (thiol or ene) groups, which reacted with the thiol–ene mixture (i.e., (3-acryloxypropyl)trimethoxysilane-modified silica surface, photopolymerized with di- or trifunctional enes with tetrafunctional thiol, DMPA, UV 365 nm),¹⁹⁴ or plainly on a surface (i.e., poly[(mercaptopropyl)methylsiloxane] (PMMS) with di- or trienes or using diacrylate-PEO with tetrafunctional thiols (either small molecules or PEO-based in the presence of DMPA, UV

365 nm)).¹⁹⁹ As with the networks formed in bulk, the functionality of the monomers strongly influence the stability of the features: more functional groups yield more stable layers.¹⁹⁴ The created patterns could be modified when, for instance, an excess of thiol was used in the original mixture, yielding free thiol groups on the surface of the 3D features (as shown using triene and tetrathiol monomers [SH]₀ : [C=C]₀ = 1.1, DMPA, UV 365 nm). The resulting features were either reacted with monofunctional enes (hexyl acrylate) or with the same monomer mixture as before ([SH]₀ : [C=C]₀ = 0.35). Further functionalization with monomer mixtures yielded features that were somewhat larger, thereby decreasing the minimum distance that can be reached by using contact-molding lithography alone.¹⁹⁶ A small degree of curing, before application of the template, was shown to improve the stability of the structures (commercially available thiol–ene photopolymer resist Norland Optical 60, containing tetra-ene with tri-thiol with photoinitiator, UV 365 nm).¹⁹⁷

The same principles have also been used to prepare microfluidic devices, which were shown to be very stable toward swelling by organic solvents. Devices were prepared using a polydimethylsiloxane (PDMS) template onto which a thiol–ene polymer network was cross-linked. The thiol–ene layer could be transferred either onto a planar substrate or be stacked with other layers after partial curing to create more complicated structures.^{202–204}

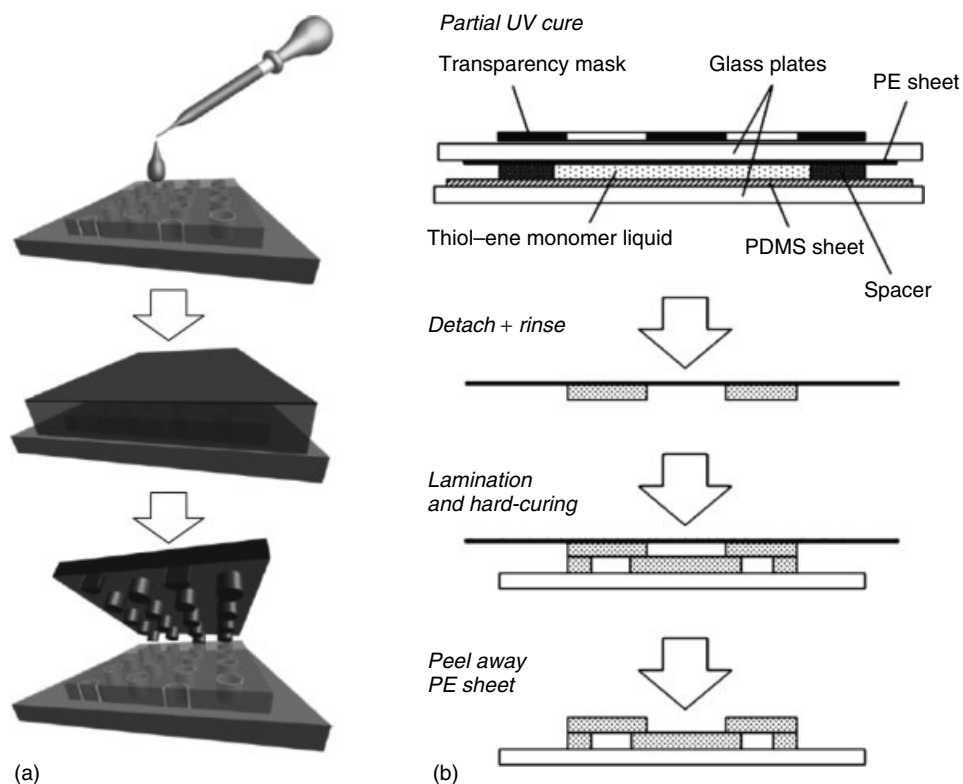


Figure 6 Illustration of the thiol–ene processes for making (a) stamps for contact-molding lithography. [Reproduced from Ref. 195. © Wiley-VCH Verlag GmbH & Co. KGaA, 2008.] (b) Patterned surfaces using photomasks. [Reproduced from Ref. 203. © Royal Society of Chemistry, 2008.]

Linear polymers could be polymerized on surfaces using difunctional thiols and alkenes. The (silica) substrate is functionalized with thiol groups (using MPTMS), which can be used to graft thiol–ene polymers onto (1,6-hexanediol and triethylene glycol divinyl ether, DMPA, 365-nm UV light). Any nonbound polymer could easily be rinsed away. The obtained layers were relatively thin, which suggests a low grafting density. Using combinations of photomasking (different irradiation times) and gradients in the concentration of thiol groups on the surface, gradients in the thickness of the polymer layer were achieved. Using photomasks, patterns could also be obtained since the polymerization was initiated locally.^{200,201}

Patton *et al.* performed a free-radical polymerization of poly(trimethylsilyl)propargyl methacrylate from a silica surface decorated with a photoinitiator (Figure 7a).²⁰⁵ Propargyl moieties were deprotected and subsequently functionalized

using radical thiol–yne chemistry. Though the conversion of alkyne groups was quantitative, some residual vinyl sulfide groups remained as a result of steric hindrance. The sequential polymerization of the surface could be shown: firstly a photomask was used to selectively functionalize the exposed surface, and, after removal of the mask, the rest of the surface was functionalized with a second thiol (Figure 7b).

Self-Assembled Monolayers

As with the radical thiol–ene functionalization of nanoparticles, the modification of self-assembled monolayers (SAM) requires the introduction of alkene or thiol groups onto the surface. When the goal of the reaction is the formation of a monolayer, monofunctional thiols or alkenes are used in the functionalization. Functional surfaces are very interesting for all kinds of applications, such as antifouling, lab-on-a-chip designs, and so on. The

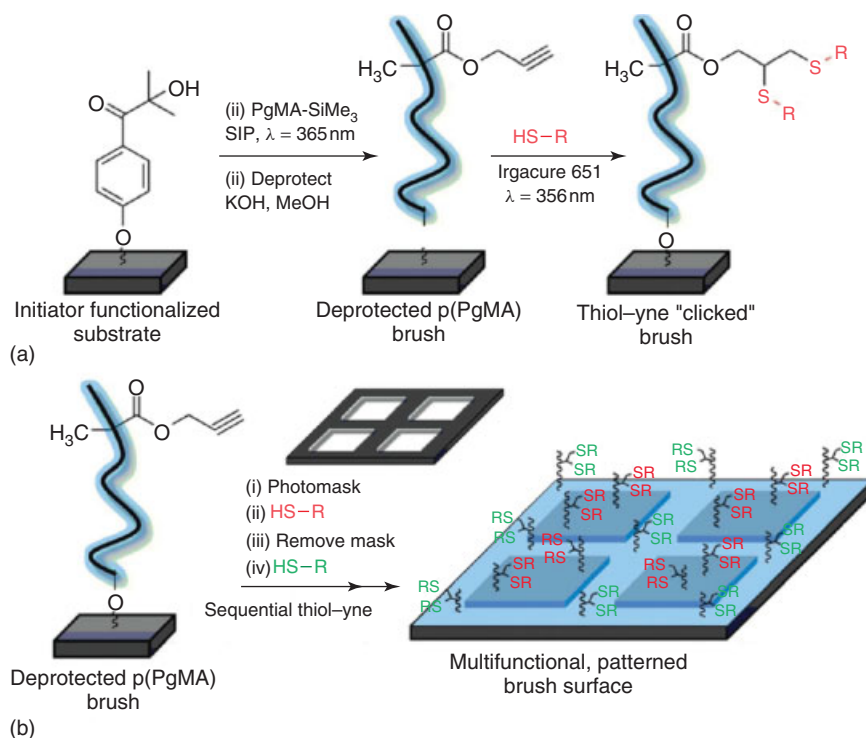


Figure 7 (a) Illustration of the procedure of surface-initiated polymerization of propargyl methacrylate and subsequent thiol-yne modification. (b) Photopatterning of the yne polymer brush with sequential thiol-yne addition. [Reproduced from Ref. 205. © American Chemical Society, 2009.]

modular nature and the photoinitiation make radical thiol-ene chemistry a very promising tool to prepare patterned surfaces.

The functionalization of a number of surfaces has been described, including polymeric surfaces, glass and silicon oxide, hydrogen-terminated silicon, and aluminum.

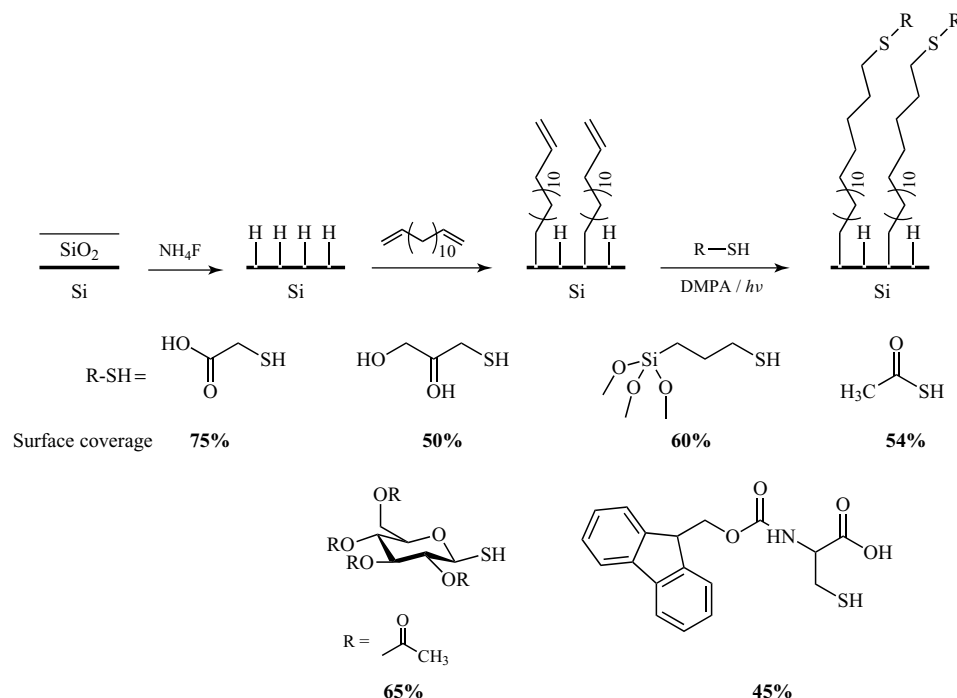
Regarding polymer surfaces, poly(vinylmethylsiloxane)-based surfaces were grafted with thiolated alcohols using AIBN.²⁰⁶ Allyl-terminated polyurethane monolayers were reacted with a tetrafunctional thiol using UV light and DMPA.²⁰⁷ Subsequently, PEO-methacrylate was polymerized in a free-radical process using DMPA as a photoinitiator.

Besides silicon oxide (*vide infra*), hydrogen-terminated silicon has been functionalized through thiol-ene photochemistry.^{208,209} The Si(111) surface was first reacted with 1,13-tetradecadiene to form a C=CH₂-terminated monolayer (see **Silicon Radical Surface Chemistry**) and then exposed to 365-nm light in the presence of different thiols and DMPA

(Scheme 25).²⁰⁸ Surface coverages with thiol were found to be between 45% (cysteine) and 75% (thioglycolic acid). Also, patterned surfaces were obtained by microcontact printing (μ CP). Alternatively, the silicon surface was first coated with 1,2-polybutadiene and then functionalized with thiols by exposure to fluorescent light (first step) and UV light (second step).²⁰⁹

Alkene-terminated SAMs on silica, which can be readily prepared by using, for instance, 11-undecenyltrichlorosilane or 3-(trimethoxysilyl)propyl methacrylate, were reacted with low molecular weight thiols (i.e., *N*-acetyl-L-cysteine, dithiothreitol, 3-mercaptopropionic acid, and galactoside-thiol) or thiolated polymers, respectively.^{210,211}

Ravoo *et al.* created well-defined patterned surfaces by photochemical thiol-ene μ CP, as illustrated in Figure 8.²¹⁰ Simply, an oxidized PDMS stamp was inked with thiol and DMPA (photoinitiator), placed on an undecenyl-terminated SAM, and irradiated with high-power UV light-emitting diode



Scheme 25 Functionalization of hydrogen-terminated silicon using thiol–ene chemistry. [Reproduced from Ref. 208. © Royal Society of Chemistry, 2010.]

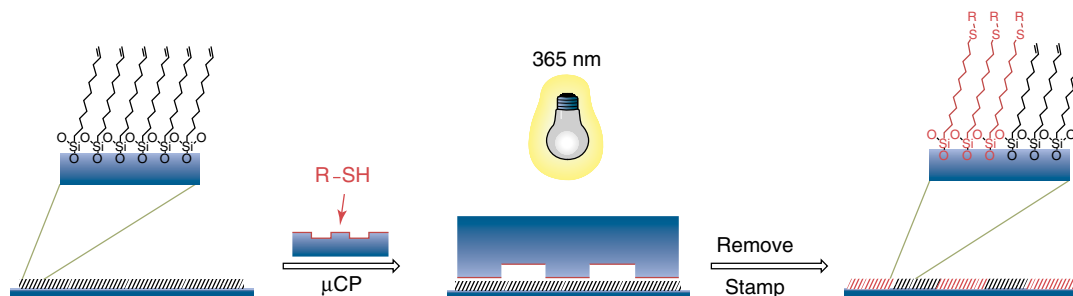


Figure 8 Thiol–ene microcontact printing (μCP): Placement of a thiol-inked stamp on an alkene-terminated surface and irradiation with UV light (365 nm). [Reproduced from Ref. 210. © American Chemical Society, 2010.]

(365 nm). High grafting densities could be reached within short reaction times of tens of seconds to minutes. Also, the photochemical modification of SAMs by thiol–yne chemistry was applied, but without reaching higher surface grafting densities. Evidently, the thiol addition to the surface-bound triple bonds did not proceed to completion, possibly yielding just the monoaddition product.

It is worth mentioning that, according to Jiang and Yin *et al.*, the photochemical route of grafting thiolated polymer onto a methacrylate-terminated

SAM was more efficient than the thermal route, as indicated by considerably higher grafting densities ($2.93 \mu\text{mol m}^{-2}$ vs $1.71 \mu\text{mol m}^{-2}$).²¹¹

Silicon wafers or glass slides were reacted with MPTMS to yield thiol-terminated SAMs, onto which hydrophobic alkenes (hexadecane, octadecyl vinyl ether, and octadecyl acrylate) were added by irradiation with 365-nm UV light in the presence of benzophenone as photoinitiator.²¹² Best results were obtained, however, for the coating with octadecyl acrylate in the absence of

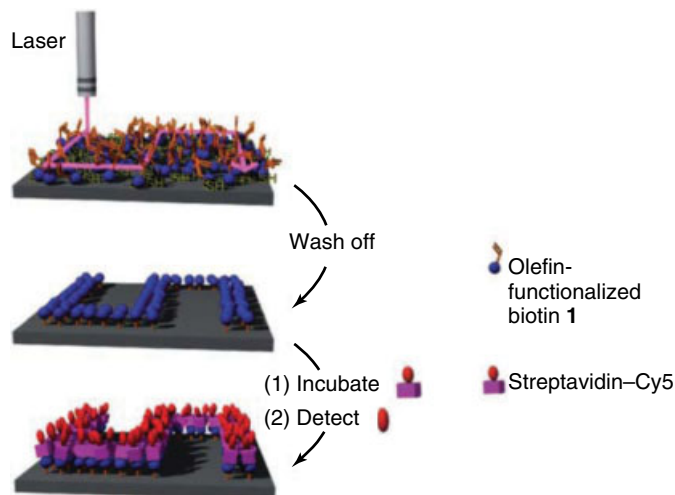


Figure 9 Illustration of the process of patterning of thiol-terminated surfaces with ene-functionalized biotin using a laser source. [Reproduced from Ref. 216. © Wiley-VCH Verlag GmbH & Co. KGaA, 2008.]

solvent. The photochemical thiol–ene modification of MPTMS-coated glass slides, for instance with alkenes or 1,2-polybutadiene, could also be achieved in the absence of a photoinitiator.²¹³ Residual double bonds in the cross-linked polybutadiene coating could further be functionalized with, for instance, sugar thiols (thiol–ene–thiol reaction).

Bowman *et al.* prepared ultrathin thiol–ene polymer films with a thickness gradient on silicon wafers.²⁰¹ Thiol–ene films were attached to the surface by first depositing a thiol-terminated SAM and performing a thiol–ene photopolymerization reaction on the surface. Property gradients were obtained either by creating and modifying a gradient in the surface thiol density and/or by changing the polymerization conditions (exposure time to UV light through photomasks).

Just like silicon, aluminum surfaces were also coated with MPTMS and subsequently reacted with unsaturated vegetable oils.^{214,215} The thiol–ene reaction was carried out using UV light and benzophenone as photoinitiator.

Niemeyer and Waldmann *et al.* applied the thiol–ene reaction for photochemical surface patterning.²¹⁶ Thiol-terminated surfaces were prepared in a multistep procedure: polyamidoamine (PAMAM) dendrimers, which were covalently bound to the silicon oxide surface, were sequentially attached to an aminocaproic acid spacer and 2-aminoethyl disulfide; the disulfide was then

reduced to the thiol. The surface was coated with ene-functional biomolecule, that is, biotin, and either exposed to UV light through a photomask or patterned with a laser light beam ($\lambda = 411$ nm) (Figure 9). The patterns could be visualized after treatment with Cy5-labeled streptavidin by fluorescence microscopy. Later, the methodology was extended to alkene-terminated surfaces and other ene- and thiol-functionalized biomolecules (e.g., glycopeptides and oligonucleotides) and to spotting of microarrays.^{217,218}

4 CONCLUSION AND OUTLOOK

Radical thiol–ene and –yne chemistry, that is, free-radical addition of a thiol to unsaturated groups, has over the last decade developed into a powerful tool in the synthesis of numerous different materials, because it can have the characteristics of a “click” reaction, which means that it is modular, achieves high yields in a short time, is selective toward a single product, and products are easy to purify.

These characteristics are of great advantage in organic chemistry as, for instance, shown by the use of this chemistry not only in the synthesis of bioactive molecules and dendrimers but also in the synthesis and modification of macromolecules by step-growth polymerization of multifunctional enes and thiols, respectively, and the addition of thiols to macromolecules bearing unsaturated groups

(or vice versa). Another upcoming application is the modification of nanoparticles and surfaces, for which free-radical thiol–X chemistry is supremely suitable because of its high yields and especially by the ease with which patterning of surfaces can be performed by using photochemical production of free radicals.

Thiol–ene chemistry has been well established and the major progress will likely be found in even more diverse applications of chemistry, owing to the ease with which the reactions can be performed and the availability of both different functional thiols and functional enes. For the same reason, it is to be expected that the number of commercial applications of this chemistry will increase dramatically over the coming years, first ventures already having started based on the photochemical polymer network formation.

Some progress can still be made with respect to thiol–yne chemistry, which has only very recently started attracting serious attention. The fact that a single group can be functionalized with two functional thiols, in certain cases perhaps even in a distinct two-step process yielding a product with two different functional thiols, has certain advantages over thiol–ene chemistry, mainly with respect to the density of functional groups.

As already mentioned, surface modification with thiol–X chemistry has received increased interest lately. The ease with which surface patterning can be performed using photomasks, laser writing, ink-jet printing, etc., to locally generate radicals was already shown to be a promising method to create monolayers and 3D structures. Building on this proof-of-principle work, this could very easily be applied to actual systems, to be used for other sophisticated lab-on-a-chip applications, microfluidics, and so on.

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Polyradicals in Batteries

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1 INTRODUCTION

Batteries are composed of cathode- and anode-active materials, a separator to separate the two electrode-active materials, an electrolyte layer, and current collectors. The cathode- and anode-active materials of conventional primary and secondary batteries are usually metal oxides, such as manganese, silver, lead, nickel, and vanadium oxides, and metals such as zinc, lead, cadmium, and lithium. All the electrodes of conventional batteries are composed of metals and metal oxides (except oxygen and carbon that are used for the air battery cathode and the lithium battery anode, respectively).

Primary batteries, such as alkaline manganese and silver oxide batteries, produce electric current by a one-way chemical reaction and are not rechargeable. Portable electronic equipments, electric vehicles, and robots require rechargeable secondary batteries. At present, Li ion, lead acid, and nickel-metal hydride batteries are generally used to power them. Ubiquitous electronic devices such as integrated circuit smart cards and active radiofrequency identification tags need rechargeable batteries that are bendable or flexible and environmentally benign for durability in daily use. Designing of soft portable electronic equipments, such as rollup displays and wearable devices, also require the development of flexible batteries.

Among the secondary batteries, Li-ion batteries are becoming the most popular. Typical Li-ion battery is configured with the cathode composed of Li-ion-containing metal oxides, such as lithium

cobalt oxide, and the anode of graphite carbon. During the charging process, Li ions are eliminated from the lattice of the metal oxide cathode and intercalated into the carbon anode. During the discharging process, the cobalt oxide is regenerated by the elimination of the Li ions. Li is one of the smallest elements to yield large specific capacity ($\text{Li}_6\text{C} \rightarrow 6\text{Li}^+ + 6\text{e}^- + \text{C}$: 372 mAh g^{-1}) and the very large electromotive force (emf) generated by the Li ion ($0.5\text{C}_6\text{Li} + \text{Li}_{0.5}\text{CoO}_2 \rightleftharpoons 3\text{C} + \text{LiCoO}_2$: 3.6 V), which result in a high energy density and the highest given voltage of the battery. Another feature of the Li-ion battery is the rocking-chair-type intercalation reactions of the Li ion between the cathode- and the anode-active materials. The intercalation of Li ions into the electrodes suppresses metallic Li (dendrite) formation by separating and immobilizing each Li ion in the lattice and the layered structure. However, the intercalating diffusion of Li ions accompanied by transformation of the lattice and the layer structure during the electrode reactions results in slow kinetics and heat generation in the charging and discharging processes, often producing overheating and occasional ignition. Indeed, battery makers often issued due to overheating accidents recall of their million-scale Li-ion batteries for mobile phones and laptop computers.

Recent development of organic batteries aiming at increasing the energy density has made them promising candidates of energy-storage devices to complement the conventional inorganic-based batteries. A new trend in materials research is emerging recently, focusing on the fabrication

of organic robust radicals to allow fully reversible one-electron redox reactions featuring fast electrode kinetics and reactant cyclability.^{5–7} Nitroxide radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (see **Nitroxides in Synthetic Radical Chemistry**) and nitronyl nitroxides, the nitrogen radicals such as triarylammonium cation radicals, diphenylpicrylhydrazyl (DPPH) derivatives, and verdazyls, and the oxygen radicals such as phenoxyls and galvinoxyls are typically examined as the pendant group of the radical polymers (Figure 1). These radicals are persistent at ambient temperatures under air and characterized by rapid and reversible $1e^-$ electrode reactions, typically with heterogeneous electron-transfer rate constants in the order of $k_0 = 10^{-1} \text{ cm s}^{-1}$.

2 RADICALS AS REDOX SITES

NO Radicals

TEMPO

PROXYL

N Radicals

Nitronyl nitroxide

Triaryl-aminium

DPPH

Verdazyl

O Radicals

Galvinoxyl

Figure 1 Robust radicals with reversible $1e^-$ redox capability in electrode reaction, characterized by large heterogeneous rate constants.

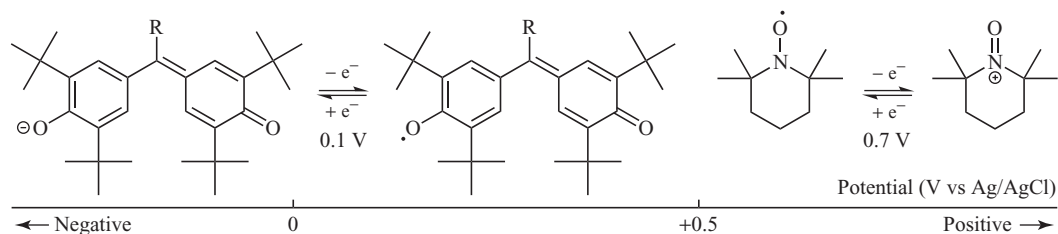


Figure 2 Redox reactions of TEMPO and galvinoxyl.

3 RADICAL POLYMERS FOR CHARGE TRANSPORT AND STORAGE

Radical polymers are defined as the aliphatic polymers which are highly populated with the robust radicals per repeating units. A variety of polymer backbones have been employed to bind the

radicals, such as poly(meth)acrylates, polystyrene derivatives, poly(vinyl ether)s, polyethers, and polynorbornenes (Figure 3).^{8–21} The radical sites must be bound to polymer chains because of the need to immobilize them at current collectors for exclusion of elution into electrolyte solutions that lead to discharging, to accomplish

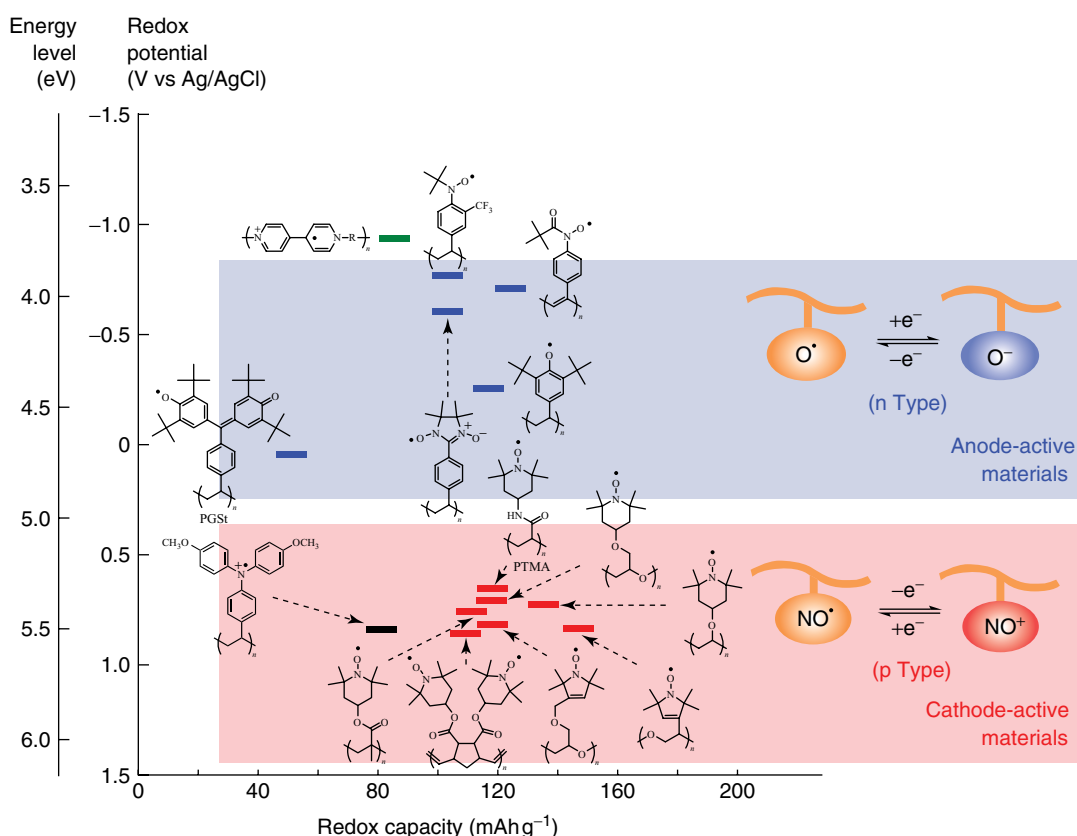


Figure 3 Map of radical polymers showing suitability for anode- and cathode-active materials. High redox capacity is desired for high-density energy storage in batteries. Redox potential and capacity depend on the structure of the redox site and the formula weight of the repeating unit, respectively.

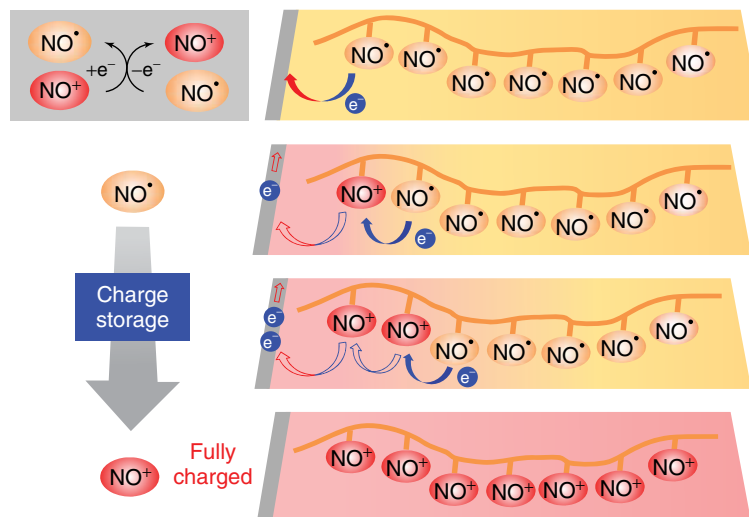


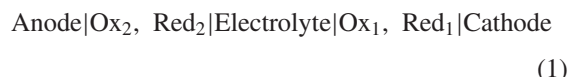
Figure 4 Charge transport and storage in radical polymers by electron self-exchange reaction throughout the polymer layer on current collectors.

appropriate mobility of the counterions, to make the electrode-active material amorphous and plasticized to accommodate deformation without heat generation, and to allow wet fabrication processes. Unpaired electron density of the polymers, determined by superconducting quantum interference device (SQUID) measurements, has revealed the presence of the radicals per repeating unit. Specific capacities based on the formula weight of the repeating unit are in the range of 50–150 mAh g⁻¹.

The unpaired electron density of the radical polymers amount to several molars in the bulk of the swollen polymer equilibrated in electrolyte solutions. Under these conditions, charge propagation within the polymer layer is sufficiently fast leading to high-density charge storage, because the redox sites are so populated that electron self-exchange reaction goes to completion within a finite distance of the polymer layer (Figure 4).^{22,23} The concentration gradient-driven charge propagation is accomplished by the electron self-exchange reaction. The exchange reaction is sufficiently fast for the diffusion-limited outer-sphere redox reactions, resulting in the efficient transfer of charge produced at the surface of the current collector. Combination of the fast electrode process ($k_0 \sim 10^{-1}$ cm s⁻¹) and self-exchange reaction ($k_{ex} \sim 10^{6-8}$ M⁻¹ s⁻¹) lead to the high rate performance of the radical battery.

4 CONFIGURATION OF RADICAL POLYMERS IN RADICAL BATTERIES

The radical polymers act as both cathode- and anode-active materials, depending on the redox potential. A couple of polymers which are different in redox potentials are used as the electroactive materials in the organic radical battery. In general, a difference in the potentials that tends to give rise to electric current is called emf. For a cell with a general configuration of



the overall reaction is $n_2 \text{Ox}_1 + n_1 \text{Red}_2 \rightleftharpoons n_2 \text{Red}_1 + n_1 \text{Ox}_2$ and the emf is given by

$$E = E_1 - E_2 = \Delta E^\circ - RT/(n_1 n_2 F) \ln \left\{ (a_{\text{Red}_1}^{n_2} a_{\text{Ox}_2}^{n_1}) / (a_{\text{Ox}_1}^{n_2} a_{\text{Red}_2}^{n_1}) \right\} \quad (2)$$

The cell voltage is $V = E - IR$ where R is the resistance of the cell. The power is $P(W) = \text{current } I(A) \times \text{cell voltage } V(V)$. In radical batteries (Figure 5), the charging process corresponds to the oxidation of the radical $\text{R}_1^\bullet$ to the cation R_1^+ at the cathode, and the reduction of the radical $\text{R}_2^\bullet$ to the anion R_2^- at the anode. The emf of the radical battery corresponds to the potential gap between the

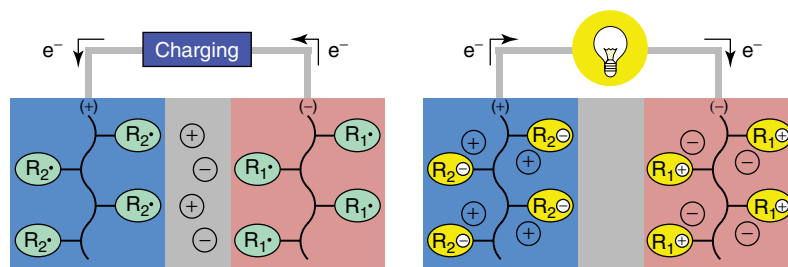


Figure 5 Configuration of cathode- and anode-active materials in batteries, sandwiching an electrolyte layer. $R_1^\bullet$ and $R_2^\bullet$ represent the radical redox sites in the cathode- and the anode-active materials, respectively.

two redox couples according to

$$E = \Delta E^\circ - RT/F \ln\{(a_{R_1^+} a_{R_2^-}) / (a_{R_1^\bullet} a_{R_2^\bullet})\} \quad (3)$$

which typically amounts to 0.5–1.5 V. The radical polymers are reversibly converted to the corresponding polyelectrolytes during the charging process, which can be isolated and identified.²⁴

The rapid electrode reaction of the radicals and the efficient charge propagation within the polymer layer (Figure 4) lead to the excellent rate performance, allowing instant charging and large discharge currents without substantial loss of output voltages V .

The amorphous radical polymers allow fabrication of flexible thin-film devices (Figure 6). A curious feature of the radical battery is the

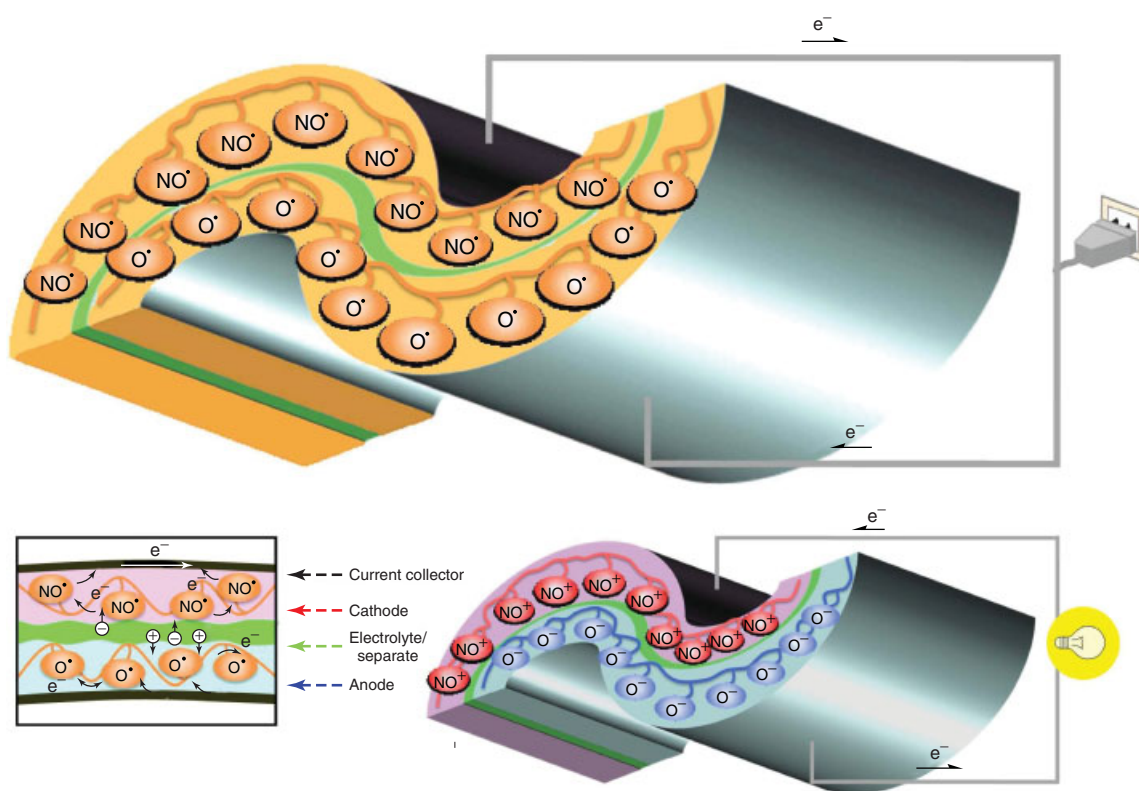


Figure 6 Structure and charge storage configuration of a flexible radical battery.

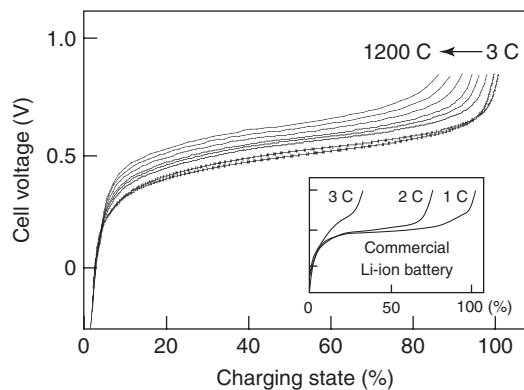


Figure 7 Comparison of charging curves obtained for a radical battery with that for the Li-ion battery, demonstrating the excellent rate performance of the radical battery allowing 3 s (1200 °C) full charging without loss of capacity. The radical battery composed of the PTMA cathode and the PGSt anode.

capability of burst power generation, which also allow instant full charging (i.e., in a few seconds) (Figure 7).¹⁵ Optimization of the entirely organic radical battery, typically fabricated with poly(2,2,6,6-tetramethylpiperidin-1-oxy-4-yl methacrylate) (PTMA) and poly(4-galvin-oxystyrene) (PGSt) (Figure 3) as the cathode and the anode-active materials, respectively, have allowed retention of >90% capacity even after 1000 charging/discharging cycles. Radical batteries have proved to be a new class of organic rechargeable devices, which are characterized by the rate performance and the moderate energy density. The mass-specific energy density is placed between those of polyacetylene- and disulfide-based organic batteries, but the power density is much larger and comparable to those of supercapacitors.

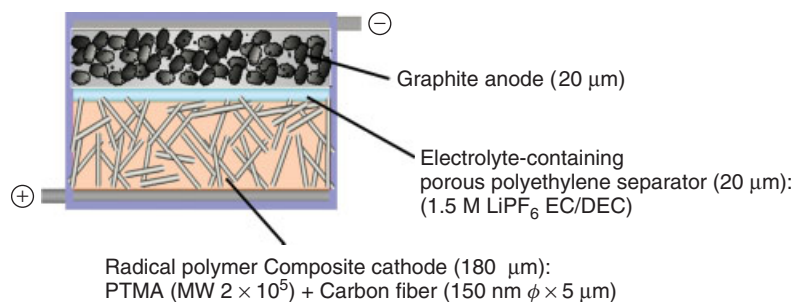


Figure 8 Prototype of the radical battery using a radical polymer as the cathode-active material. Ethyl carbonate–diethyl carbonate (EC/DEC) containing LiPF_6 is the most typically used as the electrolyte.

5 TECHNOLOGICAL TRENDS OF RADICAL BATTERIES DESIGNED FOR PRACTICAL APPLICATION

The radical battery is being developed for sub-battery and smart card applications.^{25–28} Because of their high-power characteristics, radical batteries in a compact battery pack are expected to power a desktop computer as a sub-battery for emergency use. Their environmentally benign properties are suitable for powering smart cards. A 100 mA h-class aluminum-laminated-film-packaged radical battery with the PTMA/carbon cathode²⁹ and a graphite anode has been fabricated (Figure 8). The composite electrode consists of 50 wt% PTMA and 45 wt% vapor-grown carbon fiber (VGCF). The composite electrode and graphite anode are 180- and 20- μm thick, respectively. The electrode is $45 \times 55 \text{ mm}^2$, which is half of a business card. The fabricated battery weighs 22 g and is 4.3-mm thick. A battery pack consisting of four such batteries connected in series operated a 200-W-class desktop computer without additional power input, so the battery is suitable for emergency use as a sub-battery. The battery pack is sufficiently compact to install in an expansion slot of a desktop computer. A rate capability test has demonstrated that the battery pack has a 13 A (130C-rate) discharge, although the capacity decrease to half that at a lower rate. Organic radical batteries could also be used as high-power energy sources, such as sub-batteries for electronic devices and motor assistance for electric vehicles, replacing the electric double-layer capacitors and nickel metal hydride batteries.²⁵

Thin organic radical batteries are being developed for application to smart cards. A prototype



Figure 9 Prototype of the thin and flexible radical battery (NEC Co.) loaded on flash devices and smart cards.

battery with a thickness of $800\mu\text{m}$ has been fabricated and tested, which is composed of a composite electrode containing 70 wt% poly(2,2,6,6-tetramethylpiperidin-1-oxy-4-yl vinyl ether) (PTVE) and a lithium metal anode. The electrode is $24 \times 22\text{ mm}^2$. The discharge capacity of the battery is 6.0 mA h. The I - V characteristics have been investigated using the 1-s pulse discharge method. The direct current resistance of the battery is only 1.5Ω , and the maximum power output is 2.0 W. This output power is sufficient for high-power applications such as for the luminescence of a flash device using light emitting diode (LED). The prototype battery embedded in a smart card is shown in Figure 9.^{30,31}

The pulse cyclability of the battery was examined by subjecting it to 5 mA (5 s) pulse discharges once a minute. Almost no deterioration was observed up to 10 000 pulse cycles even at 40°C . This stability further supports the practical application of the organic radical battery.²⁵

Efforts have been directed toward further increasing the theoretical energy density of the radical batteries. For this purpose, various radical polymers with even smaller formula weights per repeating unit are under development.

6 CONCLUSION AND OUTLOOK

Radical polymers are emerging as a new class of organic electrode-active materials, taking advantage of their unique charging/discharging processes allowing instant charging and excellent power rate capabilities. The electrochemical reversibility is considered a pervasive characteristic of organic robust radicals. Charging and discharging of the radical polymer layers are accomplished by the reversible $1e^-$ self-exchange reaction

between the neighboring sites to allow a redox-gradient-driven charge propagation throughout the polymer layer. The use of the radical polymers has offered design principles to explore the rechargeability of organic materials which are useful for various wet-type electronic devices such as batteries, solar cells, sensors, and electrochromic displays. It may also be added that the inherent environmentally benign properties are also advantageous for a sustainable development, based on the rare metal free, safe, and disposable features of the radical polymers.

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Radical Chemistry on Fullerenes

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1 INTRODUCTION

Free-radical reactions were one of the first investigated reactions of fullerene C_{60} .^{1–3} Since this molecule has 30 carbon–carbon double bonds, multiple additions of a variety of radicals can take place very readily, which typically results in a complex and thus difficult-to-separate mixture of products. For example, up to 11 phenyl groups, 15 benzyl groups, and 34 methyl groups have been reported to add to C_{60} .^{4,5} Owing to this property, C_{60} has been characterized as a “radical sponge”.^{4,5} On the other hand, thorough studies in the field of fullerenes’ radical chemistry have led to the development of appropriate reaction protocols that allow the selective preparation of monoaddition fullerene adducts or multiadducts with well-defined addition pattern. In addition, electron spin resonance (ESR) spectroscopic studies have provided valuable insight into the basic characteristics of the radical reactions of fullerenes, including the reactivity of radicals of various chemical nature (i.e., alkyl, perfluoroalkyl, O-, S-, P-, B-, Pt-, and Si-centered radicals) with respect to C_{60} and C_{70} , the delocalization of the unpaired electron in monofullerenyl radicals ($RC_{60}^{\bullet}$ and $RC_{70}^{\bullet}$), and their reactivity.^{1,4–30} The aim of this article is to provide a concise review of both the fundamentals and practical synthetic applications of fullerenes’ radical chemistry.

2 ADDITION OF C-CENTERED RADICALS

The addition of alkyl radicals $R^{\bullet}$ ($R = \textit{tert}$ -butyl, 1-adamantyl, isopropyl, ethyl, benzyl) to C_{60} was

among the first reactions to be studied.⁶ Initially, it was found that the unpaired electron in the resulting $RC_{60}^{\bullet}$ radical adducts is essentially confined to the three carbon atoms ortho (C1, C5, C5') and the two carbon atoms para (C3, C3') to the point of attachment of R (Figure 1), which rules out an extensive delocalization of the unpaired electron over the C_{60} sphere.^{6,7} Further studies led to a reassignment of the density of the unpaired spin; the highest spin density was found for C1, whereas almost no spin density was found on C5 and C5', which leads to only two major canonical resonance structures of $RC_{60}^{\bullet}$.^{13,27}

An important feature of fullereryl radicals is the hindered rotation about the $R-C_{60}^{\bullet}$ bond, so that the alkyl groups adopt preferred conformations relative to the C_{60} framework.^{1,8,11,14,18,27,31} For example, the $CH_3CH_2C_{60}^{\bullet}$ radical adopts asymmetrical equilibrium conformation, that is the terminal methyl group moiety is placed directly above one of the two 6-membered fused rings of C_{60} ,¹¹ whereas the terminal CF_3 group in $CF_3CH_2C_{60}^{\bullet}$ prefers the position above a pentagon (Figure 2a,b).^{19,21,27} It has been typically shown that in radicals of the general type $XYZCC_{60}^{\bullet}$, where X, Y, and Z are CF_3 , F, H, or CH_3 , a CH_3 group will never gain the pentagon position except when there is no alternative [i.e., $(CH_3)_3CC_{60}^{\bullet}$, Figure 2c], whereas a CF_3 group will never gain the hexagon(s) position except when there is no alternative [i.e., $(CF_3)_3CC_{60}^{\bullet}$].^{21,27}

A remarkable feature of the ESR spectra of a series of $RC_{60}^{\bullet}$ radicals is the increase in intensity of the spectrum with increasing temperature, which indicates that the fullereryl radicals are in an equilibrium with their diamagnetic dimers.^{7,8,22,25,31,32}

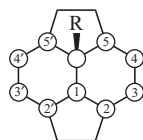


Figure 1 Atom numbering in the pyracylene unit of $\text{RC}_{60}^{\bullet}$ radicals.

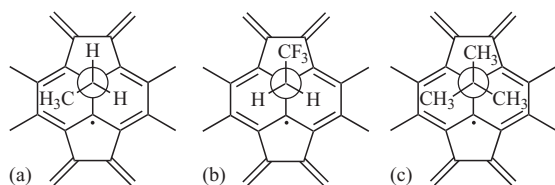


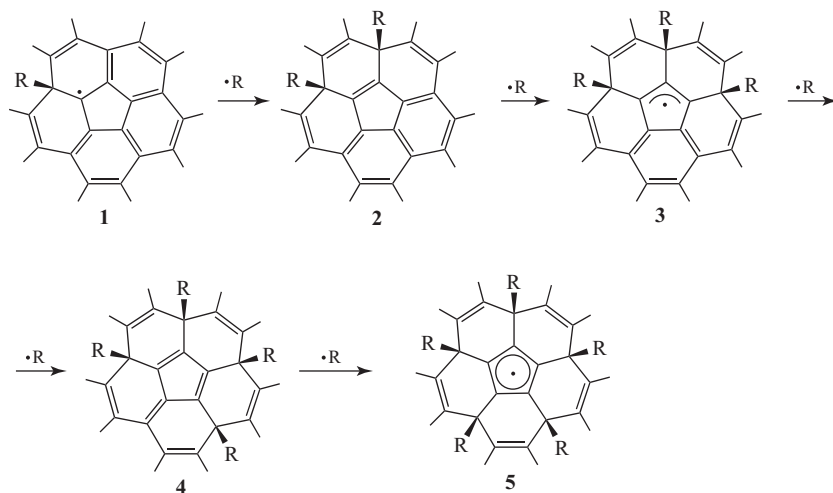
Figure 2 Preferred conformation of (a) $\text{CH}_3\text{CH}_2\text{C}_{60}^{\bullet}$, (b) $\text{CF}_3\text{CH}_2\text{C}_{60}^{\bullet}$, and (c) $(\text{CH}_3)_3\text{CC}_{60}^{\bullet}$ radicals.



The dimer bond strength depends strongly on the size of R, suggesting that bonding in the dimer is greatly influenced by steric effects.⁸ Molecular graphics calculations as well as experimental results suggest that the dimerization of the fullereryl radicals follows the “head-to-head” rather than the “head-to-tail” type and involves the C3 or C3' atoms, whereas steric hindrance prevents the dimerization at C1 atom (Figure 1).^{7,8} The tendency of fullereryl radicals for dimerization has led to

the development of appropriate protocols for the synthesis of singly bonded C_{60} dimers.^{33,34} The alkylfullerene dimers have very weak C–C bond energies, and can be photolytically cleaved into alkylfullerene radicals by excitation at 532 nm.²⁹

Prolonged irradiation of C_{60} solutions in the presence of excess radical precursors leads to multiple radical additions, as indicated by line broadening in the ESR spectra and by mass spectroscopy.^{1,4,5,31,35} For example, it has been shown that photochemically generated benzyl radicals react with C_{60} producing radical and nonradical adducts R_nC_{60} ($\text{R} = \text{C}_6\text{H}_5\text{CH}_2$) with $n = 1$ to at least 15.⁵ The radical adducts with $n = 3$ and $n = 5$ have been identified by ESR spectroscopy as the allylic radical $\text{R}_3\text{C}_{60}^{\bullet}$ (**3**) and cyclopentadienyl radical $\text{R}_5\text{C}_{60}^{\bullet}$ (**5**) (Scheme 1). The unpaired electrons were found to be highly localized on the C_{60} surface. The extraordinary stability of radicals **3** and **5** was attributed to the steric protection by three or five benzyl substituents, respectively, sheltering the surface radical sites.⁵ The initially formed radical $\text{RC}_{60}^{\bullet}$ (**1**) is probably a short-lived species and it is consumed by reaction with $\text{R}^{\bullet}$ continuously generated by photolysis.⁵ The reaction pathway leading to **3** and **5** in Scheme 1 is the result of a radical addition or coupling in a way that minimizes both steric hindrance and [5,6] double bonds.⁵ Similarly, photochemically generated methyl radicals add readily to C_{60} to afford $(\text{CH}_3)_n\text{C}_{60}$ with $n = 1$ to at least 34, as evidenced by mass spectrometric analyses.⁵



Scheme 1 Stepwise addition of five benzyl radicals $\text{R}^{\bullet}$ to C_{60} .

The use of dimer $[(\text{FC}_6\text{H}_4)\text{C}(\text{CF}_3)_2]_2$ as a radical precursor allowed the observation of a step-by-step multiaddition of benzyl radicals to C_{60} .^{1,35} The addition was performed upon dissociation of the dimer in a C_{60} -saturated toluene solution at 310 K, and the reaction was monitored by EPR and mass spectrometry.³⁵ In the case of the 3,5-dimethylphenylmethyl radicals, the fifth radical does not add, probably because of steric hindrances caused by its large size compared to that of the benzyl radical.³⁵

The rate constants for the addition of various carbon-centered radicals to fullerene have been determined with the help of laser flash photolysis and competitive addition of free radicals to spin traps.^{36,37} These rate constants are two orders of magnitude higher than those for the addition of radicals to a wide class of monosubstituted unsaturated compounds.^{1,36,37}

Unlike C_{60} in which all 60 carbon atoms are equivalent, C_{70} contains five types of carbon atoms and thus five regioisomeric radical monoadducts $\text{RC}_{70}^\bullet$ are possible.^{1,24,38} ESR studies on the addition of several photochemically generated aryl and fluoroalkyl radicals to fullerene C_{70} showed that, while simple alkyl radicals afford only three of the five expected $\text{RC}_{70}^\bullet$ regioisomers, the more reactive aryl and fluoroalkyl radicals give rise to four, whereas the $^\bullet\text{CF}_3$ and $\text{CH}_3\text{O}^\bullet$ radicals yielded the ESR spectra of all five expected isomers.^{24,25}

2.1 Radical Reactions of C_{60} Mediated by Decatungstate ($\text{W}_{10}\text{O}_{32}^{4-}$)

The use of tetrabutylammonium decatungstate [TBADT, $(n\text{-Bu}_4\text{N})_4\text{W}_{10}\text{O}_{32}$] catalysis³⁹ in nano-carbon functionalization chemistry can be regarded as a new, convenient, and highly efficient strategy for C–C bond formation in fullerenes.^{40–43} This

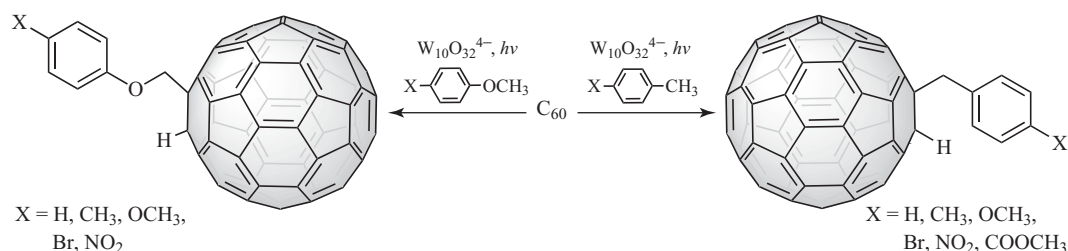
method has enabled the otherwise inaccessible chemical modification of [60]fullerene with a great variety of organic substrates, including toluenes, anisoles and thioanisole,⁴⁰ aldehydes,⁴¹ ethers, sulfides,⁴² and alcohols.⁴³

2.1.1 Addition of Benzyl, Phenoxymethyl, and Phenylthiomethyl Radicals

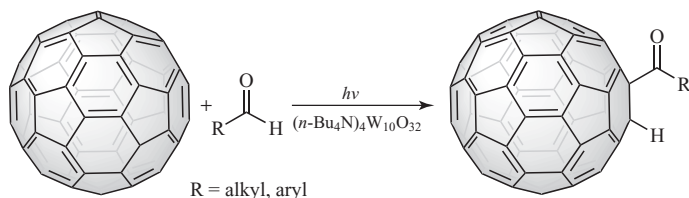
Decatungstate was recently found to promote the generation of carbon-centered radicals by activating the methyl C–H bond in a series of substituted toluenes, anisoles, and thioanisole.⁴⁰ The so-obtained radical intermediates can be successfully trapped by C_{60} to afford selectively the corresponding monofunctionalized fullerene adducts in moderate to good yields (Scheme 2). The observed single addition of radicals to C_{60} is of particular interest, given the well-established high affinity of C_{60} —a “radical sponge”—with free radicals, which results in multiple radical additions.⁵ For example, up to 15 benzyl groups have been reported to add to C_{60} .⁵ Apart from the synthetic applications of this reaction, a mechanistic approach has also been provided in which a hydrogen atom abstraction from the CH_3 or the CH_3O group occurs in the rate-determining step of the reaction. The formation of the [60]fullerene radical anion ($\text{C}_{60}^{\bullet-}$) has been proposed as one of the key intermediates of this reaction.

2.1.2 Addition of Acyl Radicals

Recently, a convenient and highly efficient photochemical methodology for the direct acylation of C_{60} has been developed.⁴¹ This method includes the reaction between C_{60} and a wide variety



Scheme 2 TBADT-mediated radical reaction of *para*-substituted toluenes and anisoles with C_{60} .



Scheme 3 TBADT-mediated radical addition of aldehydes to C_{60} .

of acyl radicals derived from the corresponding aldehydes through a hydrogen atom abstraction process mediated by TBADT³⁹ (see **Synthetic Radical Photochemistry**) (Scheme 3).⁴¹ Thus, the preparation of a novel class of fullerene-based materials, namely acylated fullerene monoadducts, has been achieved in moderate to good yields.⁴¹ Moreover, a simple, low-temperature approach has been established for overcoming decarbonylations encountered in certain acyl radical addition reactions where the acyl radical intermediates are prone to undergo rapid decarbonylation, such as in the case of phenylacetaldehyde where the decarbonylation rate constant is high ($k_d > 10^6 \text{ s}^{-1}$).⁴¹ Intra- and intermolecular deuterium isotope effect studies showed a rate-determining C–H(D) bond breaking in the transition state of the first slow carbonyl radical-forming step.⁴¹ The so-obtained acylated fullerenes have been shown to be excellent $C_{60}H_2$ precursors, since they can be quantitatively converted into the simplest [60]fullerene hydride $C_{60}H_2$, upon a simple treatment with basic Al_2O_3 .⁴⁴

2.1.3 Addition of α -Hydroxyl- or α -Oxy-alkyl radicals

Recently, a facile free-radical route toward the direct functionalization of fullerene C_{60} with ethers and thioethers has been developed.⁴² The otherwise unreactive α -C–H bond in a series of structurally diverse mono- or polyethers and sulfides was achieved via decatungstate catalysis. This method enables direct access to the simplest [60]fullerene/crown ether conjugates that possess great potential as building blocks in supramolecular materials science (Scheme 4).⁴²

Tetrahydrofuranyl radicals have been also added to C_{60} by the reaction of [60]fullerene with an arylzinc halide in a mixture of tetrahydrofuran (THF) and dimethylformamide (DMF). This reaction

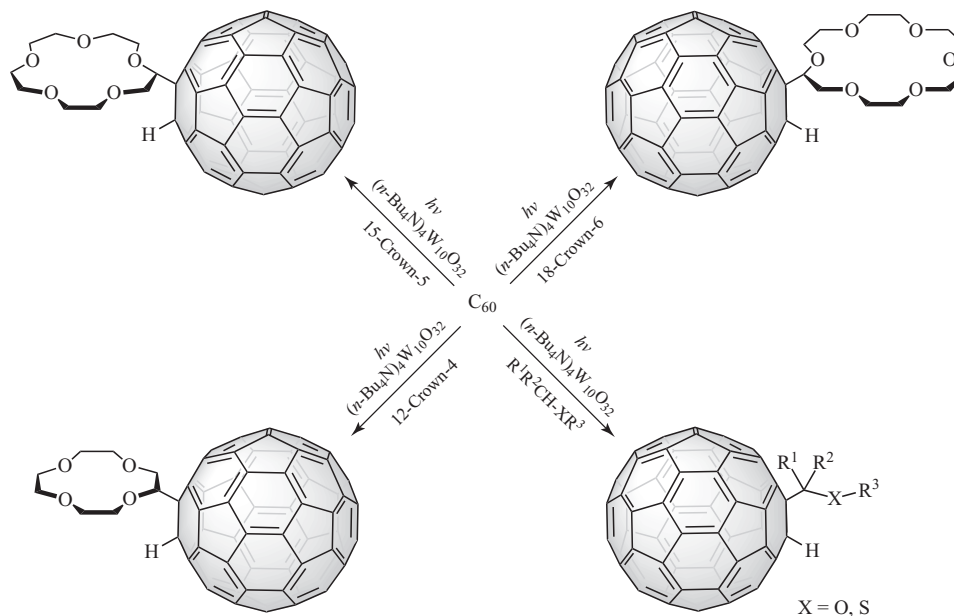
produces a mono(2-tetrahydrofuranyl) adduct of C_{60} [$C_{60}(C_4H_7O)H$] in good yield. On the other hand, in the presence of a copper(I) complex, the aryl group of the zinc reagent add four times regioselectively to the mono(2-tetrahydrofuranyl) adduct to produce a penta-adduct $C_{60}Ar_4(C_4H_7O)H$ (Scheme 5).⁴⁵

Recently, a general method for the selective, and yet direct, mono-hydroxyalkylation of C_{60} has been developed (Scheme 6).⁴³ This method includes the reaction of C_{60} with α -hydroxy C-centered radicals derived from commercially available alcohols upon decatungstate photocatalysis. In this way, the otherwise inaccessible mono-hydroxyalkylated fullerene derivatives are selectively obtained in moderate yields (Scheme 6).⁴³

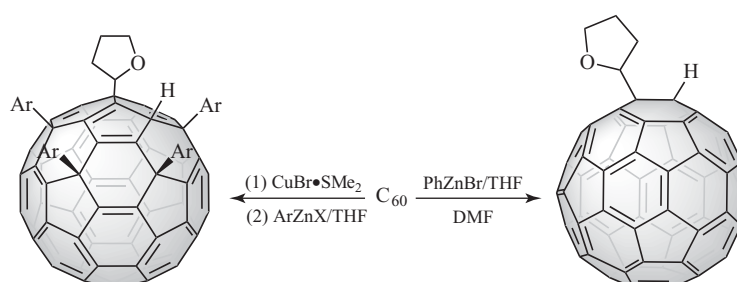
2.2 Radical Reactions of C_{60} Mediated by $Mn(OAc)_3$, $Fe(ClO_4)_3$, $Cu(OAc)_2 \cdot H_2O$

In 2003, Wang *et al.* reported the first free-radical reaction of [60]fullerene promoted by manganese(III) acetate dihydrate [$Mn(OAc)_3 \cdot 2H_2O$] (see **Manganese(III) Acetate, CAN, and Fe(III) Salts in Oxidative Radical Chemistry**).⁴⁶ In this study, free radicals were generated from various active methylene compounds (i.e., dialkyl malonates). In particular, a hydrogen atom abstraction from β -diesters by $Mn(OAc)_3 \cdot 2H_2O$, in refluxing chlorobenzene, afforded C-centered radicals which reacted with [60]fullerene to give singly bonded fullerene dimers and 1,4-bisadducts (Scheme 7). When a bromo-substituted β -diester was used, this reaction afforded the corresponding 1,4- and 1,16-bisadducts as shown in Scheme 7.

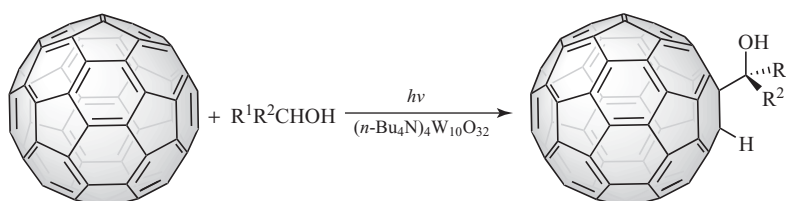
On the other hand, when cyano-substituted active methylene compounds were used, cyclopropane-fused C_{60} derivatives were exclusively obtained (Scheme 8).



Scheme 4 TBADT-mediated radical reactions of C_{60} with ethers and sulfides.



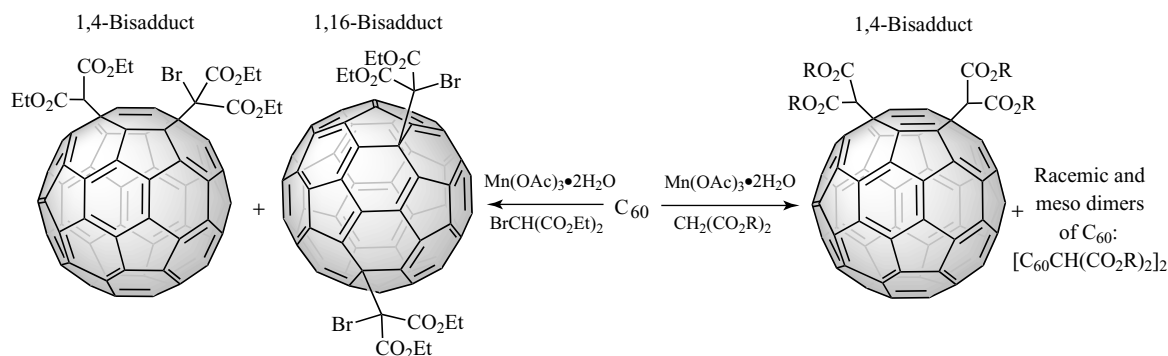
Scheme 5 Addition of tetrahydrofuran to C_{60} through arylzinc halide induced C-H bond activation.



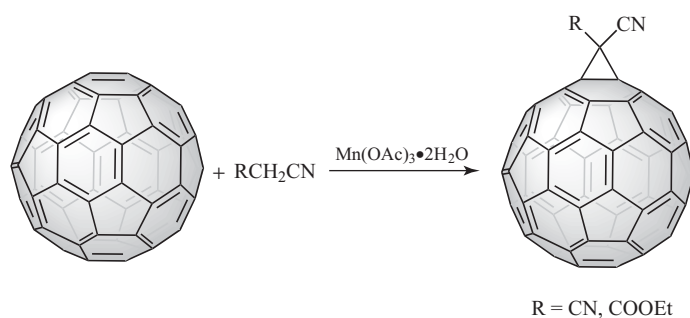
Scheme 6 TBADT-mediated radical addition of alcohols to C_{60} . [Ref. 43 - Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/C0CC02836C>.]

The same $Mn(OAc)_3$ -promoted reaction of C_{60} with substituted malonate esters or ethyl cyanoacetate in refluxing toluene gave the corresponding benzyl-substituted unsymmetrical 1,4-adducts of C_{60} , where the benzyl substituent comes from the reaction solvent (Scheme 9).⁴⁷

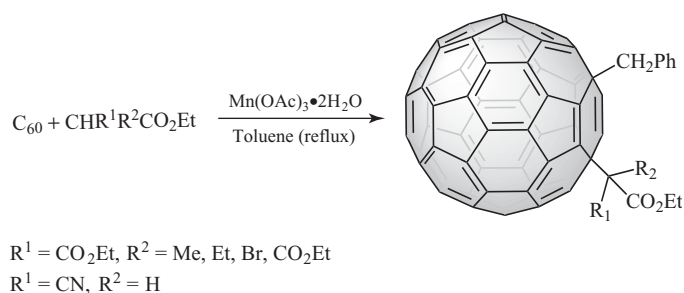
In order to avoid the participation of toluene in the reaction outcome, Wang *et al.* recently studied the $Mn(OAc)_3$ -mediated reaction of C_{60} with diethyl methylmalonate in an alternative solvent, namely *o*-dichlorobenzene, at 140 °C.⁴⁸ The major products of this reaction included the corresponding



Scheme 7 $\text{Mn}(\text{OAc})_3$ -mediated reaction of C_{60} with malonate esters or diethyl bromomalonate.



Scheme 8 $\text{Mn}(\text{OAc})_3$ -mediated reaction of C_{60} with malonodinitrile and ethyl cyanoacetate. [Ref. 46 - Reproduced by permission of The Royal Society of Chemistry. <http://dx.doi.org/10.1039/B309939C>.]

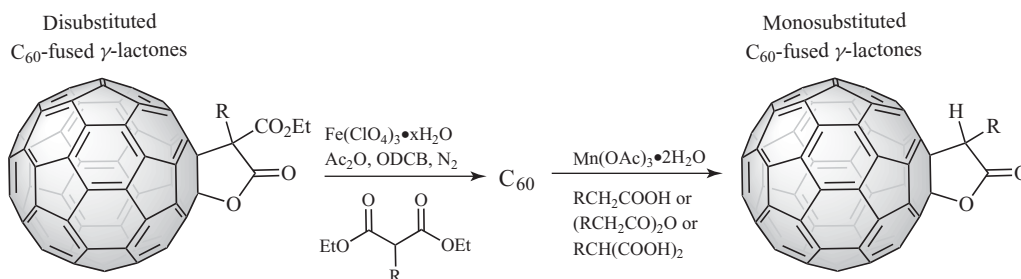


Scheme 9 $\text{Mn}(\text{OAc})_3$ -mediated reaction of C_{60} with substituted malonates or ethyl cyanoacetate in refluxing toluene.

1,4- and 1,16-adducts of C_{60} along with a disubstituted C_{60} -fused γ -lactone. The presence of dimethylaminopyridine (DMAP) in this reaction decreased the yield of the disubstituted C_{60} -fused γ -lactone. The selectivity of this reaction was, however, very poor to find further applications in fullerene chemistry. The selectivity toward the desired disubstituted C_{60} -fused γ -lactone was greatly improved when ferric perchlorate $[\text{Fe}(\text{ClO}_4)_3]$ instead of

$\text{Mn}(\text{OAc})_3$ was used as the reaction catalyst in the presence of acetic anhydride. Thus, the $\text{Fe}(\text{ClO}_4)_3$ -mediated reaction of substituted malonate esters with C_{60} afforded the rare disubstituted [60]fullerene-fused lactones (Scheme 10).⁴⁸

This study was complementary to previously reported studies by Wang *et al.*, where a series of novel [60]fullerene-fused lactones had been prepared by the $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ -mediated reaction of



Scheme 10 Fe(ClO₄)₃- and Mn(OAc)₃-mediated radical reactions leading to mono- and disubstituted C₆₀-fused lactones.

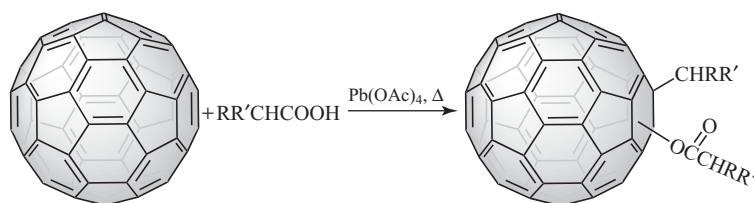
C₆₀ with carboxylic acids, carboxylic anhydrides, or malonic acids (Scheme 10).^{49–51} The majority of these C₆₀-fused γ-lactones were monosubstituted lactones. The only disubstituted C₆₀-fused γ-lactone that had been reported in these studies had been formed from the Mn(OAc)₃-mediated reaction of C₆₀ with isobutyric acid.⁵⁰ However, the desired C₆₀-fused γ-lactone was a minor product since the concurrent formation of a fullereryl ester originating from the facile generation of a secondary radical via decarboxylation from isobutyric acid predominated. The so-obtained C₆₀-fused lactones could undergo further transformations to afford reductive ring-opening products,⁴⁹ fullerene hemiketals and hemiacetals, fullerenols, and C₆₀-fused dihydrofurans.⁵²

Interestingly, Wang *et al.* showed that the lead(IV) acetate-promoted radical reaction of [60]fullerene with carboxylic acids, including those mentioned above for the construction of C₆₀-fused γ-lactones, gave selectively another type of fullerene products, namely fullereryl esters (Scheme 11).⁵⁰

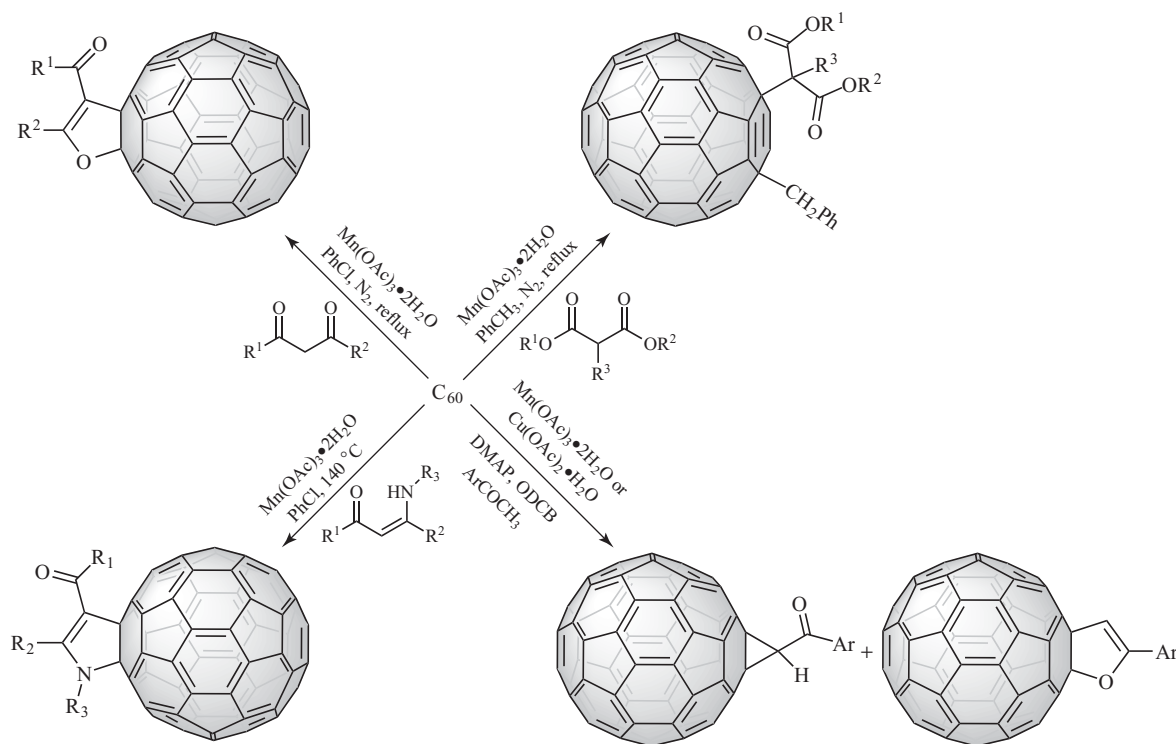
Similarly, Gao and coworkers have systematically studied the free-radical reactions of some β-dicarbonyl compounds (i.e., malonate esters, β-keto esters, and β-diketones) in chlorobenzene and/or toluene with [60]fullerene in the presence of manganese(III) acetate dihydrate

[Mn(OAc)₃·2H₂O].⁵³ These substrates showed different tendencies to generate dihydrofuran-fused [60]fullerene derivatives or 1,4-bisadducts. In particular, dihydrofuran-fused C₆₀ derivatives could be formed by treatment of α-unsubstituted β-diketones or β-ketoesters with [60]fullerene in refluxing chlorobenzene (Scheme 12). On the other hand, solvent-participated unsymmetrical 1,4-bisadducts were obtained through the reaction of [60]fullerene with dimethyl malonate or α-substituted β-dicarbonyl compounds in toluene (Scheme 12),⁵³ as has been similarly observed by Wang *et al.* (i.e., for substituted malonates, see Scheme 9).⁴⁷

Similar results on the reaction of β-diketones and β-keto esters with C₆₀ in the presence of Mn(OAc)₃·2H₂O have been independently reported by Wang *et al.*⁵⁴ In this study, the addition of 4-dimethylaminopyridine (DMAP) allowed lower reaction temperatures (80 °C), shorter reaction times, and usually higher product yields for the corresponding C₆₀-fused dihydrofuran derivatives.⁵⁴ Moreover, it was found that the copper(II) acetate monohydrate Cu(OAc)₂·H₂O could replace manganese(III) acetate dihydrate Mn(OAc)₃·2H₂O in these radical reactions of C₆₀. On the other hand, the reaction of C₆₀ with aromatic methyl ketones, under similar conditions, gave two different products, namely



Scheme 11 Pb(OAc)₄-promoted radical reaction of C₆₀ with carboxylic acids.



Scheme 12 Selected radical reactions of C_{60} mediated by $Mn(OAc)_3$.

methanofullerenes and dihydrofuran-fused C_{60} derivatives (Scheme 12). In this latter reaction, $Cu(OAc)_2 \cdot H_2O$ was found to favor the formation of methanofullerenes.⁵⁴

Dihydrofuran-fused C_{60} derivatives have been also prepared through solvent-free reactions of 1,3-cyclohexanedione, 5,5-dimethyl-1,3-cyclohexanedione, 2,4-pentanedione, and ethyl acetoacetate with C_{60} in the presence of $Mn(OAc)_3 \cdot 2H_2O$ and ceric ammonium nitrate (CAN) under the high-speed vibration milling (HSVM) conditions.⁵⁵ CAN was found to be a better oxidant than $Mn(OAc)_3 \cdot 2H_2O$ in these mechanochemical reactions of β -dicarbonyl compounds with C_{60} .

Finally, manganese(III) acetate $Mn(OAc)_3 \cdot 2H_2O$ has been also reported to catalyze the radical reaction of [60]fullerene with β -enamino carbonyl compounds.⁵⁶ The major products obtained in this reaction are C_{60} -fused pyrroline derivatives whose nitrogen atom is directly connected to the fullerene cage (Scheme 12).

2.3 Addition of Fluoroalkyl Radicals to C_{60}

Fluoroalkyl groups (R_F) are known to add to C_{60} via a radical mechanism.^{18–21,31} Perfluoroalkylation of C_{60} is among the most thoroughly studied radical reaction of [60]fullerene resulting in a plethora of new compounds, mostly polyadducts, with interesting addition patterns and physico-chemical properties. Initially, perfluoroalkylated derivatives of C_{60} were prepared by thermal or photochemical decomposition of fluoroalkyl iodides or fluorodiacyl peroxides.^{31,57} Then, 1-fluoroalkyl-1,2-dihydro[60]fullerenes ($R_F C_{60}H$) were prepared by the reaction of C_{60} with fluoroalkyl halides ($R_F X$) in the presence of Bu_3SnH [$R_F = CF_2CO_2Et$, $n-C_6F_{13}$, CF_2Br , $n-C_{12}F_{25}$, $(CF_2)_6I$].⁵⁸ Photolysis of alkyl-mercury compounds $[Hg(R_F)_2]$,^{1,59} or the high-temperature reaction of C_{60} or C_{70} with $R_F I$,^{60–66} provides also another route toward fluoroalkyl radical addition to fullerenes.

Trifluoromethylation of [60]fullerene is the most widely studied reaction of C_{60} with fluoroalkyl

radicals and is still an area of ongoing research interest.^{67–80} Similar to other perfluoroalkyl radicals mentioned above, trifluoromethyl radicals have been typically prepared by thermal decomposition of metal trifluoroacetates $[(CF_3CO_2)_nM, M = Ag, Hg, Cu, Pd, Cr]$ ^{68–71,76,79} and pyrolysis of trifluoromethyl iodide.^{72–75,77,80} Analogous methods were used for the preparation of trifluoromethylated C_{70} ,^{72,79,81–89} higher fullerenes,^{90–98} and aza[60]fullerene.⁹⁸ Variations in the conditions of these methods (e.g., nature of the perfluoroalkyl radical precursor, temperature, pressure, reaction medium, duration) allowed the preparation of variegated trifluoromethylated fullerene adducts. The majority of these reactions were shown to be nonselective and, with some exceptions,^{73,99} the separation of the product mixture into pure isomers is either difficult or impossible. On the other hand, derivatization, such as trifluoromethylation, provides an expedient route toward the structural characterization (i.e., cage connectivity) of higher fullerenes (e.g., C_{74} , C_{76} , C_{78} , C_{84} , C_{88} , C_{92} , C_{94} , C_{96})^{90,92–97} because of the easier separation of their trifluoromethylated derivatives. Cycloperfluoroalkyl adducts of fullerenes have been also prepared through the addition reaction of biradicals thermally generated from terminal diiodoperfluoroalkanes $I(CF_2)_nI$ to C_{70} or C_{60} .^{100,101}

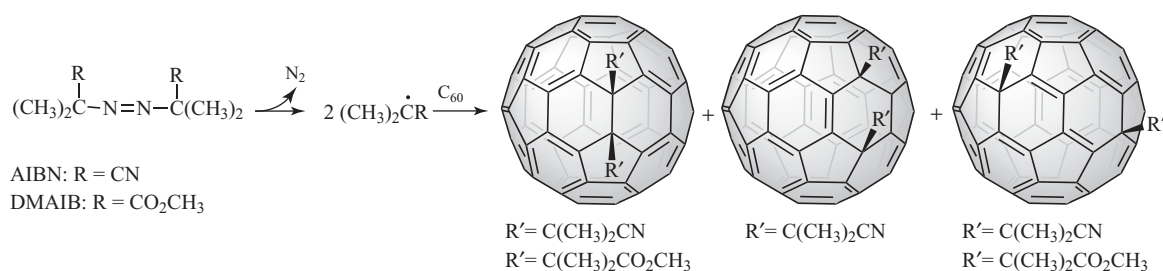
Fluoroalkyl radical addition to C_{60} has been well studied mainly by ESR spectroscopy.^{18–21,27,31}

As with alkyl radical additions, fluoroalkyl monoadducts exhibited a hindered rotation about the R_F-C_{60} bond and a tendency for dimerization. For example, the photochemical addition of perfluoroalkyl radicals [derived upon photolysis of perfluoroalkyl iodides in the presence of $(R_3Sn)_2$] to C_{60} , afforded the corresponding fullerene dimers in good yields.³³

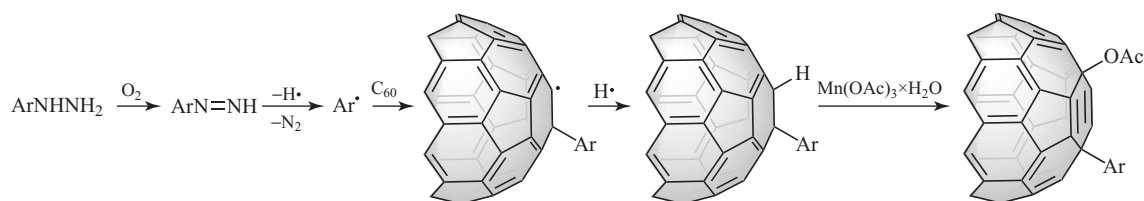
2.4 Other Reactions of C_{60} Involving C-Centered Radicals

Alkyl radicals have been also prepared by photolysis of 2,2'-azo(bisisobutyronitrile) (AIBN).^{102,103} For example, Ford *et al.* have shown that the thermal decomposition of AIBN in a 1,2-dichlorobenzene solution of C_{60} generates 2-cyano-2-propyl radicals which add to C_{60} to afford three regioisomeric fullerene adducts, namely the 1,2-, 1,4-, and 1,16-isomers (Scheme 13).^{103,104} On the other hand, thermal decomposition of dimethyl azo(bisisobutyrate) (DMAIB) in the presence of C_{60} produced only the corresponding 1,4- and 1,16-isomers (Scheme 13).¹⁰³

Another C-centered radical addition to C_{60} involves the addition of aryl radicals derived from phenylhydrazines (Scheme 14).¹⁰⁵ In particular, Wang and coworkers have found that



Scheme 13 Radical reaction of C_{60} with azo(bisisobutyronitrile) and azo(bisisobutyrate).

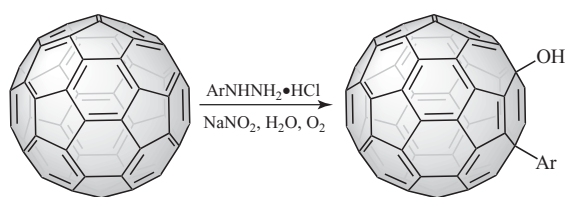


Scheme 14 One-pot sequential synthesis of acetoxylation C_{60} derivatives.

the reaction of [60]fullerene with 4-substituted phenylhydrazine hydrochlorides in refluxing chlorobenzene under aerobic conditions affords 1-aryl-1,2-dihydro[60]fullerenes (ArC_{60}H), which are subsequently oxidized to 1-acetoxyl-4-aryl-1,4-dihydro[60]fullerenes ($\text{ArC}_{60}\text{-OAc}$) by $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ in a one-pot procedure (Scheme 14).¹⁰⁵ The formation of the final adduct was rationalized through the radical addition to C_{60} of aryl radicals generated *in situ* from the phenylhydrazine derivative by oxidation via oxygen, followed by radical coupling with $\text{H}^\bullet$ and subsequent oxidation by $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (Scheme 14).

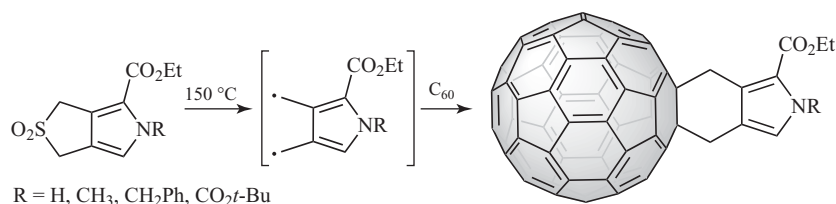
Upon the addition of sodium nitrite (NaNO_2) in the presence of O_2 and moisture, the above reaction afforded fullereneols of the type 1,4- C_{60}ArOH (Scheme 15).¹⁰⁶ The first step of this reaction involves again the addition of $\text{Ar}^\bullet$ radicals to C_{60} .

C-centered biradicals have been also employed in fullerene radical functionalization chemistry. For example, Ohno *et al.* have shown that the cycloaddition reaction of C_{60} with 3,4-fused pyrrolo-3-sulfolenes affords, after SO_2 extrusion, a C_{60} -pyrrole derivative (Scheme 16).¹⁰⁷ The proposed reaction mechanism involves the trapping of an intermediate diradical with a fullerene double bond (Scheme 16).¹⁰⁷



$\text{Ar} = \text{Ph}, 4\text{-CH}_3\text{-Ph}, 4\text{-CH}_3\text{O-Ph}, 4\text{-Cl-Ph}$

Scheme 15 Reaction of C_{60} with 4-substituted phenylhydrazine hydrochlorides and NaNO_2 .

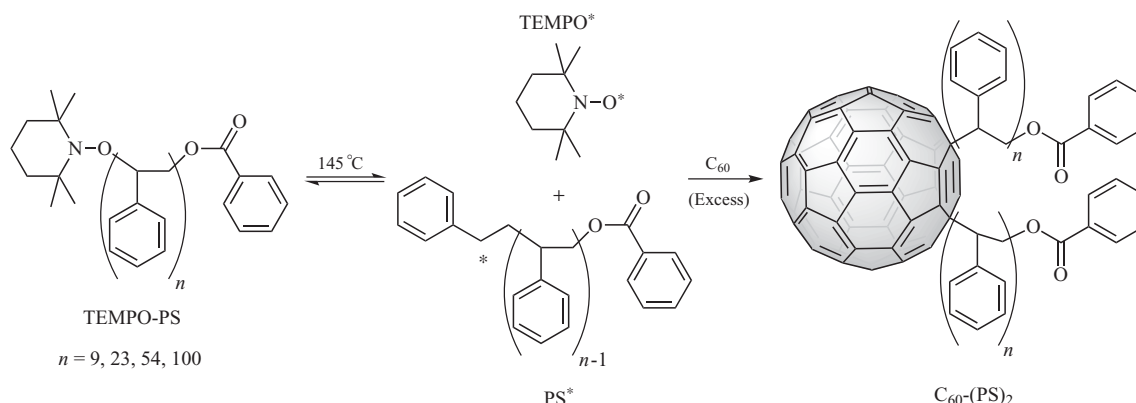


Scheme 16 Cycloaddition of C_{60} with 3,4-fused pyrrolo-3-sulfolenes.

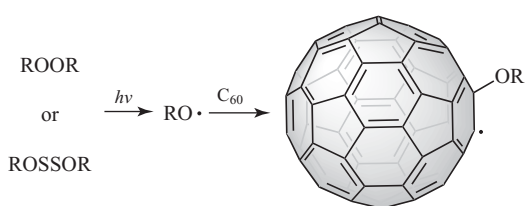
The construction of fullerene-based polymers is another research field where the addition of C-centered radicals to C_{60} is a key feature. The usual radical polymerization methods for the construction of PS-C_{60} (polystyrene- C_{60}) adducts produce, in most cases, a mixture of poorly defined multiadducts of PS. In order to control radical polymerization with C_{60} , a “living” radical polymerization has been developed which includes the reaction of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO)-terminated polystyrene with C_{60} .¹⁰⁸ Living radical polymerization (see **Fundamentals of Controlled/Living Radical Polymerization**) has led to the synthesis of well-defined disubstituted polymer derivatives of C_{60} .^{108,109} The first example included the thermolysis of TEMPO-PS adducts in the presence of excess C_{60} in *o*-dichlorobenzene to afford the corresponding 1,4-disubstituted derivatives of C_{60} in good yields (Scheme 17).¹⁰⁸ Bromo-terminated polymers, including bromo-terminated polystyrene, have been also added to C_{60} through an atom transfer radical polymerization (see **Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications**).¹¹⁰ Several other free-radical mediated polymerizations with C_{60} have been reported in the literature.¹¹¹

3 O- AND S-CENTERED RADICALS

Several alkoxy ($\text{RO}^\bullet$) and alkylthio ($\text{RS}^\bullet$) radicals are known to add to C_{60} or C_{70} sphere affording the corresponding $\text{RO-C}_{60}^\bullet$ ($\text{RO-C}_{70}^\bullet$) and $\text{RS-C}_{60}^\bullet$ ($\text{RS-C}_{70}^\bullet$) radical adducts which can be detected by ESR spectroscopy.^{15,25,112} Alkoxy radicals ($\text{RO}^\bullet$) have been generated photolytically from the appropriate peroxides ROOR ($\text{R} = t\text{-Bu}, \text{PhCMe}_2, \text{CF}_3$)¹⁵ or in a more convenient and safer way via photolysis of dialkoxy disulfides ROSSOR ($\text{R} = \text{Me}, \text{Et}, i\text{-Pr}, t\text{-Bu}, i\text{-PrCH}_2, t\text{-BuCH}_2$)



Scheme 17 Synthesis of 1,4-dipolystyryldihydro[60]fullerenes. [Reprinted with permission from Ref. 108. Copyright 1997 American Chemical Society.]



Scheme 18 Addition of alkoxy radicals to C_{60} .

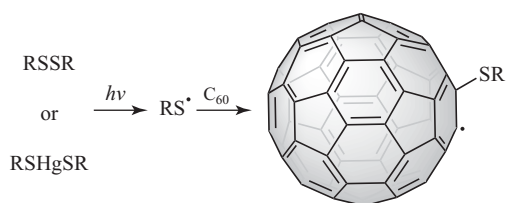
(Scheme 18),^{25,112} whereas bis(alkylthio)mercury compounds (RSHgSR) and alkyl disulfides (RSSR) have been used as the source of the alkylthio radicals ($\text{RS}^{\bullet}$) (Scheme 19).^{15,25} One regioisomer is expected for the single addition radical adducts $\text{RO-C}_{60}^{\bullet}$ (Scheme 18) and $\text{RS-C}_{60}^{\bullet}$ (Scheme 19).

On the other hand, three regioisomers of $\text{MeS-C}_{70}^{\bullet}$ adduct were obtained by photolysis of dimethyl disulfide (MeSSMe) in the presence of C_{70} , whereas all the five expected regioisomers of $\text{MeO-C}_{70}^{\bullet}$ could be detected by ESR spectroscopy, upon photolysis of MeOSSOMe in the presence of C_{70} .²⁵

Unlike the spectra of $\text{RC}_{60}^{\bullet}$ radicals, which typically become more intense at higher temperatures

owing to the dissociation of $\text{RC}_{60}\text{-C}_{60}\text{R}$ dimers present in solution,⁷ the signal intensities in the ESR spectrum of $\text{RSC}_{60}^{\bullet}$ decreased rapidly above room temperature. The reversibility of the alkylthiyl radical addition was attributed to the weaker fullerene-sulfur bond.¹⁵ Strong evidence for this was further provided by observing the change of the light amber color of the solution of phenylthiyl radical adducts ($\text{PhSC}_{60}^{\bullet}$) into the purple color of C_{60} after ceasing irradiation.⁴ This observation indicates that this radical addition, in contrast to the alkoxy fullerenyl derivatives, is reversible.¹¹²

In a few cases, the cleavage of the carbon-sulfur bonds of RSSR was observed, which led exclusively ($\text{R} = \text{benzyl}$) or partially ($\text{R} = t\text{-butyl}$) to the radicals of the type $\text{RC}_{60}^{\bullet}$, particularly if the light was not filtered through the Ni/Co sulfate solution.¹⁵ Molecular mechanics calculations performed for $\text{CH}_3\text{SC}_{60}^{\bullet}$ indicated, in accordance to the corresponding ethyl adduct,¹¹ a preference for an asymmetric conformation for this radical, that is, the methyl group of the CH_3S moiety is placed directly above one of the two 6-membered fused rings of C_{60} (Figure 3).¹⁵



Scheme 19 Addition of alkylthio radicals to C_{60} .

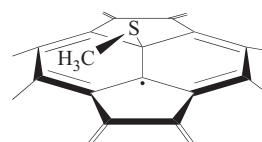
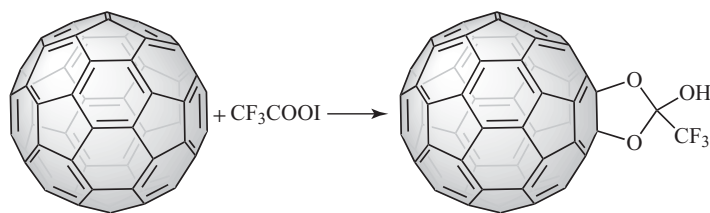


Figure 3 The preferred asymmetric conformation of $\text{CH}_3\text{SC}_{60}^{\bullet}$ radical.

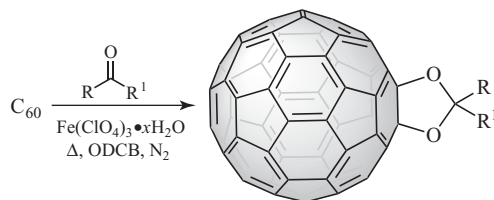
tert-Butylperoxy radicals ($t\text{-BuOO}^\bullet$) add to fullerenes C_{60} and C_{70} in a stepwise radical addition manner to afford a mixture of products with different number of *tert*-butylperoxy groups attached on the fullerene cage.^{113–116} For C_{60} , this reaction gave adducts with the general formula $\text{C}_{60}(\text{O})_m(\text{OO}t\text{Bu})_n$ ($m = 0, n = 2, 4, 6$; $m = 1, n = 0, 2, 4, 6$) through a stepwise cyclopentadienyl addition mechanism.^{113,114} Low concentration of *tert*-butylperoxy radicals, long reaction time, and irradiation of visible light favor epoxide formation [i.e., $\text{C}_{60}(\text{O})(\text{OO}t\text{Bu})_4$], whereas high concentration of *t*-butylperoxy radical favors homo-peroxy adducts [i.e., $\text{C}_{60}(\text{OO}t\text{Bu})_6$].¹¹⁴ On the other hand, no epoxy moiety was present on the corresponding products of C_{70} [$\text{C}_{70}(\text{OO}t\text{Bu})_n, n = 2, 4, 6, 8, 10$], which were formed through both equatorial and cyclopentadienyl addition modes.¹¹⁵ Other peroxy radicals such as cumyl peroxy radical [$\text{Ph}(\text{Me}_2)\text{COO}^\bullet$] react similarly with C_{60} in the presence of a catalytic amount of $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$, but in this case it was difficult to purify the mixture formed.¹¹⁴

In another study, Troshin *et al.* showed that the reaction of C_{60} with acyl hypohalogenites CF_3COOBr or CF_3COOI —formed *in situ* from CF_3COOAg and Br_2 or I_2 , respectively—in the presence of water results in the formation of an orthoester-type 1,3-dioxolanofullerene in good yield (Scheme 20).¹¹⁷ This method, however, is limited to a specific range of substrates that are stable toward radical halogenation.¹¹⁷

More recently, a facile synthesis of a series of C_{60} -fused 1,3-dioxolanes has been achieved by the $\text{Fe}(\text{ClO}_4)_3$ -promoted reaction of C_{60} with aldehydes or ketones (Scheme 21).¹¹⁸



Scheme 20 Reaction of C_{60} with CF_3COOI .

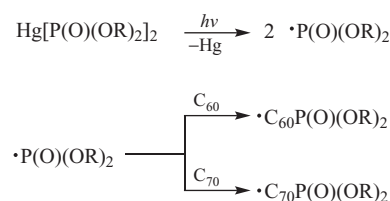


Scheme 21 Ferric perchlorate-mediated reaction of C_{60} with aldehydes ($\text{R}^1 = \text{H}$) and ketones.

4 PHOSPHORUS-CENTERED RADICALS

So far, only a few phosphorus-centered radicals have been reported to add to C_{60} and C_{70} .^{1, 8–10, 28, 30, 119–122} Owing to the exceptionally high constants of hyperfine coupling of the unpaired electron with the phosphorus nucleus, phosphoryl radicals can be utilized as “paramagnetic reporters”.¹ Phosphoryl radicals have been prepared either by the photolysis of diphosphoryl mercury compounds (Scheme 22)^{1, 10, 28, 30, 119–121} or by hydrogen abstraction from the appropriate hydrophosphoryl compound.^{9, 122}

Similar to the alkylfullerenyl radicals,^{13, 27} the unpaired electron in the phosphoryl-fullerenyl radicals is delocalized mainly over the two six-membered rings adjacent to the C–P bond.^{1, 123} Moreover, a rotation barrier of $4.8 \text{ kcal mol}^{-1}$ was calculated for the radical $^\bullet\text{C}_{60}\text{P}(\text{O})(\text{O}i\text{Pr})_2$.¹²⁴



Scheme 22 Addition of $^\bullet\text{P}(\text{O})(\text{OR})_2$ radicals derived from photolysis of diphosphoryl mercury compounds to C_{60} and C_{70} .

5 SI-CENTERED RADICALS

Hydrogen atom abstraction from silanes (HSiR_3) by photolytically generated *tert*-butoxyl radicals generates trialkylsilyl radicals which add to C_{60} to afford $\text{R}_3\text{SiC}_{60}^\bullet$ radicals.¹⁴ The Si– C_{60} bond is slightly longer than the C– C_{60} bond in an alkyl fullerenyl radical, thus exhibiting a lower rotational barrier compared to their alkyl analogs.

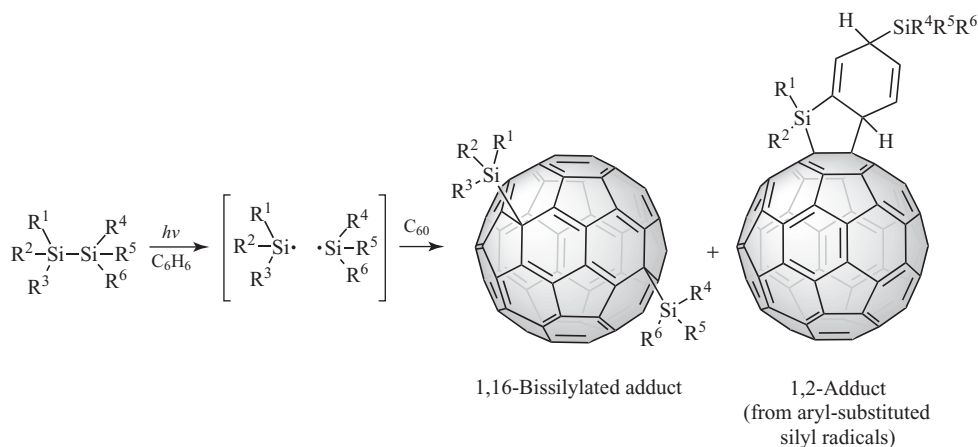
Silylated fullerenes have been prepared by the addition of silyl radicals generated upon photolysis of the corresponding di- or polysilane.^{125–130} For example, the 1,16-bissilylated adduct was isolated as the major product upon reaction of C_{60} with trialkylsilyl radicals $\text{R}_3\text{Si}^\bullet$ (Scheme 23).^{125–127} On the other hand, aryl-substituted silyl radicals generated upon photolysis of the corresponding unsymmetrical disilanes add to C_{60} to afford, apart from the 1,16-bisadduct, an unexpected 1,2-adduct in which the silyl and phenyl groups are attached on the 1,2-positions of C_{60} (Scheme 23).^{125,126} In

some cases, this latter adduct was the only isolated product.¹²⁶

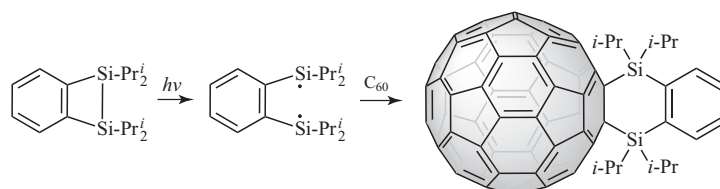
Disilylcyclobutanes (Scheme 24)^{131,132} and cyclotetrasilanes (Scheme 25)^{131,133} also react with C_{60} through the formation of an intermediate Si-centered biradical generated upon photolytically induced cleavage of the four-membered ring, followed by a formal cycloaddition to the [6,6] double bond of C_{60} .

6 METAL-CENTERED RADICALS

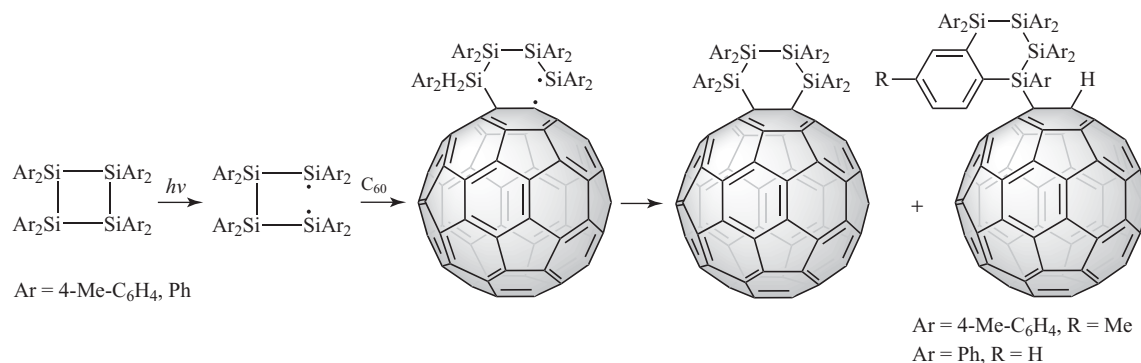
Rhenium pentacarbonyl radicals $^\bullet\text{Re}(\text{CO})_5$ —generated upon photodissociation of the Re–Re σ -bond in $\text{Re}_2(\text{CO})_{10}$ —add to C_{60} in benzene to form $\text{C}_{60}[\text{Re}(\text{CO})_5]_2$.¹³⁴ This adduct was similarly obtained from the thermal reaction of C_{60} with $(\eta^3\text{-Ph}_3\text{C})\text{Re}(\text{CO})_4$ —a known source of $^\bullet\text{Re}(\text{CO})_5$ —in the presence of CO (Scheme 26). The compound $\text{C}_{60}[\text{Re}(\text{CO})_5]_2$ is unstable and decomposes at room temperature.¹³⁴



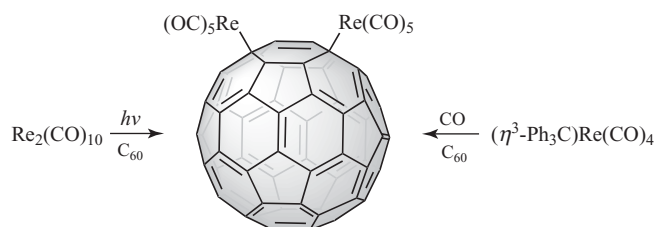
Scheme 23 Photochemical reactions of phenylsilanes with C_{60} .



Scheme 24 Photochemical reaction of 3,4-benzo-1,1,2,2-tetraisopropyl-1,2-disilacyclobutene with C_{60} .



Scheme 25 Photochemical addition of cyclo-(Ar₂Si)₄ to C₆₀.



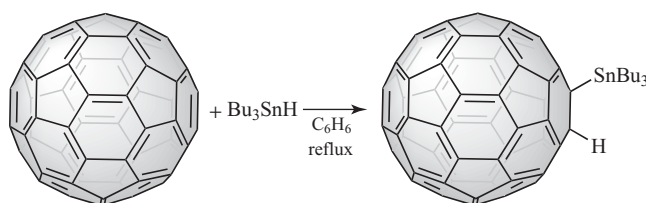
Scheme 26 Addition of pentacarbonylrhenium radicals to C₆₀.

Tumanskii *et al.* have shown that photolysis of *cis*-(CF₃)₂CF–Hg–Pt(PPh₃)₂–CH=CPh₂ generates the platinum-centered free radical [•]Pt(PPh₃)₂–CH=CPh₂, which add to C₆₀ to afford a moderately stable platinum containing fullerenyl radical *cis*-Ph₂C=CH–Pt(PPh₃)₂–C₆₀.¹³⁵ EPR studies revealed, in addition to this radical adduct, the presence of products of multiple addition of carbon-centered fluorinated radicals formed upon homolysis of the (CF₃)₂CF–Hg bond.¹³⁵

Moreover, Hirsch *et al.* have shown that thermal treatment of benzene solutions of C₆₀ with a 20-fold excess of Bu₃SnH leads to a regioselective 1,2-hydrostannylation of [60]fullerene (Scheme 27).¹³⁶

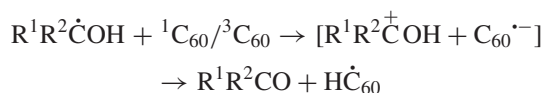
7 ADDITION OF HYDROGEN ATOM(S)

Hydrogenated C₆₀ radicals (HC₆₀[•]) have been generated by (i) photolysis of di-*t*-butylperoxide to produce *t*-butoxy radicals, which in turn abstract a hydrogen atom from an alcohol, (ii) photoreduction of acetophenone, benzophenone, or acetone in the presence of various alcohols (i.e., 2-propanol), (iii) photolysis of thiophenol, tri-*n*-butyltin hydride, or 1,4-cyclohexadiene in a C₆₀-saturated benzene solution, (iv) by reacting C₆₀ with hydrogen atoms followed by matrix isolation in cyclohexane at 77 K¹³⁷ or neon at 4 K,¹² and (v) in the presence of atomic hydrogen from a microwave discharge.^{12,137,138} In the first two methods, in



Scheme 27 Addition of tributyltin hydride to C₆₀ in refluxing benzene.

which a hydrogen atom abstraction from alcohols by *tert*-butoxy radical or by photoexcited carbonyl group of various ketones occurs, the formation of $\text{HC}_{60}^{\bullet}$ is the result of a sequential electron/proton transfer reaction:



where $\text{R}^1\text{R}^2\dot{\text{C}}(\text{OH})$ derives from activated alcohol or photoreduced ketone in the first and second method, respectively. The generation of $\text{HC}_{60}^{\bullet}$ has been also studied by means of electrochemistry (i.e., protonation of the radical anion of C_{60}).^{139,140} As with alkyl fullereryl radicals ($\text{RC}_{60}^{\bullet}$),^{7,8,32,33,141} $\text{HC}_{60}^{\bullet}$ tend to dimerize to $(\text{C}_{60}\text{H})_2$.^{137,142}

Hydrogen atoms have been used also for the hydrogenation of fullerite (a mixture of crude C_{60} and C_{70}) at elevated temperatures (400°C) under high hydrogen pressure in the presence of iodoethane.¹⁴³ Analysis of the reduced fullerite by fast atom bombardment mass spectrometry (FAB MS) revealed a mixture of hydrofullerenes comprising mainly $\text{C}_{60}\text{H}_{36}$ and $\text{C}_{70}\text{H}_{36}$.¹⁴³

The addition of hydrogen atoms to C_{70} has been achieved by irradiation of C_{70} in dry benzene solution containing benzophenone and isopropanol. This reaction afforded adducts of five different types: four isomers of HC_{70} and a single isomer of H_3C_{70} .¹⁴⁴ At the same time, three of the five possible isomers of $\text{HC}_{70}^{\bullet}$ were detected by ESR studies upon photolysis of a saturated benzene solution containing 1,2-cyclohexadiene.³⁸

8 ADDITION OF HALOGENS

Halogenation of fullerenes is a radical process and can be achieved for fluorination, chlorination, and bromination, but not iodination.^{145–150}

Fluorination of C_{60} has been achieved through the reaction of C_{60} with fluorine gas (F_2), metal fluorides (e.g., MnF_3 , K_2PtF_6 , CoF_3 , TbF_4 , CeF_4), or noble gas fluorides (e.g., XeF_2 , KrF_2), or less efficiently with halogen fluorides (e.g., BrF_5 , IF_5).¹⁴⁹ Except $\text{C}_{60}\text{F}_{48}$,^{151–154} direct fluorination of C_{60} with F_2 results in a mixture of C_{60}F_n with a wide range of compositions.^{145,146} A more selective fluorination method of C_{60} is the high-temperature treatment of metal fluorides (MnF_3 , CoF_3 , K_2PtF_6 ,

etc.) in the presence of C_{60} . For example, MnF_3 leads selectively to the formation of $\text{C}_{60}\text{F}_{36}$,¹⁵⁵ whereas fluorination of C_{60} with K_2PtF_6 affords $\text{C}_{60}\text{F}_{18}$.¹⁵⁶ Several other examples can be found in the literature.^{145,146,157,158} Fluorination of lower polyfluorofullerenes by fluorine also proceeds by a radical mechanism.¹⁵⁰ As for C_{70} , Morton *et al.* reported the detection by EPR spectroscopy of four isomers of FC_{70} derived from the addition of fluorine atoms (from SF_5Cl) to C_{70} .¹⁵⁹ Moreover, it has been shown that fluorination of C_{70} by MnF_3 affords a mixture of $\text{C}_{70}\text{F}_{36/38/40}$ with $\text{C}_{70}\text{F}_{38}$ as the major product.¹⁵⁵

Apart from polyfluoro[60]fullerenes, polychloro derivatives of C_{60} have been also studied.^{145,146,160} Chlorination of C_{60} by chlorine gas at 250°C gives a light orange mixture of chlorinated fullerenes C_{60}Cl_n where an average of 24 chlorine atoms have been attached to C_{60} .¹⁶¹ Reaction of C_{60} with an excess of iodine monochloride (ICl), in either benzene or toluene, produces mainly C_{60}Cl_6 , which was proved to be isostructural with C_{60}Br_6 .^{162,163} The synthesis of C_{60}Cl_6 in toluene is slower than in benzene, indicating that a radical mechanism is operative since toluene is a good radical scavenger. More recently, the preparation of other highly chlorinated [60]fullerenes, including $\text{C}_{60}\text{Cl}_{24}$,¹⁶⁴ $\text{C}_{60}\text{Cl}_{28}$,¹⁶⁵ and $\text{C}_{60}\text{Cl}_{30}$,^{165,166} has been reported.¹⁶⁷ The aforementioned synthesis have been achieved by treating C_{60} with chlorinated agents such as VCl_4 , ICl , ICl_3 , or SbCl_5 .^{165,166,168} Chlorination of C_{70} with ICl in benzene leads to the C_s symmetric compound $\text{C}_{70}\text{Cl}_{10}$.¹⁶⁹ More recently, the preparation of highly chlorinated derivatives of C_{70} , such as $\text{C}_{70}\text{Cl}_{28}$ ¹⁷⁰ and $\text{C}_{70}\text{Cl}_{16}$,¹⁷¹ as well as of higher fullerenes such as $\text{C}_{80}\text{Cl}_{12}$,¹⁷² $\text{C}_{84}\text{Cl}_{32}$,¹⁷³ $\text{C}_{76}\text{Cl}_{18}$,¹⁷⁴ $\text{C}_{76}\text{Cl}_{24}$,¹⁷⁵ $\text{C}_{76}\text{Cl}_{34}$,¹⁷⁶ has been reported.

Bromination of fullerenes is also a radical process. Treatment of C_{60} with neat bromine affords the bromofullerene $\text{C}_{60}\text{Br}_{24}$, which is a yellow orange crystalline compound.¹⁷⁷ This reaction proceeds in a stepwise manner to give successively C_{60}Br_8 , $\text{C}_{60}\text{Br}_{14}$, and finally $\text{C}_{60}\text{Br}_{24}$.¹⁷⁸ On the other hand, bromination of C_{60} with bromine in benzene or CCl_4 affords C_{60}Br_6 , whereas in CS_2 or CHCl_3 affords C_{60}Br_8 .¹⁷⁹ It was later found that C_{60} reacts with bromine in organic solvents (i.e., 1,2- and 1,3-dichlorobenzene, 1,2-dibromobenzene, 1,2,4-trichlorobenzene, chlorobenzene, bromobenzene, and CS_2) to afford bromides C_{60}Br_6 ,

$C_{60}Br_8$, or $C_{60}Br_{24}$ depending on the bromine concentration.¹⁸⁰ Similarly, the bromination of C_{70} in neat bromine, in *o*-dichlorobenzene, or in carbon disulfide produces $C_{70}Br_{10}$.¹⁸¹

9 ION RADICAL REACTIONS OF FULLERENES

Apart from the radical reactions involving neutral radical species, fullerene radical chemistry involves radical ion reactions, that is, the reactions of the radical anion ($C_{60}^{\bullet-}$) or radical cation ($C_{60}^{\bullet+}$) of C_{60} generated upon photoinduced or in some cases thermally induced electron transfer processes.^{1,182} In this section, we will describe some of the most outstanding and representative examples of this type.

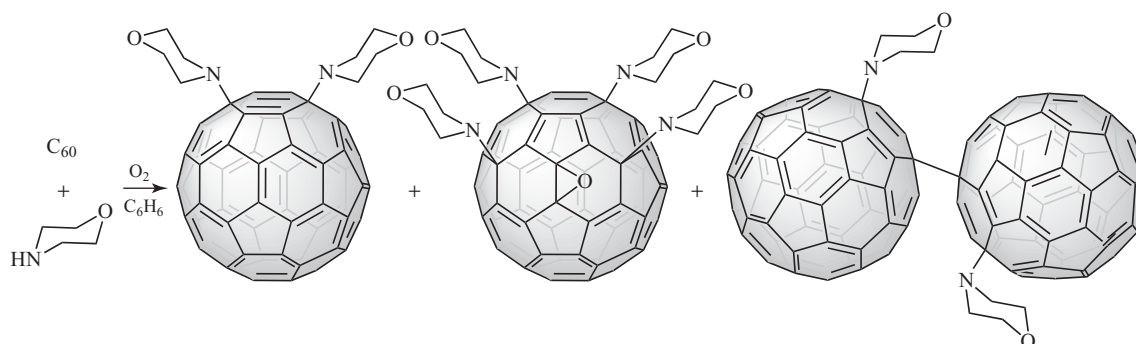
9.1 Addition of Amines to C_{60}

Typically, the addition of primary and secondary aliphatic amines to C_{60} is initiated by a

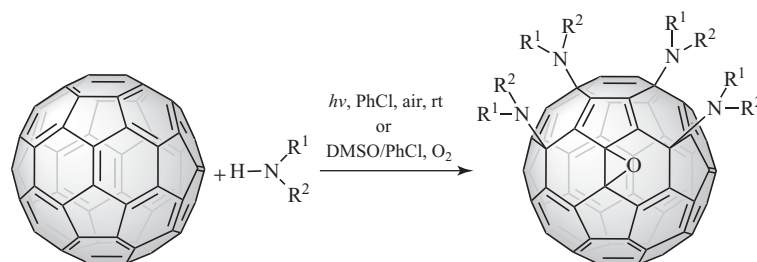
single-electron transfer (SET) process (from amine to C_{60}) to afford a radical ion pair, namely C_{60} radical anion ($C_{60}^{\bullet-}$) and amine radical cation ($R_2NH^{\bullet+}$).¹⁸³ This process is favored in polar solvents.

As an example, the reaction between an excess of a secondary amine, namely morpholine, and [60]fullerene in the presence of oxygen affords exclusively dehydrogenated aminoadducts with a defined 1,4-addition pattern of the amino groups (i.e., bismorpholino[60]fullerene, tetrakis(morpholino)[60]fullerene epoxide) as well as morpholino[60]fullerene dimer (Scheme 28).¹⁴¹ The presence of a free-radical mechanism is strongly supported by this addition pattern as first reported for free-radical additions to [60]fullerene by Krusic *et al.* (i.e., successive 1,4-radical additions to the [5]radialene structure of [60]fullerene to generate a pentaalkylated C_{60} , see Scheme 1).⁵ The reaction of [60]fullerene with piperidine showed similar results.¹⁴¹

More recent advances included the one-step multiple addition of amines to C_{60} , under either photochemical or thermal aerobic conditions, for the synthesis of tetra(amino)fullerene epoxides in moderate to excellent yields (Scheme 29).^{184,185}



Scheme 28 Reaction of morpholine with a benzene solution of C_{60} in the presence of oxygen.



Scheme 29 Oxygenative tetraamination of C_{60} .

Under the photochemical conditions, the tetrakis-morpholino [60]fullerene epoxide has been prepared in a much higher yield compared to that described above for the thermal conditions.¹⁸⁴ After careful reexamination of this photoreaction, it was found that addition of dimethylsulfoxide (DMSO) to the reaction mixture allows the reaction to take place without photoirradiation.¹⁸⁵ This latter tetraamination reaction of [60]fullerene with secondary aliphatic amines was found to be far superior to the photochemical method in terms of the range of applications and the product yield.¹⁸⁵

The radical photoaddition of mono *N*-substituted piperazines to C₆₀ was later reported by Troshin *et al.*¹⁸⁶ The reactions of C₆₀ with piperazines bearing bulky electron-withdrawing groups (i.e., 2-pyridyl, 2-pyrimidinyl) were found to be the most selective and yielded C₆₀(amine)₄O as major products accompanied with small amounts of C₆₀(amine)₂. On the other hand, interactions of fullerene with *N*-methylpiperazine and *N*-(*tert*-butoxycarbonyl) piperazine were found to have low selectivity due to different side reactions.¹⁸⁶

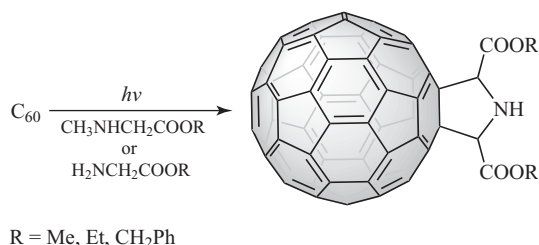
Glycine esters (H₂NCH₂COOR) add directly to C₆₀ upon photolysis to form pyrrolidine ring-fused fullerenes (Scheme 30).¹⁸⁷ The photochemical reactions between C₆₀ and sarcosine esters (CH₃NHCH₂COOR), which have one more methyl group than their glycine analogs, yielded the same pyrrolidine derivatives C₆₀(ROOCCNHCHCOOR) along with another pyrrolidine-type derivative C₆₀-(CH₂N(Me)CHCOOR).¹⁸⁷ The initial addition of a ¹O₂-mediated C-centered radical to C₆₀ and a C–N bond breakage are among the most critical steps involved in the reaction mechanism (Scheme 30).¹⁸⁷ It was later found that the reaction between

glycine- or sarcosine-methyl ester and C₆₀ can be effectively controlled by different iodo-reagents, namely DIB [(diacetoxyiodo)benzene], DIB-I₂, or I₂.¹⁸⁸

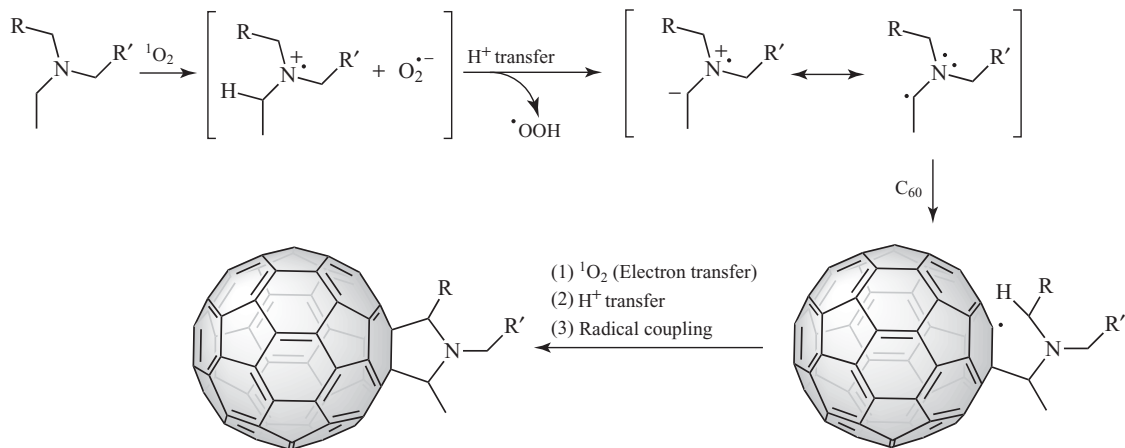
The addition of tertiary amines to C₆₀ is also a radical process.^{189–193} The reaction in this case takes place at the carbon α to the nitrogen of the amine. The intervention of singlet oxygen (¹O₂) in the radical reaction of C₆₀ with tertiary amines (i.e., triethylamine) has been proposed when the reaction is carried out in the presence of molecular oxygen or in air-saturated solutions.^{189,190} A plausible reaction mechanism involves primary interaction of singlet oxygen with the amine followed by addition of the resulting radical to the fullerene to afford, after repeating the same sequence of proton and electron transfer steps, the final pyrrolidine adduct of C₆₀ (Scheme 31).^{189,190}

On the other hand, when the photochemical addition of triethylamine to C₆₀ is carried out in deoxygenated toluene, the major product obtained is the corresponding adduct RC₆₀H (Scheme 32).¹⁹⁰ Similar to that of primary and secondary amines, the mechanism proposed for the photoreactions between [60]fullerene and tertiary amines (i.e., Et₃N) starts with a photoinduced electron transfer (PET) from the amine to photoexcited [60]fullerene, to give a radical ion pair.^{190–193} This is followed by deprotonation of the amine cation radical (R₃N^{•+}) by [60]fullerene anion radical (C₆₀^{•−}) to yield the corresponding radical pair, which combine to afford the final adducts (Scheme 32). The final monoadduct can react further through similar electron/proton transfer and radical pair recombination processes to afford the corresponding cycloadducts.^{191,192}

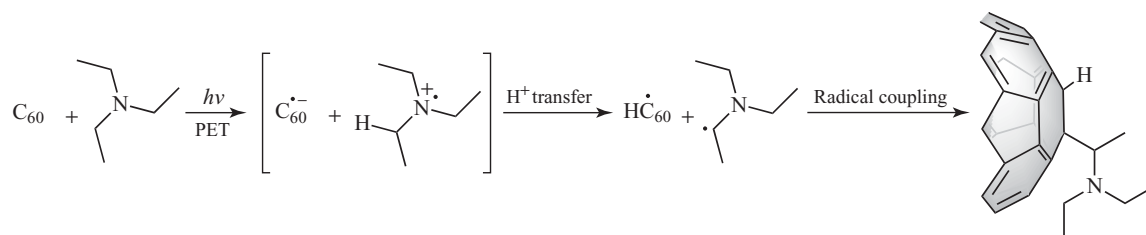
Similar to the reaction of C₆₀ with glycine- or sarcosine- methyl ester (Scheme 30),^{187,188} pyrrolidine ring-fused fullerene multicarboxylates have been produced upon photolysis of aminopolycarboxylic esters in the presence of C₆₀.¹⁹⁴ For example, irradiation of the tetramethyl ester of ethylenediaminetetraacetic acid (EDTA) with C₆₀ afforded the corresponding EDTA-containing fullerene monoadducts along with two adducts where the nitrogen ethylene bond N–CH₂CH₂ of EDTA has been broken (Scheme 33). Similar results were observed with pentamethyldimethylethylenetriaminepentaacetate (DTPA).¹⁹⁴ Aminocarboxylic acids are also reactive toward C₆₀ under photochemical conditions, affording upon decarboxylation



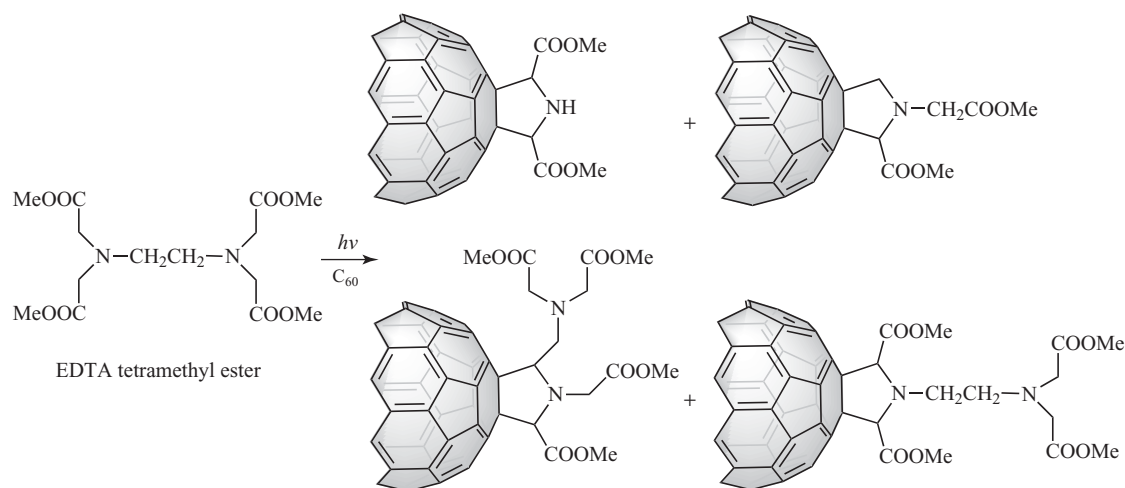
Scheme 30 Photochemical reaction of C₆₀ with glycine and sarcosine esters.



Scheme 31 Proposed mechanism for photocycloaddition of tertiary amines to C_{60} .



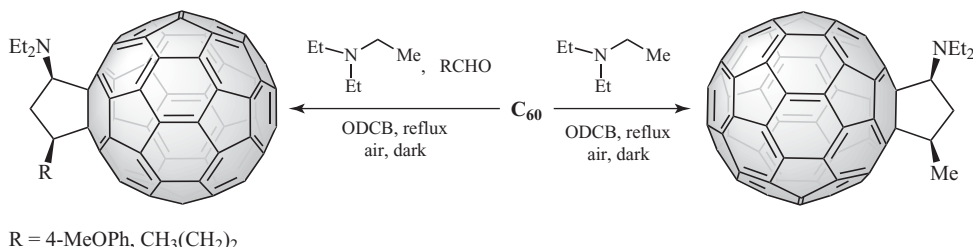
Scheme 32 Proposed mechanism of photoreaction between [60]fullerene and triethylamine.



Scheme 33 Photochemical reaction of C_{60} with tetramethyl ethylenediaminetetraacetate.

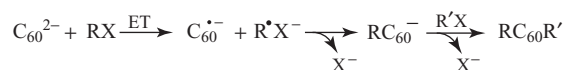
the corresponding organodihydrofullerenes.¹⁹⁴ A radical mechanism has been proposed for these photochemical reactions.¹⁹⁴ A series of similar pyrrolidinofullerenes bearing ester group

functionalities has been prepared through the $\text{Pb}(\text{OAc})_4$ -mediated reaction of [60]fullerene with the methyl esters of nitrilotriacetic acid, EDTA, and hexamethylenediaminetetraacetic acids.¹⁹⁵



Scheme 34 Reactions of C₆₀ with Et₃N in the presence or absence of aldehydes.

In 2006, Wang *et al.* reported that thermal reactions of [60]fullerene with amino acid ester hydrochlorides and triethylamine in refluxing *o*-dichlorobenzene afford pyrrolidinofullerene derivatives containing a CH₃CH fragment derived from Et₃N through C–N bond cleavage.¹⁹⁶ Further investigations revealed interesting reactions between C₆₀ and tertiary amines or reactions of C₆₀ with tertiary amines and aldehydes, which afford cyclopentafullerene derivatives with high stereoselectivity (Scheme 34).¹⁹⁶ These reactions are initiated by an electron transfer from amine to C₆₀ to form the corresponding amine radical cation and C₆₀^{•−}, respectively.



Scheme 35 Formation of organofullerenes RC₆₀R' through the reaction of C₆₀^{2−} with alkyl halides.

upon radical coupling with C₆₀^{•−}, the intermediate RC₆₀[−] (Scheme 35). The final alkylation of RC₆₀[−] with RX or R'X takes place via an S_N2 mechanism (Scheme 35).

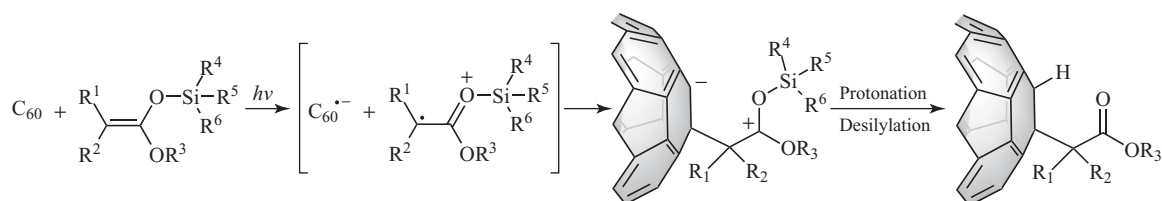
9.2 Addition of Alkyl Halides to C₆₀

The formation of organo[60]fullerenes of the type R₂C₆₀ or RR'C₆₀ has been described to occur via combination of electron transfer and S_N2 reactions from C₆₀^{2−} and alkyl halides (RX or R'X) in benzonitrile (Scheme 35).¹⁹⁷ It has been proposed that the first step of this reaction involves an electron transfer from C₆₀^{2−} to RX to form an intermediate radical pair C₆₀^{•−} and R'X^{•−}. The R–X bond is cleaved upon dissociative electron transfer to afford,

9.3 Addition of Ketene Silyl Acetals and Allylic Stannanes to C₆₀

The first step in the monoaddition reaction of ketene silyl acetals to fullerene includes a photoinduced SET from ketene silyl acetals to the triplet excited state of C₆₀ (Scheme 36).^{198,199} Radical coupling leads to a zwitterionic species, which upon water-assisted removal of the silyl group and protonation, affords the final adducts. No free-radical species are involved since the addition of a radical trap (i.e., TEMPO) had no effect on the reaction.

The mono- and penta-addition of enol silyl ethers to C₆₀ was later reported.²⁰⁰ In particular, it was



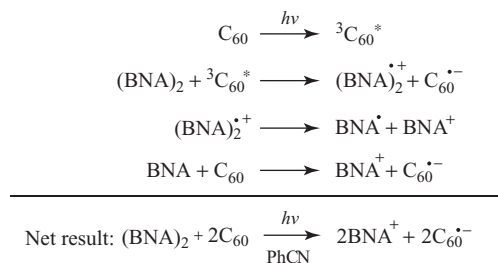
Scheme 36 Photoinduced C–C bond formation of C₆₀ with ketene silyl acetals.

found that the reaction of 1-alkoxy-1-siloxyethene with C_{60} in 20% DMSO/chlorobenzene at ambient temperature under O_2 atmosphere affords a penta-addition product, while the reaction of 1-alkoxy-1-siloxyalkenes or 1,2-siloxyalkenes under argon atmosphere affords monoaddition products.²⁰⁰

Apart from ketene silyl acetals, allylic stannanes can also efficiently add to C_{60} via photoinduced electron transfer to the triplet excited state of C_{60} .^{201,202}

9.4 One- and Two-Electron Reduction of C_{60} with NADH and NAD Dimer Analogs

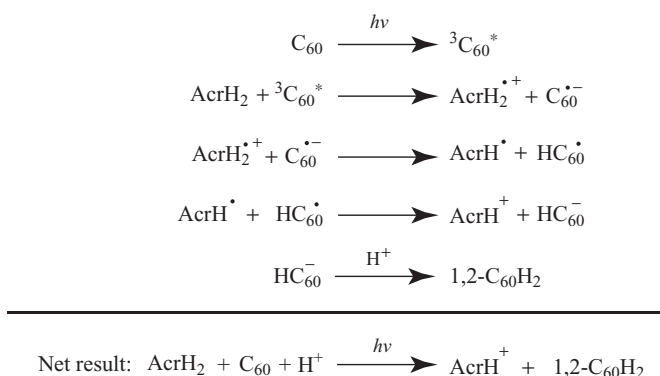
The triplet excited state of C_{60} has a reduction potential of $E_{red}^0 = 1.14$ V versus standard calomel electrode (SCE) and thus a variety of organic compounds can reduce C_{60} to the C_{60} radical anion. In homogeneous systems, however, fast back-electron transfer to the reactant pair results generally in an extremely short lifetime of the generated $C_{60}^{\bullet-}$ and no net formation of $C_{60}^{\bullet-}$ is observed. To overcome these problems, Fukuzumi *et al.* used nicotinamide adenine dinucleotide (NADH) analogs as electron donors.²⁰³ In particular, it was found that the photoinduced electron transfer from an NADH analog 1-benzyl-1,4-dihydronicotinamide (BNAH) and the dimer analog [(BNA)₂] to the triplet excited state of C_{60} ($^3C_{60}^*$) yields stable $C_{60}^{\bullet-}$ in benzonitrile solution with a high quantum yield.²⁰³ The reaction mechanism in the latter process is initiated by an electron transfer from (BNA)₂ to the triplet excited state ($^3C_{60}^*$) followed by fast C–C bond cleavage



Scheme 37 Selective one-electron reduction of C_{60} via photoinduced electron transfer from 1-benzyl-1,4-dihydronicotinamide dimer (BNA)₂ to $^3C_{60}^*$.

in the resulting $(BNA)_2^{\bullet+}$ to give $BNA^{\bullet}$ and BNA^+ . A second electron transfer from $BNA^{\bullet}$ to C_{60} yields BNA^+ and $C_{60}^{\bullet-}$ (Scheme 37).²⁰³

When BNAH is replaced by 4-*tert*-butylated BNAH (*t*-BuBNAH), the photochemical reaction with C_{60} yields selectively instead of the $C_{60}^{\bullet-}$ the *tert*-butylated anion (*t*-Bu $C_{60}^{\bullet-}$).²⁰³ The selective two-electron reduction of C_{60} to 1,2-dihydro[60]fullerene (1,2- $C_{60}H_2$) was also achieved by using another NADH analog 10-methyl-9,10-dihydroacridine (AcrH₂) under visible light irradiation in deaerated benzonitrile solution containing trifluoroacetic acid (Scheme 38).²⁰³ This reaction proceeds via photoinduced electron transfer from AcrH₂ to $^3C_{60}^*$, followed by proton transfer from AcrH₂^{•+} to $C_{60}^{\bullet-}$ and a second electron transfer from the deprotonated acridinyl radical (AcrH[•]) to $HC_{60}^{\bullet-}$ in the presence of trifluoroacetic acid, to yield the final products 10-methylacridinium ion (AcrH⁺) and 1,2- $C_{60}H_2$ (Scheme 38).



Scheme 38 Selective two-electron reduction of C_{60} to $C_{60}H_2$ via photoinduced electron transfer.

9.5 Cation Radical Reactions of C₆₀

Initially, Foote *et al.* reported the generation of the radical cation of C₆₀ via electron transfer to singlet *N*-methylacridinium hexafluorophosphate (NMA⁺).²⁰⁴ Higher yield production of C₆₀^{•+} could be achieved by cosensitization, using high concentrations of biphenyl to form biphenyl radical cation which is the ultimate oxidant for C₆₀.²⁰⁴ Later, Schuster *et al.* reported the generation of C₆₀ radical cations by photosensitized electron transfer from electronically excited 1,4-dicyanoanthracene (DCA), which resulted in the addition of alcohols or hydrocarbons to C₆₀.²⁰⁵ Mattay *et al.* also reported the generation of C₆₀^{•+} via photoinduced electron transfer.^{206,207} It was later found that, when 2,4,6-triphenylpyrylium tetrafluoroborate (TPP⁺BF₄[−]) is used as a sensitizer, an electron transfer from C₆₀ to TPP occurs without the application of a cosensitizer.²⁰⁸ The existence of C₆₀^{•+} has been proved by using ESR studies.²⁰⁸ The proposed mechanism for the formation of C₆₀^{•+} by the aforementioned cosensitization method is depicted in Scheme 39.

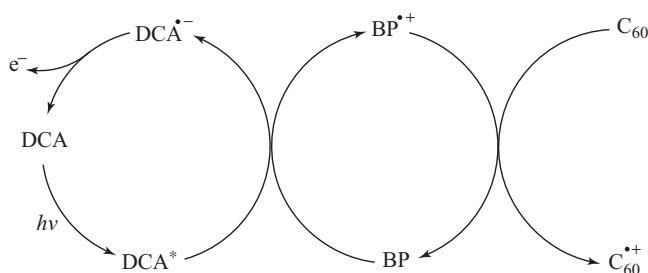
The generated radical cation C₆₀^{•+} abstracts a hydrogen atom from the appropriate H-donor (i.e., *tert*-butylmethyl ether, propionaldehyde, *N,N*-dimethylformamide, 1,3-dioxolane, phenylacetaldehyde, methyl formate, *tert*-butanol, propionic acid, glycol and methoxyethanol) to give, after reduction of HC₆₀⁺ to HC₆₀[•] (i.e., from reduced sensitizer) and recombination with R[•], the corresponding 1-substituted 1,2-dihydro[60]fullerenes (Scheme 40).^{206,207}

10 CONCLUSIONS

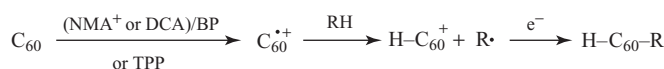
In this article, we have outlined some of the progress made in the radical chemistry of fullerenes from both practical and fundamental points of view.

From a fundamental perspective, we have shown that ESR spectroscopic studies have provided valuable insight into the basic characteristics of the radical reactions of fullerenes. These and other physical/chemical studies have led to the establishment of key features of the radical reactions of fullerenes, some of which are as follows: (i) the rate constants for the addition of various C-centered radicals to fullerene are two orders of magnitude higher than those for the addition of radicals to a wide class of monosubstituted unsaturated compounds; (ii) the multiple addition of free radicals to C₆₀ results in stable fullereryl radicals with an allylic or cyclopentadienyl structural pattern; (iii) the unpaired electron in the RC₆₀[•] radical adducts is essentially confined to definite carbon atoms incorporated into the two hexagons adjacent to the radical center and is not extensively delocalized over the C₆₀ sphere; (iv) fullereryl radicals demonstrate a tendency to dimerize in a “head-to-head” type; (v) there is a hindered rotation about the R–C₆₀[•] bond in the alkyl fullereryl radicals, whereas the rotation barrier is lower for the Si–C₆₀[•] radicals owing to the slightly longer bond of Si–C₆₀ compared to C–C₆₀.

From a practical point of view, the employment of radical reactions in fullerene chemistry has led to the synthesis of a variety of structurally diverse fullerene derivatives which would be otherwise inaccessible. Such reactions include the addition of



Scheme 39 Formation of C₆₀^{•+} by cosensitization. [Reprinted from Ref. 206. Copyright (1997), with permission from Elsevier.]



Scheme 40 Reaction of C₆₀^{•+} with organic hydrogen donors RH.

radicals of different chemical nature, including C-, Si-, O-, S-, P-, and metal-centered radicals, to C₆₀ and/or C₇₀.

Some of the most recent developments outlined in this article, as well as the ongoing research interest on the radical reactions of fullerenes, convey that there are more, still unexplored radical reactions that will likely emerge in the future.

ACKNOWLEDGMENTS

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Tin Hydrides and Functional Group Transformations

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1 INTRODUCTION

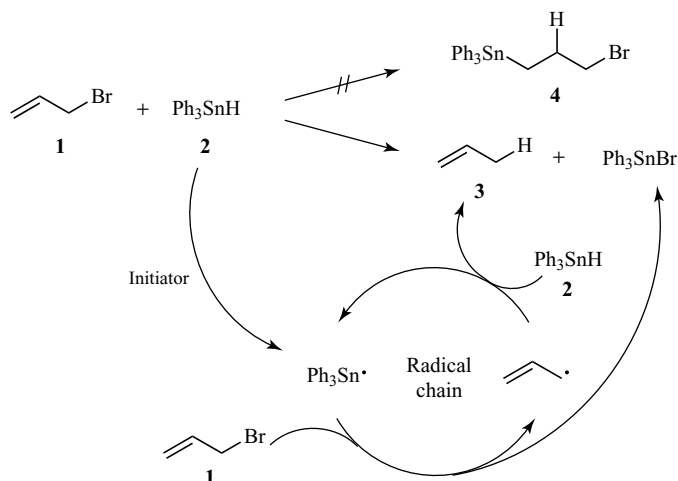
There is probably hardly any reagent that organic chemists would associate more with radical chemistry than tributyltin hydride. Unfortunately, this popularity is also the reason for a certain reluctance among chemists to apply radical reactions since the toxicity and the sometimes troublesome removal or purification are known as well as the reagent itself. In this article, we give an overview of the manifold reaction types that have so far been put into practice by employing tin hydrides. Since several new tin reagents have been reported in recent years together with improved reaction conditions, significant advances could be made over the above-mentioned disadvantages associated with the traditional organostannanes. In this way, the whole field of tin hydride-mediated radical reactions becomes increasingly attractive, as a variety of modern replacements are now available for the still widely used tributyltin hydride.

As it often happens in chemistry, major advances arise from observations that are first regarded as experimental failures. When van der Kerk and his group attempted the hydrostannylation of allyl bromide (**1**) with triphenyltin hydride (**2**) by performing a reaction type that was already well established at that time, they were surprised to find propene (**3**) as a reaction product.¹ Instead of forming the desired adduct **4**, triphenyltin hydride (**2**) had effectively removed the allylic bromine atom

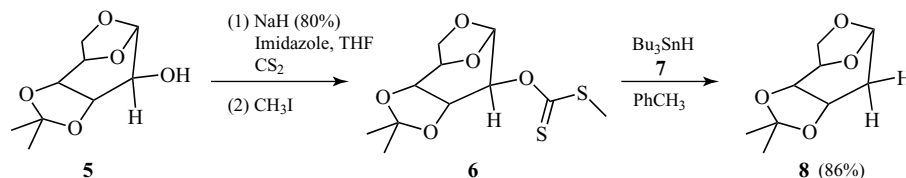
by radical chain mechanism requiring only trace amounts of an initiator which most probably was oxygen (Scheme 1).

The new method for the deoxygenation of secondary alcohols, which was reported by Barton and McCombie in 1975, considerably increased the interest in radical chemistry, and especially in tin hydrides.² Under mild conditions, and avoiding rearrangements caused by alternative cationic intermediates, hydroxy groups could now be selectively removed from structurally complex compounds. An example from the field of sugar chemistry, which has been part of Barton's first article, is depicted in Scheme 2. The secondary alcohol **5** was first converted to xanthate **6** and then reduced in the presence of tributyltin hydride (**7**) to give the corresponding deoxygenated carbohydrate **8**.

The deoxygenation methodology, which was initially limited to secondary alcohols, could later be successfully extended to primary and tertiary alcohols by varying the reaction conditions and structural modifications of the original dithiocarbonate. Even today, and mainly due to the mild reaction conditions, the Barton–Combie deoxygenation is one of the methods of choice in natural product synthesis. In many cases, dispensable oxygen-containing substituents have to be removed in the final stages, which had earlier been required to build up the desired carbon skeleton.³



Scheme 1 Radical dehalogenation of allyl bromide (1) by triphenyltin hydride (2).¹



Scheme 2 Barton–McCombie deoxygenation of the secondary alcohol 5.²

In the 1980s and 1990s, a large number of reports in the field of radical chemistry appeared disclosing many new transformations using tin hydrides as key reagents. At the same time, the attempts to address the disadvantages were also beginning to intensify. Tris(trimethylsilyl)silane (see **Silanes as Reducing Reagents in Radical Chemistry**) was introduced as a potential replacement, and a growing community of investigators started to feel that it was time to start the “flight from the tyranny of tin”.⁴

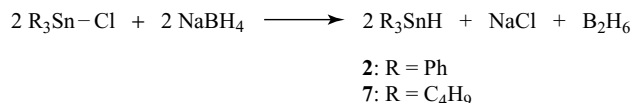
Owing to the limitations of space, it will be impossible to comprehensively cover the whole field of radical tin hydride chemistry in this article. As the newly developed tin reagents and related reaction conditions can be considered as a key to the future applications of tin hydrides, we will first focus on this issue. In the second part, we will show which functional groups can act as radical sources in tin hydride-mediated reactions. Illustrative examples have been chosen to give insight into the large variety of radical transformations feasible by employing tin hydrides. For further reading, the reader is referred to a number of reviews that have

appeared covering the field of radical tin hydride chemistry.^{5–23} An excellent article has recently been published by Clark.²⁴

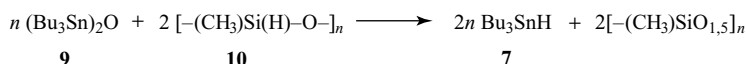
2 TIN HYDRIDES

2.1 Preparation of Tin Hydrides

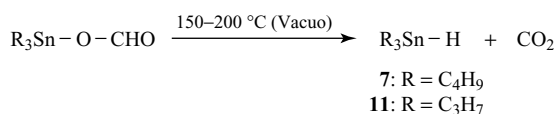
Organostannanes, which represent derivatives of stannane (SnH_4), show an increasing thermal stability when more hydrogen atoms are replaced by alkyl or aryl groups. While stannane itself readily decomposes to tin and hydrogen, trialkyl or triaryl-stannanes can be stored and handled much more conveniently.²⁵ Among the organostannanes that are used in radical chemistry, tributyltin hydride (7) is certainly the most important congener. Similar to its triphenyl derivative 2, it is usually prepared from the corresponding organotin chlorides by reaction with sodium borohydride^{26–29} (Scheme 3) or lithium aluminum hydride.^{30–40}



Scheme 3 Preparation of triphenyl and tributyltin hydride (2 and 7) by reduction of organotin chlorides with sodium borohydride.²⁸



Scheme 4 Preparation of tributyltin hydride from tributyltin oxide 9 and polysiloxane 10.⁴³



Scheme 5 Preparation of tripropyl and tributyltin hydride by thermal decarboxylation of tin formiates.⁴⁵

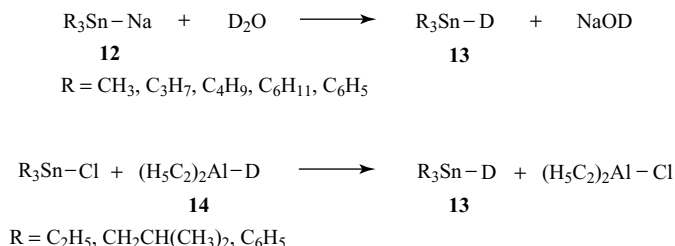
Diborane⁴¹ and aluminum hydride⁴² were found to be suitable reagents for the preparation of tin hydrides from alkyl stannyl ethers. The most convenient access to tributyltin hydride (7), although it does not represent the frequently used method (Scheme 3), is the reduction of bis(tributylstannyl) ether (9) with polymethylhydrosiloxane (PMHS, 10) (Scheme 4).⁴³ Because of a favorable equilibrium in exchange reactions of hydrogen, the reducing siloxane 10 can be replaced by other more reactive organostannanes such as diaryltin hydrides.⁴⁴

Alternatively, trialkyltin hydrides such as 7 and 11 can be readily prepared by thermal decarboxylation of the corresponding trialkyltin formiates⁴⁵ (Scheme 5) or by decomposition of organostannyl amines.⁴⁶

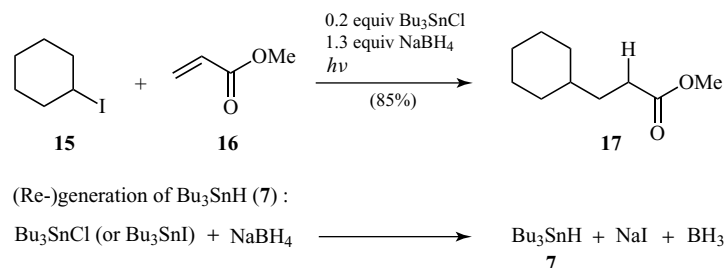
In addition to the broad use of tin hydrides as reducing agents, the deuterated or tritiated analogs have been successfully employed in the synthesis of isotope-labeled compounds.^{47,48} Concerning the

preparation of these stannane analogs, two main strategies have been followed. Solvolysis of (triorganostannyl) metal compounds such as R₃SnNa 12,^{49,50} R₃SnLi,⁵¹ or R₃SnMgX^{52–55} with deuterium oxide leads to the desired tin deuterides 13 as well as the reduction of organotin chlorides with dialkyl aluminum deuterides 14 (Scheme 6).⁵⁶

The main drawback of the commonly used organotin hydrides is their comparatively high toxicity, which has to be largely attributed to the good permeability and adsorption of these compounds through the skin.⁵⁷ In general, tin hydrides bearing short alkyl chains, such as trimethyltin hydride, are more difficult to handle because of their higher volatility. In addition to the immediate toxicity of the tin hydride reagents, problems are often again encountered during work-up, and special care has to be taken concerning the final waste disposal. For the separation of remaining organostannanes and related by-products arising from the respective reaction mixtures, several “classical” methods have been established. Given that the desired reaction product is sufficiently polar, the tin-containing compounds can largely be removed by extraction with hydrocarbons from solutions in acetonitrile.⁵⁸ Alternatively, the organostannyl derivatives have been converted to insoluble iodides or fluorides by the use of either



Scheme 6 Preparation of triorganotin deuterides 13.^{49–51, 56}



Scheme 7 Carbon–carbon bond formation via *in situ* formation and regeneration of tributyltin hydride (**7**).⁶²

iodine and DBU (1,8-diazabicycloundec-7-ene) or potassium fluoride.⁵⁹

However, the removal of the tin-containing residues from the reaction mixture by these classical methods is in most cases by far not quantitative. For this reason, and especially due to the fact that applicability of toxic, tin-contaminated products would later be severely restricted, a number of strategies have been developed to make tin hydride-mediated reactions more attractive.

2.2 In situ Generation and Catalytic Reactions

One successful approach to facilitate work-up and separation of tin-containing residues is to run the respective reactions catalytically in tin hydride. On the basis of the pioneering work of Hayashi published in 1967,⁴³ who discovered that organostannanes can efficiently be prepared from siloxanes (Scheme 4), the principle of *in situ* generation of tin hydrides was first put into practice by Grady and Kuivila in 1969.³⁴ Sodium borohydride, which was also known to effect the conversion of tributyltin halides to hydrides, was introduced as an alternative reagent for the *in situ* generation and regeneration of tributyltin hydride by Corey.⁶⁰ Given that the functional groups of the substrates showed sufficient stability toward sodium borohydride, the borohydride–organotin chloride couple emerged as a reagent pair of choice for reactions run catalytically

in tin hydride.⁶¹ An example featuring a catalytic tributyltin hydride-mediated carbon–carbon bond formation is depicted in Scheme 7.⁶² Under photochemical initiation, cyclohexyl iodide (**15**) and methyl acrylate (**16**) were cleanly converted to ester **17** in the presence of only 0.2 mol equivalents of tributyltin chloride.

More recent reports describe the use of siloxanes, activated by potassium fluoride, for the *in situ* regeneration of trialkyltin halides.⁶³ Alternatively, catalytic amounts of tributylstannyl phenyl ether can be employed in combination with siloxanes for the same purpose.⁶⁴ In addition to the above-shown carbon–carbon bond-forming reactions, the catalytic tin hydride-mediated reductions have been shown to be highly useful for the mild removal of nitro and azide groups from alkanes.^{65,66} An interesting review including reactions with catalytic amounts of organotin hydride in combination with PMHS has been compiled by Lawrence.⁶⁷

2.3 Supported Tin Hydride Reagents

A relatively new strategy focusing on the facilitated removal of the tin-containing reagents and products is to employ polymer-bound tin hydrides. The preparation of the macromolecular reagents can be realized in two ways: either the functionalization of an existing polymer with organostannane moieties,^{68,69} or by copolymerization of tin



Figure 1 Polymer-supported trialkyltin hydrides **18**^{72,73} and **19**.⁷⁰

hydride-containing monomers (Figure 1).^{68,70,71} The applicability of such reagents was initially demonstrated in simple reductions of organohalides.⁷²

A later report by Neumann showed that the concept of polymer-bound reagents could moreover successfully be combined with the principle of *in situ* regeneration, so that only substoichiometric amounts of the polymer were required for the reduction of alkyl bromides and iodides.⁷³ The dramatic improvement with respect to the amount of tin-containing residues remaining after work-up, which can be achieved by the use of macromolecular tin hydrides, became obvious from a study by Dumartin.⁷⁴ For comparison, the reduction of 1-bromoadamantane (**20**) with the Bu_3SnCl – NaBH_4 couple to give adamantane (**21**) was first combined with the traditional treatment of the product mixture with potassium fluoride (to give insoluble tributyltin fluoride) or with purification by column chromatography (Scheme 8). The adamantane isolated from these experiments still contained remarkable amounts of tin as 15.2 and 9.8×10^4 ppm, respectively (see table in Scheme 8, entry 1). The application of a polymer-bound dibutyltin iodide (0.5 M equiv with respect to **20**) together with sodium borohydride led to a decrease in tin pollution of the product to only 26 ppm (entry 2). By further reducing the amount of polymer-bound tin hydride to 0.05 molar, the adamantane was obtained cleanly, since no more tin could be detected in the product by inductively coupled plasma mass spectrometry (ICP-MS) (entry 3). Moreover, the tin-containing polymer recovered from the reduction could be reused without a significant loss of reactivity.

To produce polymeric materials with a higher tin hydride loading than that of the so-far-known

macromolecular reagents, solid networks have been prepared from Grignard reagents and phenyltin trichloride.⁷⁵ Upon further treatment with bromine and reduction with sodium borohydride, a highly solvent-penetrable but insoluble tin hydride was obtained. The new reagents showed complete regeneration capability in NaBH_4 , and during their reactions no detectable leaching of tin into the solution was observed.

Remarkable advances with respect to permanent porosity, Sn-H site accessibility, solvent tolerance, and applicability in continuous flow systems have also been achieved with elusion-derived foams.⁷⁶ The new polymer-supported tin hydride reagents of this type were prepared by copolymerization of a stannylated styrene derivative, styrene, and *p*-divinylbenzene.

Since the accessibility of the Sn-H groups within polymeric reagents is an important prerequisite to a successful application, a detailed study concerning the effects of the polymer structure on the reactivity has been conducted. Within this report, effects such as coil formation in the polymer or structural changes due to dilution of the reaction mixture are discussed.⁷⁷

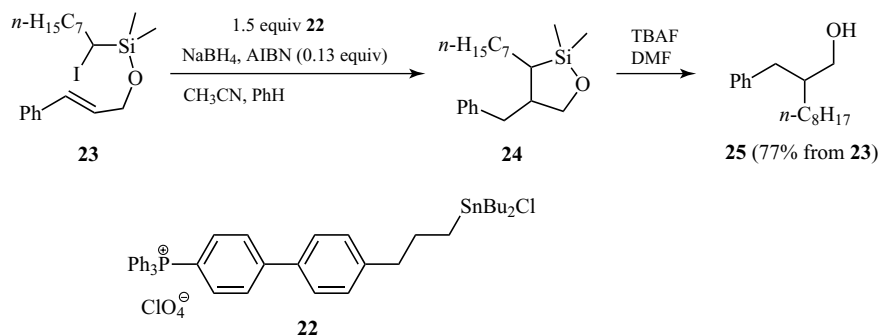
Comparable to polymer-bound tin hydrides, a facilitated work-up was also put into practice with organostannanes attached to polyaromatic hydrocarbons such as pyrene. In this case, separation is achieved by adsorption of the reagents and their by-products on activated carbon.⁷⁸ In a recent study, triarylphosphonium-supported tin hydrides were evaluated as reagents for Stille couplings, radical dehalogenations and cyclizations, as well as carbonyl allylations (Scheme 9).⁷⁹ For this particular reagent type, removal of the tin hydride

20 $\xrightarrow[\text{EtOH}]{\text{SnX/NaBH}_4, \text{AIBN}}$ **21**

	SnX/NaBH ₄	Molar ratio of SnX/ 20	Yield (% adamantane (20))	Tin pollution (ppm)
1	$\text{Bu}_3\text{SnCl/NaBH}_4$	0.5	70	15.2×10^4 ^a 9.8×10^4 ^b
2	$\text{P-(CH}_2)_4\text{SnBu}_2\text{I/NaBH}_4$	0.5	94	26
3	$\text{P-(CH}_2)_4\text{SnBu}_2\text{I/NaBH}_4$	0.05	75	Blank

P = Amberlite XE 305 (c.f. polymer **19**, Figure 1). ^aAfter purification by column chromatography. ^bAfter treatment with KF.

Scheme 8 Comparison of the effectiveness of tin removal by conventional methods and by polymer-bound reagents.⁷⁴



Scheme 9 Triarylphosphonium-supported tin reagents in radical cyclization reactions.⁷⁹

(generated *in situ* from chloride **22**) from the crude reaction mixture is possible by precipitation upon addition of an unpolar solvent such as hexane. In this way, residual tin amounts as low as 5 ppm were found in the products obtained from a series of dehalogenation reactions. Moreover, separation by precipitation led to a recovery of the triarylphosphonium-supported tin reagents in high purity which enabled their successful recycling and reuse without loss of reactivity. An illustrative example from the same study featuring the radical 5-exo-type cyclization of iodide **23** is shown in Scheme 9. The silicon tether was later cleaved from product **24** by tetrabutylammonium fluoride (TBAF) to give alcohol **25**.

Closely related to polymer support, a high degree of tin removal from the desired products can alternatively be attained in reactions in which a polymer-bound substrate is reacted with standard tributyltin hydrides. Relative rates and approximate rate constants for the corresponding inter- and intramolecular hydrogen-transfer reactions are available from the literature.⁸⁰ A collection of illustrative examples of this reaction type can be found in a review by Ganesan.⁸¹

2.4 Fluorous Tin Hydrides

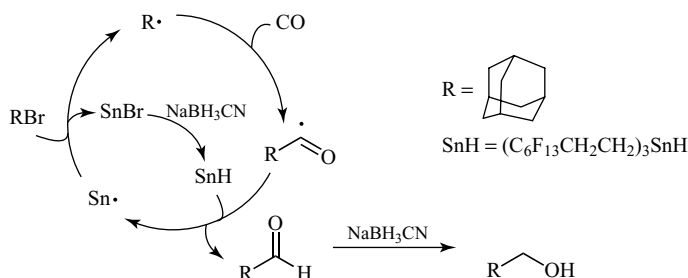
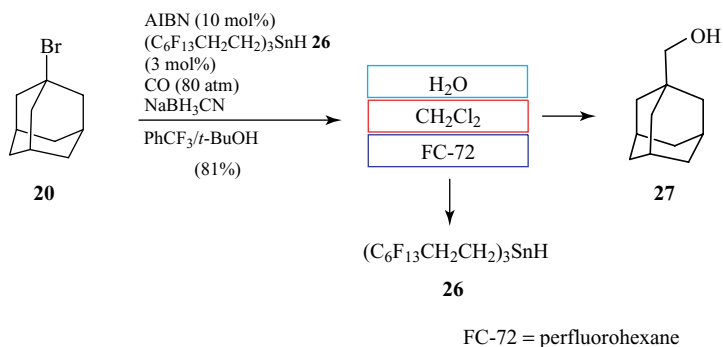
Owing to their unique properties, fluorinated reagents have become increasingly popular for various purposes in the past two decades. A number of review articles summarizing general developments and advances in this field have appeared.^{82–89}

Pioneering work on polyfluorinated organotin hydrides and their use in radical reactions was

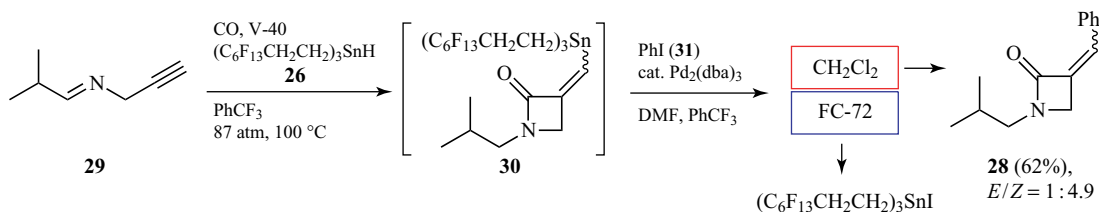
reported by Curran in 1996.⁹⁰ Compared to classical tributyltin hydride, fluorinated derivatives such as $(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_3\text{SnH}$ are even slightly more reactive (by a factor of 2) concerning the transfer of hydrogen to a primary carbon radical center.⁹¹ Given a comparable reactivity, the main advantage of the polyfluorinated over classical tributyltin hydride reagents arises from the far less complicated reaction work-up. Separation of polyfluorinated reagents is readily achieved by simple biphasic fluorous–organic extraction. An early application of this technique in radical hydroxymethylation reactions is shown in Scheme 10, together with the underlying reaction mechanism.⁹² Catalytic amounts of the fluorous tin hydride **26** were sufficient to achieve a good conversion of 1-bromoadamantane (**20**) to alcohol **27**, since sodium cyanoborohydride could be employed as a regenerating reagent.

The ability of triorganostannyl radicals to efficiently add to carbon–carbon triple bonds (see also Section 3.3.6) can be exploited to achieve the synthesis of lactam **28** from azaenyne **29** in the presence of carbon monoxide (Scheme 11).^{93,94} Polyfluorinated organostannyl radicals (as available from reagent **26**) proved equally effective for this purpose, and since a vinyltin intermediate **30** is formed from the cyclization introducing the CO unit, the reaction is well suited for combination with a subsequent Stille-type cross-coupling.^{95,96} No purification of **30** was necessary prior to the palladium-catalyzed reaction with iodobenzene (**31**), and the fluorous tin reagent was again easily separated from the crude reaction mixture by extraction with perfluorohexane (FC-72).

The results of an extensive study comparing the properties of eight different fluorous tin hydrides



Scheme 10 Radical hydroxymethylation employing fluorous tin hydrides.⁹²

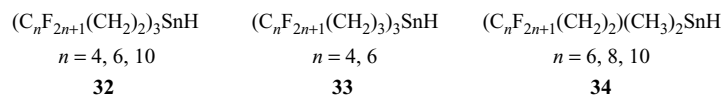
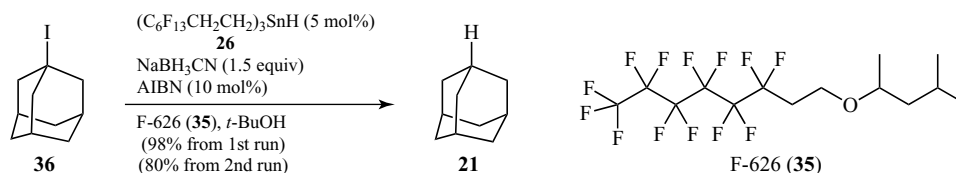


Scheme 11 Fluorous tin hydride-mediated synthesis of β -lactam **30** combined with a Stille-type cross-coupling reaction.^{95,96}

from three structural subgroups **32**, **33**, and **34** (group 32 includes reagent **26**) have been reported by Curran (Figure 2).⁹⁷ Insights are given on how the substitution pattern and the degree of fluorination influence the respective partition coefficients between perfluorohexanes and common organic solvents, which are important for the easy and quantitative separation during work-up. The reagents were found generally useful for a replacement of tributyltin hydride in stoichiometric as well as in catalytic radical reactions, which gives them an excellent potential for applications in large-scale processes as well as combinatorial and parallel synthesis.

Despite the rapid development of new methodologies employing polyfluorinated reagents,

investigations on improved solvents were largely neglected with the exception of benzonotrifluoride (BTF).⁹⁸ For the reason of solubility, those reactions are ideally conducted in fluorous/organic amphiphilic solvents which readily dissolve both organic and fluorous compounds and lead to a homogeneous reaction medium. Advances in this field were made by the introduction of the perfluorinated ether F-626.^{99,100} An example from the first report on the use of F-626 (**35**) in the reduction of haloalkanes, such as **36**, is depicted in Scheme 12.¹⁰¹ Advantageously, the new fluorinated solvent **35** was easily recovered together with the fluorous tin reagent **26** during work-up by simple extraction with perfluorohexane (FC-72). Moreover, both **26** and **35** could successfully be reused for

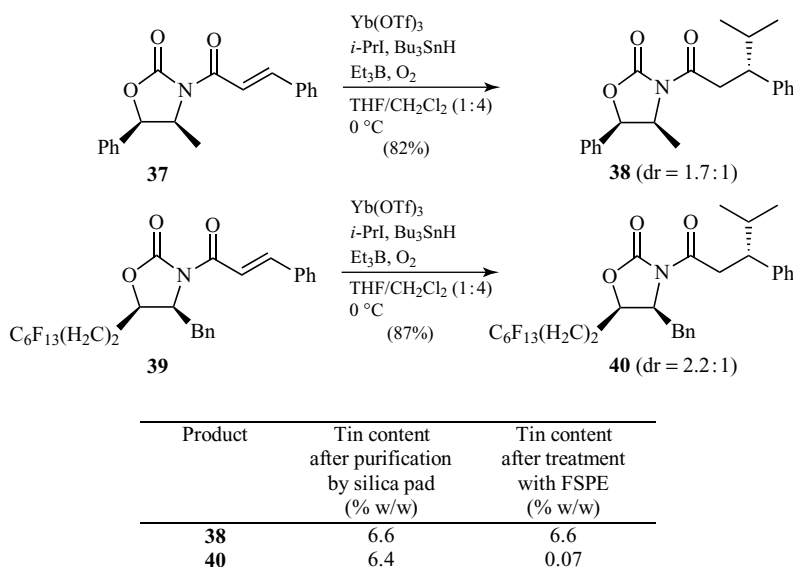
**Figure 2** Fluorous tin hydrides.⁹⁷**Scheme 12** Fluorous tin hydride reduction of 1-iodoadamantane (**36**) using the perfluorinated ether F-626 (**35**) as solvent.¹⁰¹

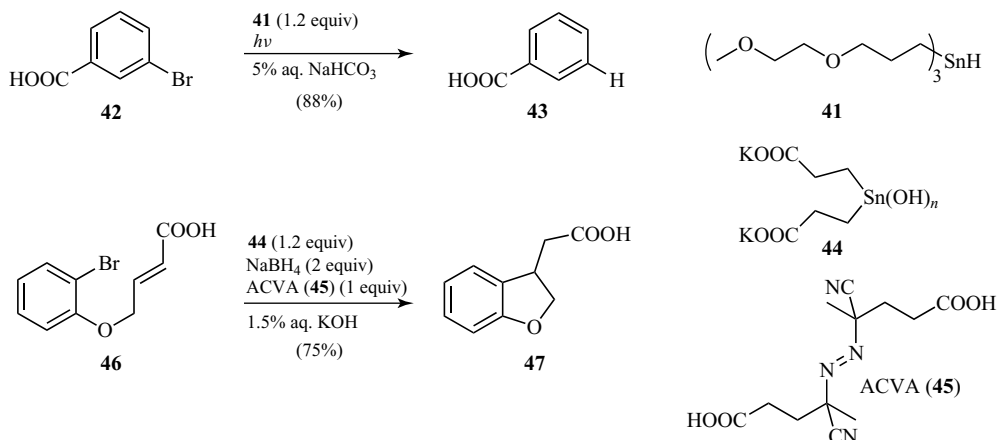
the same reaction type without further purification, which is mainly due to the low partition coefficients observed for general organic solvents to a fluorous phase. In this respect, F-626 proved superior to BTF because of its increased fluorophilicity.

Regarding the separation and recovery of fluorous tin species from crude reaction mixtures, silica tethered with fluorinated chains has been evaluated with respect to its ability to release and capture fluorous tin reagents depending on temperature.¹⁰²

Similar to the reversed strategy presented in Section 2.3, in which polymer-bound substrates were employed instead of supported tin hydride reagents, the difficulty of organotin removal can

alternatively be circumvented by attaching the fluorous side chain to the substrate instead of to the tin reagent. A recent example from a report in which this principle has been put into practice is depicted in Scheme 13.¹⁰³ The radical conjugate addition to substrate **37**, bearing a typical norephedrine-based chiral auxiliary (see **Stereoselective Radical Reactions**) leads to the product **38** which was found difficult to be purified from tin-containing residues. After the same radical reaction was performed with the polyfluorinated derivative **39**, the respective product **40** could easily be separated from remaining tributyltin hydride and its by-products by fluorous solid-phase extraction (FSPE).

**Scheme 13** Comparative study on classical and fluorous chiral auxiliaries in tin hydride-mediated alkylations.¹⁰³



Scheme 14 Water-soluble tin reagents **41** and **44**.^{104,106}

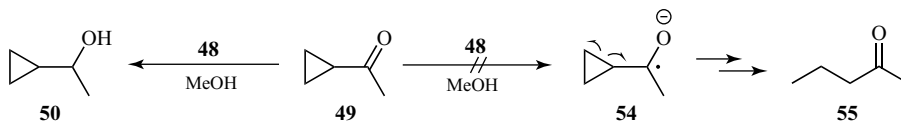
An excellent summary on the developments in the field of fluorinated tin hydrides, including fluororous organotin reagents for allylation reactions, was published by Ryu *et al.*⁹⁶

2.5 Water-Soluble Tin Hydrides

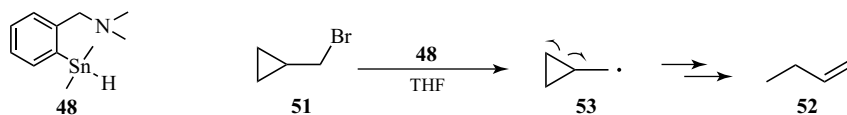
The first water-soluble organotin hydride **41**, in which the three butyl groups of Bu₃SnH were replaced by methoxyethoxypropyl units, was reported by Breslow (Scheme 14).¹⁰⁴ This reagent was successfully used for the reduction of halogenated carbohydrate derivatives and aromatic carboxylates, such as 3-bromobenzoic acid **42**, to give benzoic acid **43** in buffered aqueous solutions. It could easily be recovered in the form of its

chloride during work-up by simple extraction upon acidification with hydrochloric acid. Shortly after, Maitra demonstrated that unmodified tributyltin hydride is also effective as a radical reducing agent in water at elevated temperatures using longer reaction times.¹⁰⁵ To achieve the conversion of certain very unpolar substrates in water, suitable detergents had to be added. Although widely applicable, the main drawback of the etheral tin hydride **41** remained its multistep synthesis from monomethyl glycol. For this reason, the dipotassium salt **44**, which is conveniently prepared from tin metal and acrylic acid, was evaluated with respect to its applicability as a substitute (Scheme 14).¹⁰⁶ An example from the study by Collum is depicted below. *In situ* reduction of the organotin diol **44** by sodium borohydride, and using 4,4'-azobis(4-cyanovaleic acid) (ACVA) (**45**) as initiator, led to the desired

Tin hydride **48** as an ionic reductant



Tin hydride **48** as a radical reductant



Scheme 15 Tin hydride **48** acting as ionic hydride or radical hydrogen donor.¹⁰⁷

cyclization of **46** to dihydrobenzofuran **47** in 1.5% potassium hydroxide solution. Interestingly, **47** was also obtained from **46** in the absence of diol **44** by applying an eightfold excess of sodium borohydride.

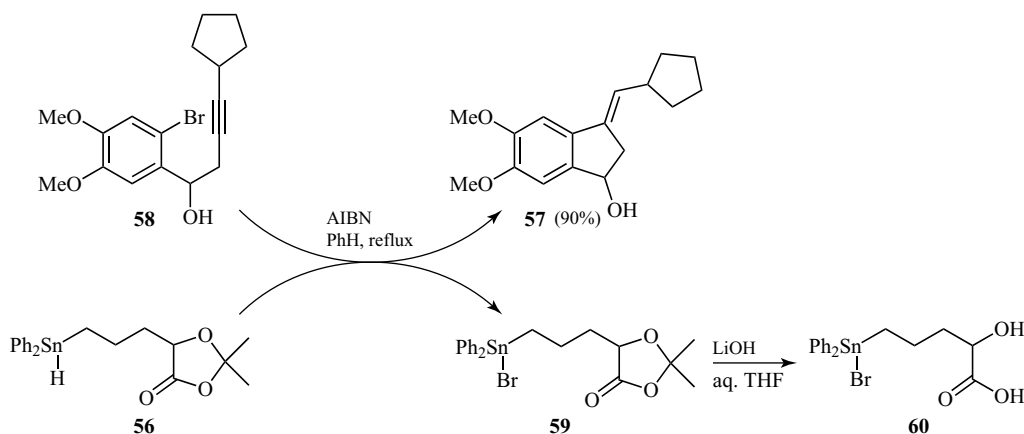
Depending on the reaction conditions, the organostannylated *N,N*-dimethylbenzylamine **48** can act as a potent ionic hydride transfer reagent as well as a radical reductant.¹⁰⁷ When applied in protic solvents such as methanol, tin hydride **48** led to the reduction of various ketones to alcohols. As shown in Scheme 15, cyclopropyl methyl ketone (**49**) was cleanly converted to the corresponding alcohol **50**. Interestingly, **49** was not reduced to **50** when the same reaction was attempted in aprotic solvents such as tetrahydrofuran or acetonitrile. Under the latter conditions, **48** behaved like a standard tin hydride-type radical reagent which is able to induce reactions such as the dehalogenation of cyclopropylmethyl bromide **51** to give butene **52** via a fast ring-opening of the radical **53**. Single-electron transfer can be ruled out for the formation of alcohol **50** from **49**, since a radical reaction mechanism of this type would cause ring-opening of the cyclopropane **54** to give 2-pentanone (**55**).

Beneficially, the tin hydride **48** and its by-products could efficiently be removed from crude reaction mixtures by filtration through silica gel, taking advantage of the basic benzylamine moiety. A facilitated work-up and organotin removal was recently also achieved with organotin hydride **56** (Scheme 16).¹⁰⁸ Several test reactions including

reductions of chlorides, bromides, iodides, and selenides as well as Barton–McCombie type deoxygenations, revealed a reactivity of **56** comparable to those of tributyltin hydride (**7**) or triphenyltin hydride (**2**). Within this survey, indanol **57** could be prepared from aryl bromide **58**. As a part of the work-up procedure, the dioxolone moiety of tin bromide **59** was hydrolyzed under mild alkaline (or alternatively acidic) conditions to give the corresponding α -hydroxycarboxylic acid **60**, which was easily separated by alkaline extraction.

2.6 Tin Hydrides for Stereoselective Reactions

Although the main strategies to achieve stereocontrol in radical reactions are based on chiral information from the substrates,¹⁰⁹ there have also been a few attempts to reach this goal by employing chiral reagents. As far as tin hydride chemistry is concerned, the preparation and use of chiral organostannanes was first reported by Curran¹¹⁰ and Metzger.¹¹¹ Concerning their chemical structures, these early reagents were characterized by a divalent binaphthyl backbone and a more or less demanding third alkyl substituent on the tin atom. Shortly after, a chiral tin hydride with a benzylamine substructure was introduced, which is closely comparable to the reagent shown in Scheme 15.¹¹² In a third group of tin hydrides discovered by Schiesser, chirality was created by attaching up to three menthyl groups to the tin center.^{113,114} With these reagents, only moderate yields and enantiomeric excess values

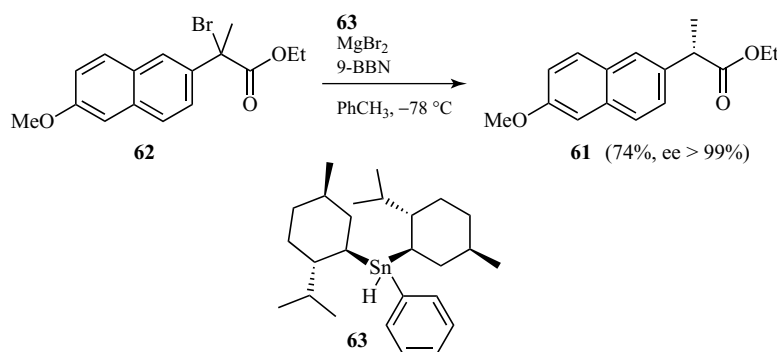


Scheme 16 Radical cyclization mediated by tin hydride **56**.¹⁰⁸

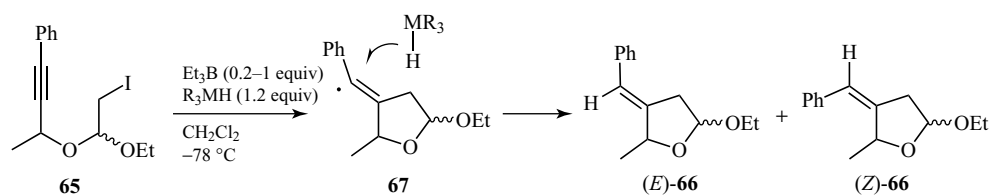
were however at first obtained from reduction of model substrates including α -halogenated esters or ketones. While the performance of the chiral organostannanes of the binaphthyl type could later be improved by a careful optimization of the reaction conditions,¹¹⁵ a major advance was made by combining the menthyl-derived reagents with Lewis acids.¹¹⁶ An example featuring the synthesis of (*S*)-naproxene (**61**) by reduction of bromide **62** with the chiral tin hydride **63** in the presence of magnesium bromide is depicted in Scheme 17. The first application of Lewis acids as additives in tin hydride-mediated radical reactions had earlier been described by Hoshino.¹¹⁷

Moreover, chiral oxazoline-based dialkyltin hydrides have been briefly studied in free-radical addition and cyclization reactions.¹¹⁸ A review

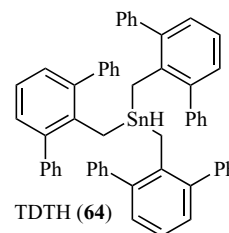
article on asymmetric free-radical reductions mediated by chiral stannanes, germanes, and silanes has recently been prepared by Schiesser.¹¹⁹ Comparable to the chiral tin hydrides mentioned above, which preferentially deliver the hydrogen atom to one or the other enantiotopic side of a planar trivalent carbon-centered radical, sterically more demanding tin hydrides can be used to achieve selectivity in the reduction of vinyl radicals. An increase in regioselectivity had already been observed in several reactions in which tributyltin hydride had been replaced by the more bulky tris(trimethylsilyl)silane (see **Silanes as Reducing Reagents in Radical Chemistry**).^{120,121} A far greater effect was achieved by Maruoka¹²² when he employed the bowl-shaped tin hydride TDTH [tris(2,6-diphenylbenzyl)tin hydride] (**64**)



Scheme 17 Synthesis of (*S*)-naproxene (**61**) by radical reduction with chiral trialkyltin hydride **63** in the presence of the Lewis acid magnesium bromide.¹¹⁶



	Molar ratio of Et ₃ B: 65	Reducing agent R ₃ MH	Yield 66 (%)	E/Z
1	0.2	Bu ₃ SnH	92	1:3.1
2	0.2	Ph ₃ SnH	98	1:4.3
3	1.0	(Me ₃ Si) ₃ SiH	76	1:6.7
4	1.0	TDTH	76	1:65.8



Scheme 18 Stereoselective hydrogen transfer from the bowl-shaped tin hydride **64**.¹²²

as reducing agent (Scheme 18). While the radical cyclization of iodide **65** led to a mixture of stereoisomers (*E*)- and (*Z*)-**66** when common hydrogen donors were employed (see table in Scheme 18, entries 1–3), reagent **64** reacted far more selectively (entry 4). As a matter of fact, delivery of hydrogen to the intermediate vinyl radical **67** has been achieved with far higher preference from the less hindered face.

3 FUNCTIONAL GROUP TRANSFORMATIONS

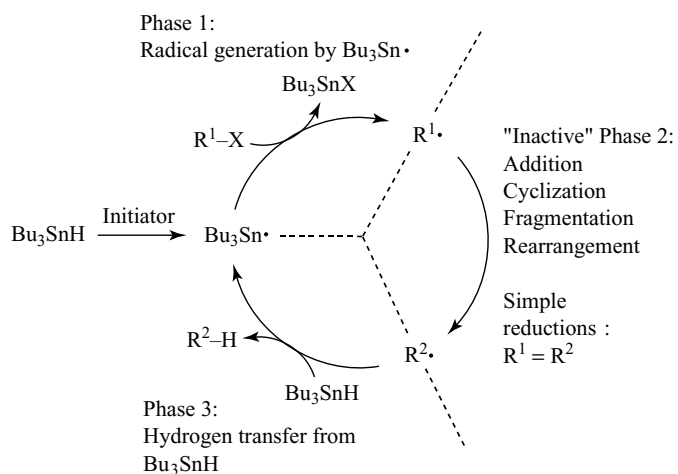
3.1 Reaction Types and Principles

Most radical reactions in which organostannanes are involved can be easily understood by a closer look at three basic steps. Exemplified for tributyltin hydride, the general chain process is shown in Scheme 19.

First arising from the initiation reaction, the tributylstannyl radical $\text{Bu}_3\text{Sn}^\bullet$ generates radicals $\text{R}^1\cdot$ by transfer of an atom or group X, or alternatively by addition of $\text{Bu}_3\text{Sn}^\bullet$ to suitable functional groups such as alkynes. The large variety of atoms and functional groups that are susceptible to organotin radicals according to phase 1 of the cycle will be presented in Section 3.3. In this context, it is important to mention that $\text{R}^1\cdot$ does not necessarily have to be a carbon-centered radical.

Once radical $\text{R}^1\cdot$ has been formed, the mechanism enters phase 2, in which the tin reagent is usually inactive. As will be shown with illustrative examples, manifold reactions have so far been developed using radicals generated by tin reagents. The main reaction types of phase 2 are intermolecular addition reactions of $\text{R}^1\cdot$ to the radical acceptors, intramolecular additions or cyclizations, rearrangements of $\text{R}^1\cdot$, and fragmentation reactions. From the modification of $\text{R}^1\cdot$ in phase 2, a new radical $\text{R}^2\cdot$ is formed, which can again be carbon- or heteroatom-centered. Only for simple reductions, which may occasionally also be desired, no reaction of radical $\text{R}^1\cdot$ should occur. The requirement that the tin hydride has to stay “inactive” to allow further conversion of $\text{R}^1\cdot$ by the above-named reaction types or combinations thereof is often only fulfilled by well-defined reaction conditions, since most organostannanes are potent hydrogen-atom donors which may as well reduce the radical $\text{R}^1\cdot$ directly.

The hydrogen-donor abilities of tin hydrides are the key properties for a successful passage through phase 3. At this point of the reaction mechanism, a hydrogen atom has to be transferred from the organostannane to radical $\text{R}^2\cdot$, which in turn furnishes the final product $\text{R}^2\text{-H}$ as well as a new “chain-carrying” or propagating tin-centered radical ($\text{Bu}_3\text{Sn}^\bullet$). More details on the hydrogen transfer are presented in Section 3.2.



Scheme 19 Three phases of tin hydride-mediated radical reactions.

Table 1 Rate constants for the reductions of different types of carbon- and heteroatom-centered radicals by tributyltin hydride and tris(trimethylsilyl)silane.¹²³

Radical	k_{SnH}	k_{SiH}
$t\text{-BuO}^\bullet$	2.0×10^8	1.1×10^8
$\text{RCH}_2^\bullet$	2.4×10^6	3.8×10^5
$\text{R}_2\text{CH}^\bullet$	1.5×10^6	1.4×10^5
$\text{R}_3\text{C}^\bullet$	1.9×10^6	2.6×10^5
$\text{Ph}^\bullet$	7.8×10^8	3.0×10^8
$n\text{-C}_8\text{F}_{17}^\bullet$	2.0×10^8	5.1×10^7
$\text{RC}(\text{O})^\bullet$	4.5×10^5	1.8×10^4

R, alkyl.

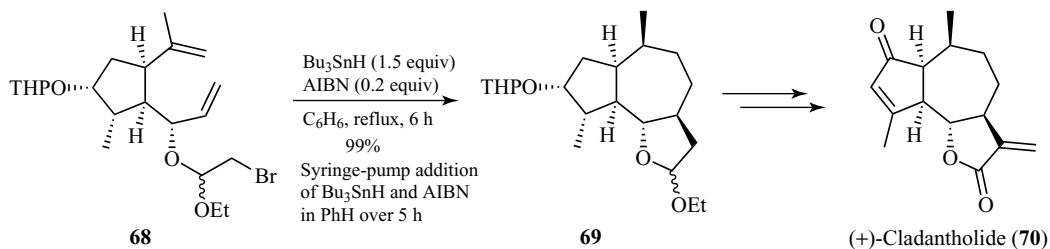
3.2 Hydrogen-Donor Abilities

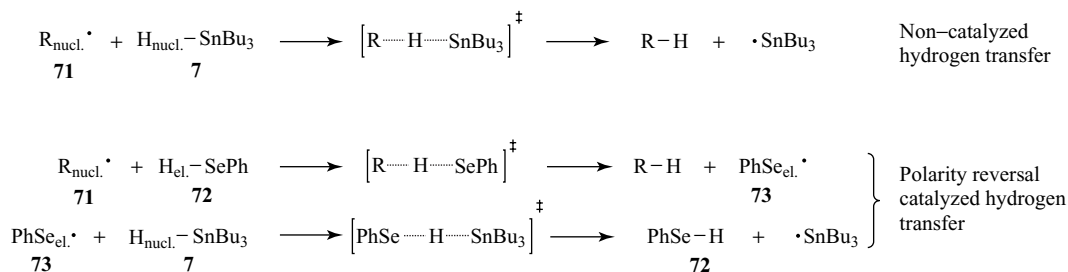
Including such simple molecules as isopropanol as well as structurally complex substances such as vitamin E, a wide range of compounds are known to act as hydrogen donors in radical reactions. Among all commonly used reagents, tin hydrides still show comparably good properties with respect to the rate of hydrogen transfer to a wide range of carbon- and heteroatom-centered radicals (Table 1).¹²³ Not surprisingly, there are continuing efforts to develop competitive replacements that are both cheap and effective. Probably, the most prominent substitute for tributyltin hydride known today is tris(trimethylsilyl)silane (**Silanes as Reducing Reagents in Radical Chemistry**).^{120,121} Recent developments have also focused on NHC-boranes (see **Boron in Radical Chemistry**) and the reagents for the activation of water (**Epoxides in Titanocene-Mediated and -Catalyzed Radical Reactions**).

Although high rate constants for the hydrogen-transfer step from tributyltin hydride to a designated target radical $\text{R}^{2\bullet}$ may appear advantageous at first sight (Scheme 19) because undesired side-reactions of $\text{R}^{2\bullet}$ prior to phase 3

can be minimized, this property sometimes also turns out to be problematic. This is especially true for those cases in which the addition, cyclization, fragmentation, or rearrangement step in phase 2 is not particularly fast, so that the hydrogen transfer from Bu_3SnH to radical $\text{R}^{1\bullet}$ becomes a competing process to the envisaged pathway. When facing this type of complication, one countermeasure certainly is to structurally modify the participating reactants. For example, for intramolecular radical additions to alkenes, a different type of alkene may be chosen to speed up the addition step. This approach, however, is often time consuming since a number of additional reactions may be needed to get back to the originally planned synthetic route. Far easier, if applicable, is the alternative strategy to decrease the overall reducing abilities of the tin hydride by lowering its concentration. For this purpose, the tin hydride is often added to the reaction mixture slowly by a syringe pump, together with the radical initiator. An impressive example showing the positive effects of a controlled addition of the tin hydride is the cyclization of bromide **68** to the tricyclic compound **69**, which has been part of the total synthesis of the natural product (+)-cladantholide (**70**) (Scheme 20).¹²⁴ Although two primary alkyl radicals occur on the way from **68** to **69**, no remarkable reduction of those intermediates was observed, indicating that the concentration of Bu_3SnH had been sufficiently reduced.

On the other hand, also higher rates of hydrogen transfer than those reported in Table 1 can be required for some reactions. For radicals $\text{R}^{1\bullet}$ arising from phase 1 (Scheme 19), for example, which show a strong but undesirable tendency to fragment or rearrange, a very rapid reduction by the tin hydride is needed to keep the molecular structure unchanged. The goal to formally further increase

**Scheme 20** Key step in the total synthesis of (+)-cladantholide (**70**).¹²⁴



Scheme 21 Polarity-reversal catalysis by benzeneselenol (**72**) in tin hydride-mediated reductions of nucleophilic alkyl radicals.^{126,127}

the hydrogen-transfer abilities of tin hydrides can be nicely achieved by applying the principle of polarity-reversal catalysis.¹²⁵

In reactions featuring this type of catalysis, one slow polarity-mismatched step is usually replaced by two more rapid but polarity-matched steps. For the hydrogen transfer from hydric stannane **7** to nucleophilic alkyl radicals **71**, which is a polarity-mismatched reaction, Crich has found benzeneselenol (**72**) to be a well-suited additive (Scheme 21).^{126,127} Regarding the catalyzed process, the nucleophilic alkyl radical is now first reduced by the acidic (electrophilic) benzeneselenol (**72**) to give an electrophilic selenyl radical **73**, which is converted back to **72** by hydrogen transfer from the nucleophilic tributyltin hydride **7**. In this way, the reaction passes through two polarity-matched steps.

The concept of polarity-reversal catalysis can easily be understood by the polar effects shown above.^{125,127} An alternative explanation has been proposed by Zavitsas and Chatgililoglu based on repulsion energies at the transition state.^{128,129} Other examples for polarity-reversal catalysis include hydrogen-transfer reactions from silanes and germanes, which can be catalyzed by thiols.¹²⁷ An approximate idea of the increase in reaction rate can be derived from a closer inspection of Table 2.

Table 2 Reaction rates for the hydrogen transfer to primary alkyl radicals from tributyltin hydride,¹³⁰ benzeneselenol,¹³¹ thiophenol,¹³² and tributylgermanium hydride.¹³³

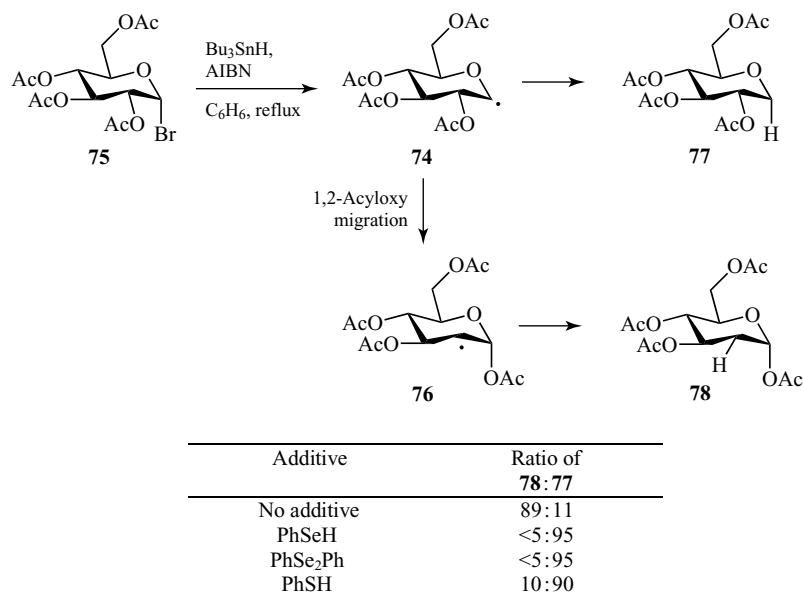
Reductant	<i>k</i> (s ⁻¹) at 25 °C
Bu ₃ SnH (7)	2.4 × 10 ⁶
PhSeH (72)	1.2 × 10 ⁹
PhSH	1.4 × 10 ⁸
Bu ₃ GeH	1.0 × 10 ⁵

From the fact that primary (nucleophilic) alkyl radicals are reduced 500 times faster by benzeneselenol than by tributyltin hydride, an increase in reaction rate by the factor of 25 can be expected from the use of only 5 mol% of benzeneselenol. Selected results from a study on the inhibition of the acyloxy migration (**Radical Rearrangements: Ester-Substituted Radicals and Hydrogen Atom Migrations**) by an accelerated hydrogen to radical **74** are shown in Scheme 22.¹²⁶

Starting from bromide **75**, the rearrangement of **74** to give **76** could not be avoided under the standard tributyltin hydride conditions. By the addition of benzeneselenol, diphenyl diselenide, or thiophenol, in contrast, a faster hydrogen transfer to radical **74** was achieved and thus far larger amounts of the non-rearranged product **78** were obtained as compared to **77**. A review on the catalysis of stannane-mediated radical chain reactions by benzeneselenol, which contains many more interesting examples, was published by Crich.¹²⁷

3.3 Functional Groups Sensitive Toward Organotin Radicals

The aim of this section is to give an overview of those functional groups that are sensitive to organotin hydrides in the sense that carbon- or heteroatom-centered radicals are generated by an attack of the organostannyl radical on the respective group.¹³⁴ The following examples have been chosen to give a more detailed insight into how phase 1 of the general mechanism (Scheme 19) can look like. Radical generation by organostannanes from suitable functional groups has by now been combined with a tremendous number of follow-up processes or applications in phase 2, which cannot comprehensively be presented in

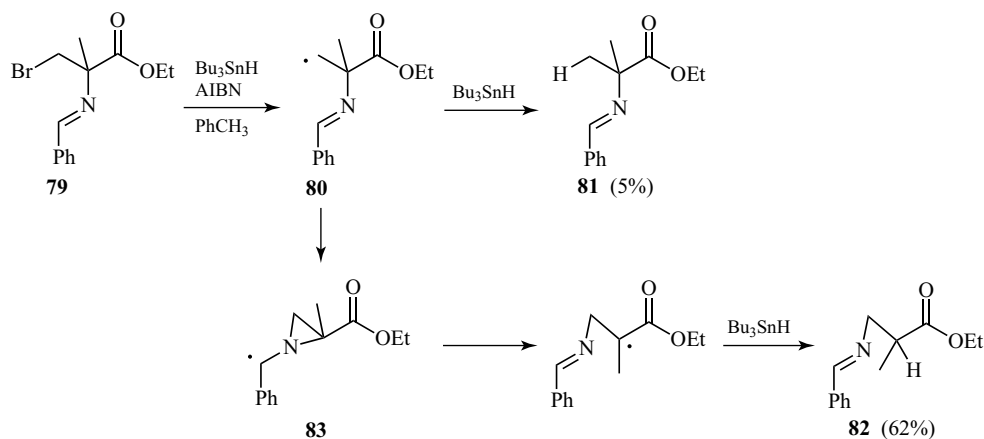


Scheme 22 Acyloxy migration depending on the rate of hydrogen transfer.¹²⁶

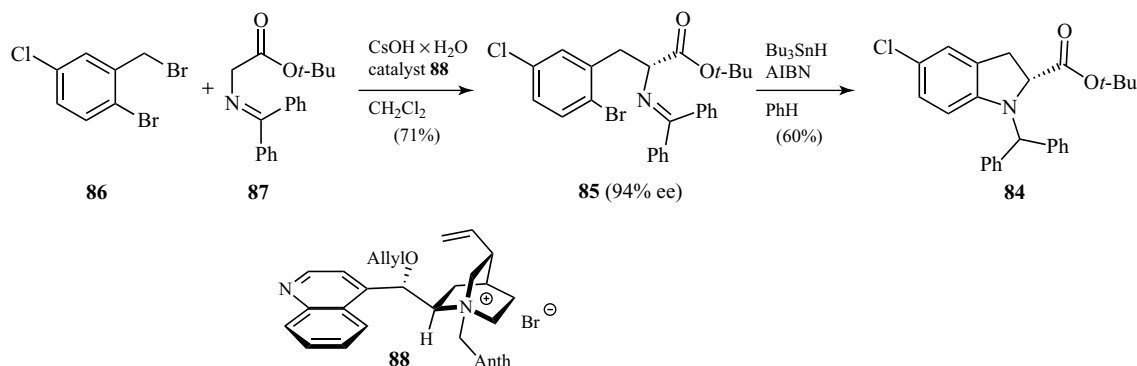
this article. Nevertheless, to give an idea about the vast possibilities, we have tried to include examples showing very different subtypes of the above-mentioned five general reaction modes of reduction, cyclization, intermolecular addition, rearrangement and fragmentation. More information on which reactions are feasible in phase 2 can be found in other articles of this encyclopedia. Functional group transformations achieved by ionic reactions of tin hydrides have been reviewed by Shibata and Baba.¹³⁵

3.3.1 Radical Generation from Carbon–Halogen Bonds

Carbon-centered radicals are readily generated from many types of iodides and bromides. Owing to the relative ease of their preparation, this group of starting materials has emerged as the most popular in reactions with organostannanes. The earliest example described by van der Kerk has been shown in the introductory section (Scheme 1).¹



Scheme 23 Radical generation from alkyl bromide **79** leading into a 1,2-imino rearrangement.¹³⁶

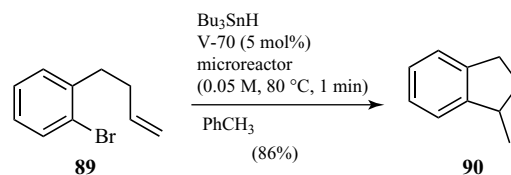


Scheme 24 Radical generation from aryl bromide **85** as part of the synthesis of indoline **84**.¹³⁷

More recently, the treatment of alkyl bromide **79** with tributyltin hydride and AIBN led to the formation of the primary alkyl radical **80**, of which only a small part was directly reduced to **81** (Scheme 23).¹³⁶ On the major reaction pathway, **80** rearranged via cyclization to the benzylic aziridine **83**. Subsequent ring-opening and final reduction by Bu_3SnH gave **82**. Despite the ring strain, the formation of aziridine **83** can be explained by the stabilizing benzylic nature of radical **83** as well as the Thorpe–Ingold effect induced by the quaternary carbon center in **80**. This reaction also represents a first chemical example for a radical 1,2-imino rearrangement and it has been proposed as chemical model for an aminomutase.

As part of a new enantioselective approach to indoline **84**, aryl radicals have been generated from aryl bromide **85** by tributyltin hydride (Scheme 24).¹³⁷ The synthesis of **85**, which was required as starting material, was achieved by phase-transfer-catalyzed alkylation of 2-bromobenzyl bromide **86** with glycine imine **87** in the presence of the cinchonidinium salt **88**. The reaction further demonstrates that aryl chlorides are usually stable under standard radical tributyltin hydride reaction conditions.

In a recent study, the use of microreactors (see **Radical Chemistry by Using Flow Microreactor Technology**) has led to significantly accelerated reactions of tributyltin hydride and tris(trimethylsilyl)silane (Scheme 25).¹³⁸ When conducted in a continuous flow system, the cyclization of bromide **89** to indane **90** was completed in less than 1 minute, demonstrating that tributyltin



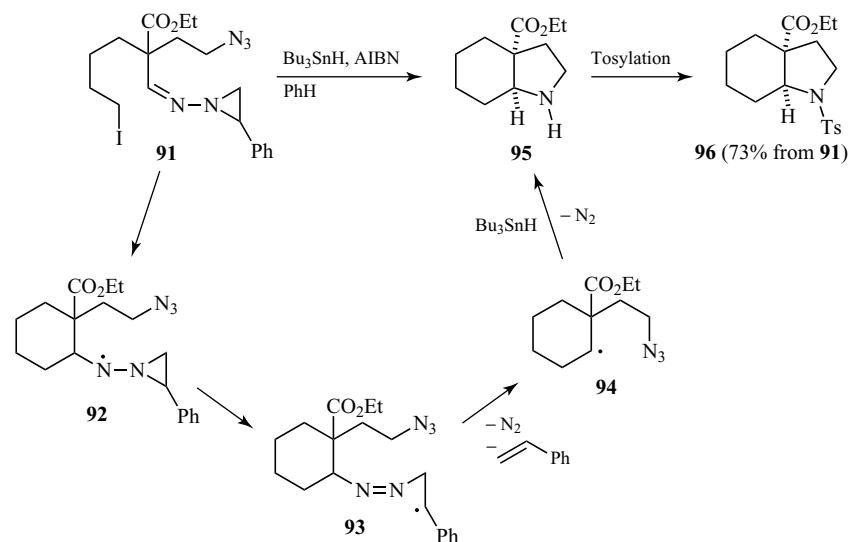
Scheme 25 Tributyltin hydride-mediated radical generation and cyclization in a microreactor.¹³⁸

hydrides are well compatible with this new technology.

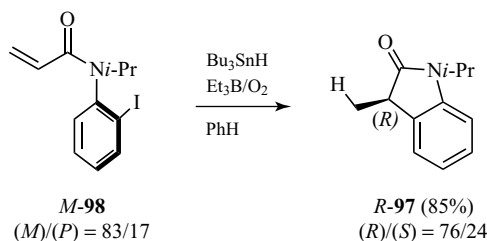
The ability of tributyltin hydride and AIBN to selectively generate radicals from more complex reactants became obvious from the tandem reaction starting from alkyl iodide **91** (Scheme 26).¹³⁹ Via cyclization of the alkyl radical onto the aziridinyl imine moiety and a unique fragmentation mechanism including the intermediates **92** and **93**, cyclohexyl radical **94** was formed. Subsequent intramolecular radical addition to the azido group (**Unusual Radical Acceptors**) was followed by a loss of nitrogen and a reduction of the aminyl radical to a secondary amine **95**. For the purpose of isolation, the amine was converted to sulfonamide **96**.

The versatile concept of tin hydride-mediated aryl radical generation from aryl iodides was used for a transfer of axial chirality to centrochirality by a 5-exo-type cyclization. In one of the reactions reported by Curran (Scheme 27), indolone **97** was obtained from acrylanilide **98** in high yield and with a high degree of chirality transfer.^{140,141}

Very recent applications of aryl iodides as radical precursors include syntheses of penitremes¹⁴² and of natural products such as acutumine.^{143,144} While in



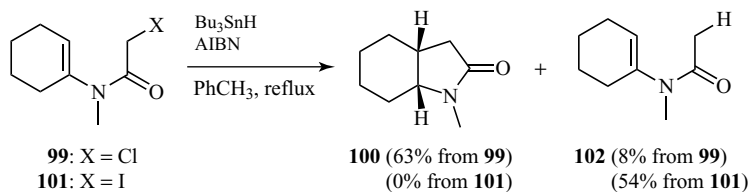
Scheme 26 Radical generation from alkyl iodide **91** combined with intramolecular cyclizations onto imine and azide moieties.¹³⁹



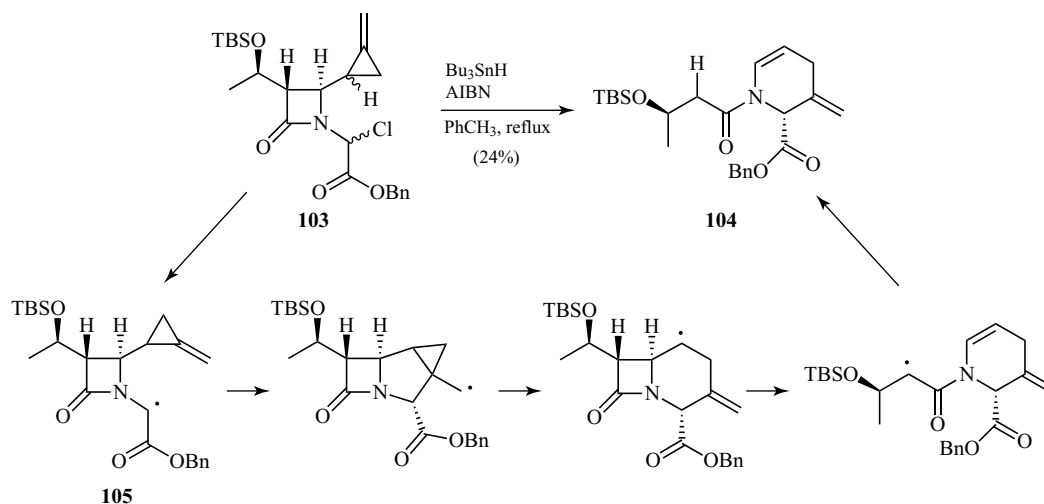
Scheme 27 Aryl radical generation from aryl iodides for the purpose of chirality transfer.^{140,141}

the case of bromides or iodides the generation of carbon-centered radicals is practically independent of the nature of the carbon atom, remarkable differences are observed when organochlorides are employed as the radical sources. A pioneering study in this field that already gave evidence for these effects was reported by Kuivila *et al.*¹⁴⁵

From activated positions, such as polychlorinated carbon atoms, α -positions of esters and ketones, captodatively substituted carbon atoms, or benzylic positions, the chlorine atom transfer to the organostannyl radical still proceeds sufficiently fast. Acyl radicals can be generated from acid chlorides, but this is done preferably in the presence of samarium reagents (see **Organic Synthesis Using Samarium Diiodide**).¹⁴⁶ Non-activated alkyl chlorides usually react slowly, whereas aryl and vinyl chlorides tend to be stable under common reaction conditions. An example featuring the Bu_3SnH -mediated 5-endo radical cyclization of α -halogenated amides is shown in Scheme 28.¹⁴⁷ In this special case, the cyclization of α -chloro amide **99** to the bicyclic amide **100** proceeded significantly smoother than that of the corresponding α -iodo derivative **101**, which mainly led to the non-cyclized but reduced product **102**. A more detailed investigation revealed that this effect is probably due



Scheme 28 Comparative study on the cyclization of radicals generated from α -haloamides **99** and **101**.¹⁴⁷

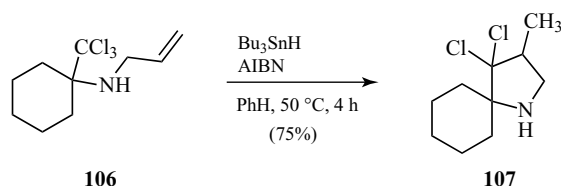


Scheme 29 Reaction cascade leading from chloride **103** to the unsaturated piperidine **104**.¹⁴⁹

to differences between the initial conformations of the α -halo amides **99** and **101** and the respective radicals. The ability of the α -iodo derivative **101** to undergo the cyclization could finally be restored by adding Bu_3SnCl or Bu_3SnF to the reaction mixture. A recent study on comparable cyclizations of α -halo amides has been reported by Curran.¹⁴⁸

An interesting transformation of azetidinone **103** was observed when the compound was treated with tributyltin hydride and AIBN (Scheme 29).¹⁴⁹ Owing to the fact that a comparatively well-stabilized carbon-centered radical **105** occurs as first intermediate opens up the option to use an α -chloro glycine derivative as precursor. Via one cyclization and two ring-opening steps, radical **105** was subsequently converted to a structurally unique piperidine **104**. The yield of product **104** has most probably to be attributed to its relatively low stability under the reaction conditions applied.

An overview over radical cyclization reactions that contains many more examples on related tinhydride-mediated processes has been reported by Giese.¹⁵⁰ Tin hydride-mediated reactions of polychlorinated substrates in which radicals are selectively generated by the abstraction of chlorine atoms located in activated positions have already been developed.¹⁵¹ From trichloromethane groups, the first chlorine atom is far more easily removed by the tributyltin radical than the remaining halogen substituents. An example taking advantage of this effect is shown in Scheme 30.^{152,153}



Scheme 30 Cyclization of **106** via radical generation from a trichloromethyl group.¹⁵²

Under standard tributyltin hydride conditions, the trichloromethyl-substituted cyclohexylamine **106** was converted to the spirocyclic product **107**. For a complete dehalogenation of dichloromethylene units, such as the one present in **107**, reaction times have to be prolonged and excess tributyltin hydride has to be applied.

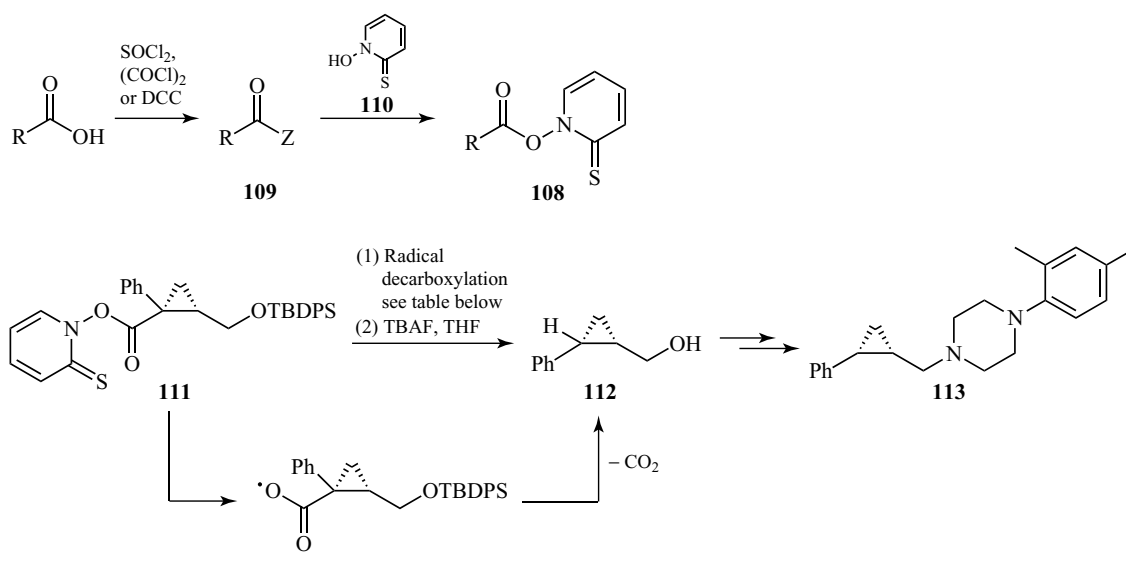
The ability of Bu_3SnH to differentiate between aryl chlorides and bromides has previously been shown in Scheme 24. Given that the halogen atoms are located at a comparably activated carbon atom, the overall rate for an abstraction by tributyltin hydride decreases in the order iodides > bromides > chlorides. The gap arising from the inability of tin hydrides to generate aryl radicals from aryl chlorides can be closed by employing a common substitute for Bu_3SnH , that is, tris(trimethylsilyl)silane.^{120,121} Under very high pressures, reductions of organic chlorides by tributyltin hydride even proceed in the absence of radical initiators.¹⁵⁴

3.3.2 Radical Generation from Carbon–Carbon Bonds: Radical Decarboxylations

A suitable strategy to achieve the cleavage of terminal alkyl carbon–carbon bonds is radical decarboxylation reactions. For the generation of the usually short-lived carboxyl radicals, which readily fragment carbon dioxide, *O*-acyl-thiohydroxamates (Barton esters, Pyridine-2-thione-*N*-oxycarbonyl (PTOC) esters) have emerged as well-known precursors over the last decades. The first report on this compound class by Barton dates back to 1983.¹⁵⁵ Barton esters **108** usually decompose via the homolytic cleavage of the nitrogen–oxygen bond in the hydroxamate, which can be induced by irradiation, by heating, or by application of standard radical initiators (Scheme 31). In the presence of reducing agents such as organotin

hydrides, a hydrogen atom is then transferred to the carbon (or heteroatom) centered radical arising from the decarboxylation step.^{156–161} The most common method for the preparation of Barton esters with the general structure **108** relies on the coupling of activated carboxylic acids **109** to *N*-hydroxy thiopyridone **110**.¹⁶² Below, a recent example is depicted, in which Barton esters **111** were reductively decarboxylated under various conditions to give *cis*-substituted cyclopropanes **112**.^{163,164} The final products **113** of the synthetic study were designed as conformationally restricted analogs of the antipsychotic haloperidol.

By employing Barton esters in combination with different types of radical scavengers, a large variety of functional group transformations can be achieved, which is by far not limited to simple reductive decarboxylations. An informative recent review on this topic has been provided by de Almeida.¹⁶²



Reductant	Initiator	Solvent	Temperature (°C)	Yield 112 (%)	<i>cis/trans</i> 112
Bu ₃ SnH	Et ₃ B	THF	rt	70	2.8/1
Bu ₃ SnH	<i>hν</i>	THF	rt	36	2.6/1
Bu ₃ SnH	AIBN	PhH	80	80	2.7/1
<i>t</i> -BuSH	Et ₃ B	THF	rt	80	3.0/1
(Me ₃ Si) ₃ SiH	Et ₃ B	THF	rt	74	10/1

Scheme 31 Preparation of Barton esters **108** and reductive decarboxylation of cyclopropane **111** as key step in the synthesis of new antipsychotics.^{163,164}

3.3.3 Radical Generation from Carbon–Nitrogen Bonds

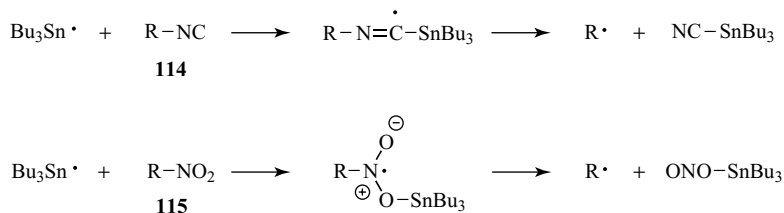
For the generation of carbon-centered radicals by an organostannyl-induced cleavage of carbon–nitrogen bonds, two functional groups have been found particularly useful (Scheme 32). The first report on the tributyltin hydride-mediated reduction of isocyanides (see **Unusual Radical Acceptors**) appeared in 1968.¹⁶⁵ The behavior of nitro groups under comparable conditions was first investigated by Ono and reported in 1981.¹⁶⁶ Both reaction types can be rationalized by an addition of the organostannyl radical onto the isonitrile **114** or nitro group **115** and a subsequent carbon–nitrogen bond cleavage leading to the desired carbon-centered radical.

The methodology involving isonitriles has so far successfully been used for the reductive deamination of steroids, carbohydrate derivatives, and amino acids.^{167–169} While all types of aliphatic isonitriles are cleanly reduced, aromatic derivatives tend to be stable. An impressive example in which the selective removal of one out of four amino groups was achieved from a disaccharide is depicted in Scheme 33.¹⁶⁹ The differentiation among the amino groups was possible due a selective conversion of a tetraformamide to (mono-)isonitrile **116**, which gave **117** upon treatment with tributyltin hydride and AIBN.

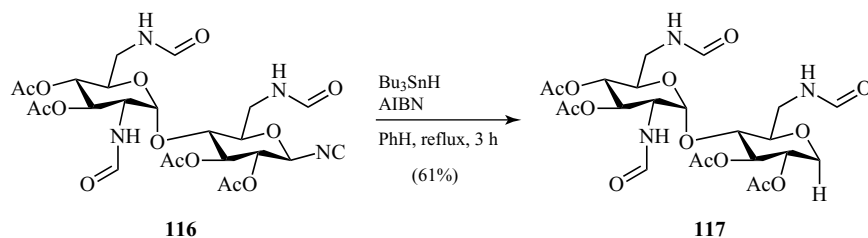
Tin hydride-mediated formation of carbon-centered radicals from organic nitro compounds is slightly more limited in its scope than the isonitrile methodology presented earlier. Nitro groups are usually only then smoothly transferred to organotin radicals when tertiary or better stabilized carbon-centered radicals arise from this step.^{170,171} In a preparative study, tin hydride-mediated radical denitration has been employed as part of a sequence leading from [2 + 3] cycloadducts **118** of nitroalkenes **119** and camphor-derived oxazoline-*N*-oxides **120** to denitrated tetracycles **121** and aldol-type products **122** (Scheme 34).¹⁷²

The denitration methodology has been further applied in the synthesis of kainic acid derivatives¹⁷³ as well as for the stereoselective preparation of *C*-glycosides taking advantage of the anomeric effect.¹⁷⁴ A denitration procedure catalytic in tin hydride, employing phenylsilane as regenerating agent, was reported by Fu.¹⁷⁵

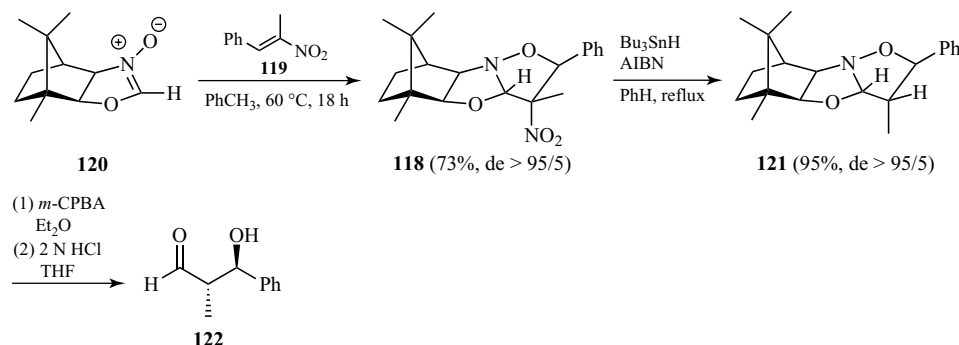
The generation of secondary carbon-centered radicals already requires harsher conditions, and primary alkyl radicals have so far not been accessible from nitro compounds by using tin hydride reagents.^{176–178} When applied to the reduction of aromatic nitro compounds, organostannanes usually lead to the undesired formation of anilines.^{40,166} Nevertheless, to achieve the cleavage of carbon–nitrogen bonds in which the carbon atom is



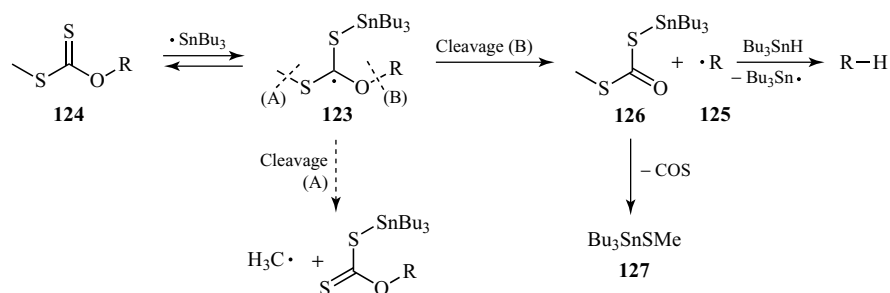
Scheme 32 Tin radical-mediated cleavage of carbon–nitrogen bonds from isonitriles **114** and nitro compounds **115**.^{165,166}



Scheme 33 Radical deamination of disaccharide **116** by tin hydride-mediated cleavage of an isonitrile.¹⁶⁹



Scheme 34 Radical denitration of the tetracyclic nitro compound **118**.¹⁷²



Scheme 35 Tributyltin hydride-mediated Barton–McCombie deoxygenation of xanthate **124**.

part of an aromatic system, arenediazonium salts have been found as suitable precursors in combination with tin hydrides.¹⁷⁹ A review on the reductive cleavage of aliphatic nitro groups, which also includes many examples from ionic chemistry, was published by Ono.¹⁸⁰

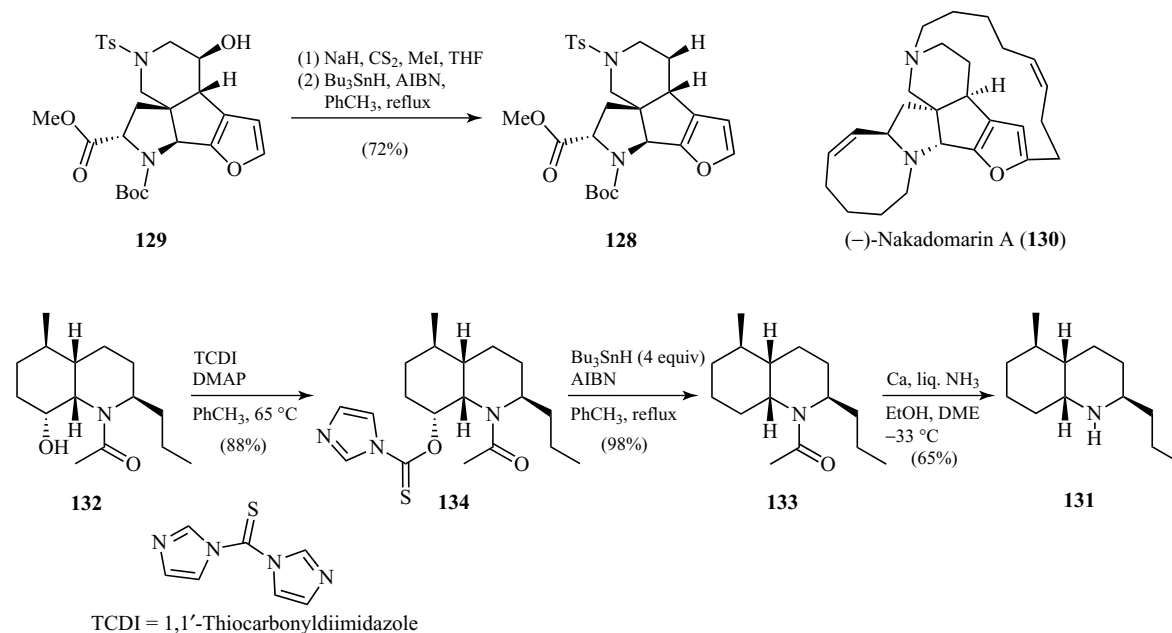
3.3.4 Radical Generation from Carbon–Oxygen Bonds

As mentioned in the introduction, the development of Barton–McCombie deoxygenation reactions in the 1970s represented a major advance not only in radical chemistry but in the whole field of organic chemistry (Scheme 2).² For the first time, carbon–oxygen bonds could be cleaved under comparably mild conditions, and carbon-centered radicals were available from alcohols by the simple strategy of converting them to xanthates (or dithiocarbonates).^{159,181} Exemplified for the tributyltin radical, the underlying mechanistic principle of the deoxygenation protocol is shown in Scheme 35.^{182,183} In the first step, adduct **123** is

reversibly formed from the addition of a stannyl radical to xanthate **124**. Taking advantage of the fact that the undesired carbon–sulfur bond cleavage is slow due to the reactivity of the methyl radical potentially arising from this process (A), the overall reaction pathway can be directed towards the scission of the carbon–oxygen bond (B). In its simplest version, the carbon-centered radical **125** is then reduced by hydrogen transfer from tributyltin hydride, while the stannyl dithiocarbonate **126** further decomposes to carbon oxysulfide and the stannyl thioether **127**.

Owing to the structure of the xanthate and the reaction conditions that were applied, the early deoxygenation protocols gave the best results for secondary alcohols. The xanthates of tertiary alcohols, which are likely to decompose through the Chugaev elimination, were later deoxygenized under milder conditions, preferably at lower temperatures.¹⁸⁴

In the case of xanthates derived from primary alcohols, the selectivity in the fragmentation step (**123** → **125/126**) is no longer well defined since primary carbon-centered radicals are



Scheme 36 Barton–McCombie deoxygenations in synthetic studies toward (–)-nakadomarin A (**130**)¹⁸⁹ and pumiliotoxin C.¹⁹⁰

formed from both types of bond cleavage A and B (Scheme 35). To circumvent this problem, modified thiocarbonyl compounds have been developed, such as thiocarbonyl imidazolides^{159,185} and *O*-aryldithiocarbonates,^{186–188} which show a far more distinct preference towards the cleavage of the carbon–oxygen bond once they have been converted to adducts of type **123**.

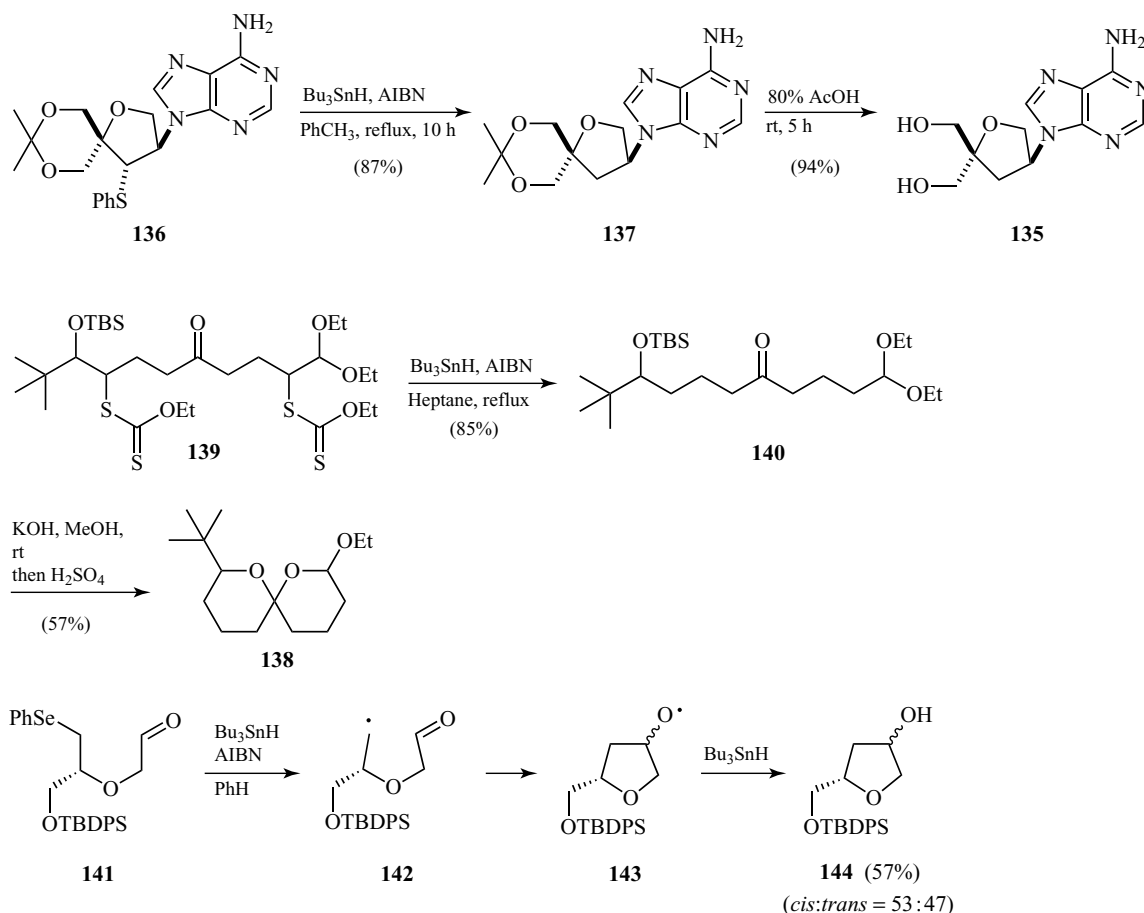
Two recent examples from the field of natural product synthesis are shown in Scheme 36. The tetracyclic core of *ent*-nakadomarin A **128** was prepared according to the classical Barton–McCombie protocol, in which tributyltin hydride was used to reduce a xanthate previously obtained from a secondary alcohol **129** upon treatment with sodium hydride, carbon disulfide and methyl iodide.¹⁸⁹ The manzamine-related marine alkaloid (–)-nakadomarin A (**130**) represents an interesting target because of its cytotoxic and antimicrobial activity.

The efficacy of a new cycloaddition approach to pumiliotoxin alkaloids **131** was demonstrated by Fearnley.¹⁹⁰ In the final steps of the synthesis, alcohol **132** was cleanly converted to target compound **133** by a modified Barton–McCombie procedure using the imidazolyl-thiocarbonyl derivative **134**. Further examples for the application of tin

hydride-mediated radical deoxygenation reactions that have recently appeared in literature include the syntheses of calystegine A3,¹⁹¹ (*S*)-dapoxetine,¹⁹² and (+)-makassaric acid.¹⁹³

3.3.5 Radical Generation from Carbon–Sulfur and Carbon–Selenium Bonds

The most commonly used functional groups for the generation of radicals by homolytic cleavage of carbon–sulfur or carbon–selenium bonds are thio- and selenoethers as well as xanthates. Already in early studies, the phenylsulfides,^{194,195} xanthates (see **Xanthates and Related Derivatives as Radical Precursors**),¹⁹⁶ and phenylselenides^{197,198} were not just reduced by hydrogen transfer in the presence of tin hydrides but also employed for carbon–carbon formations. More recently, thioethers appeared as intermediates in organotin hydride-catalyzed radical desulfurizations of thionoesters and thionolactones¹⁹⁹ as well as in syntheses of carbohydrates.²⁰⁰ As part of the preparation of isoadenosine **135**, thioether **136** was cleanly reduced by tributyltin hydride to give **137** (Scheme 37).²⁰¹



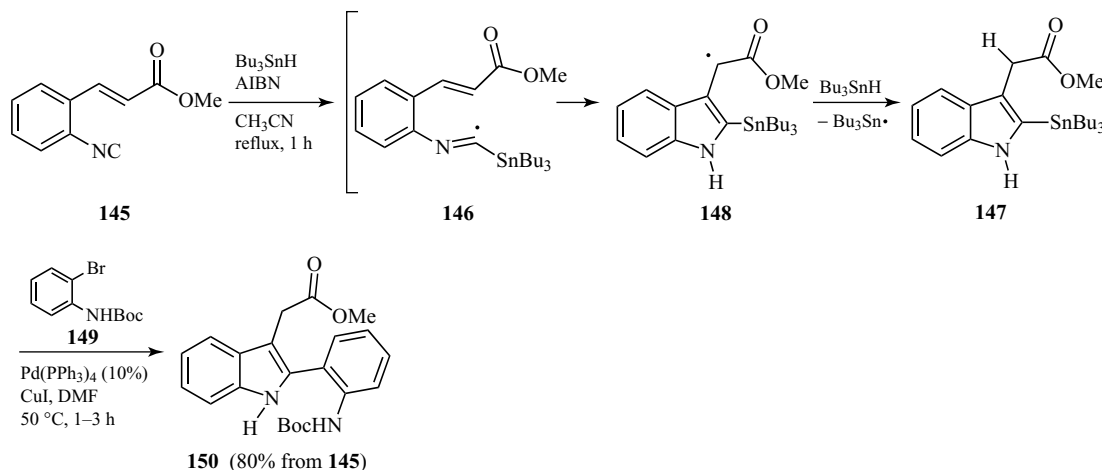
Scheme 37 Radical generation from thioether **136**,²⁰¹ bis-xanthate **139**,²⁰² and selenoether **141**.²⁰³

Further demonstrating the vast possibilities of radical xanthate transfer chemistry, a new way of access to spiroketal **138** has been developed by Zard.²⁰² The reductive removal of two xanthate functionalities from **139** to give **140** was possible by either combining dilauroyl peroxide and isopropanol or tributyltin hydride and AIBN. A recent report on the use of phenyl selenides as radical sources focuses on the synthesis of tetrahydrofurans.²⁰³ Starting from selenoether **141**, the carbon-centered radical **142** arising from the selenophenyl group transfer was found to cyclize onto an aldehyde to give oxygen-centered radicals **143**, which were further reduced by Bu_3SnH to the final product **144**. Moreover, selenoesters have been shown to be convenient precursors for acyl radicals.²⁰⁴

3.3.6 Radical Generation by Addition of Tin Radicals to Unsaturated Systems

In contrast to the examples presented up to this point (Sections 3.3.1–3.3.5), in which the generation of radicals was achieved by atom or group transfer reactions to organostannyl radicals, carbon-centered radicals are also available from the addition of tin-centered radicals to unsaturated systems such as isonitriles, alkynes, and carbonyl compounds.

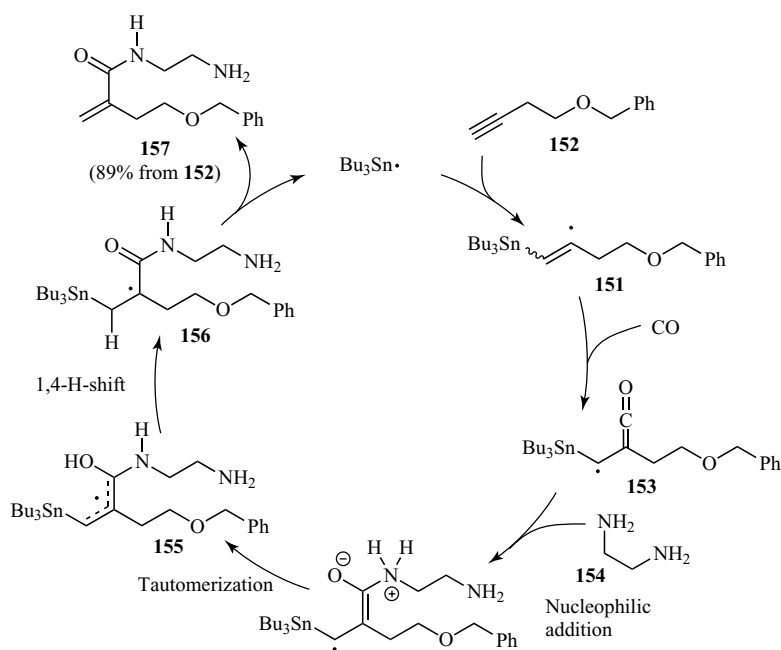
While aliphatic isonitriles are suitable precursors for tin-mediated radical deamination reactions (see Section 3.3.3), their aromatic counterparts do not decompose in the same way once they have formed an adduct with organostannyl radicals. Instead, the



Scheme 38 Indole synthesis proceeding via α -stannoimidoyl radical **146**.²⁰⁶

α -stannoimidoyl radical adducts can be used for cyclization reactions. Pioneering work in this field, in which the special feature of aromatic isonitriles was exploited for a novel synthetic access to indoles, has been presented by Fukuyama (**Unusual Radical Acceptors**).²⁰⁵ An example from a recent application of the methodology is depicted in

Scheme 38.²⁰⁶ Addition of a tributyltin radical to isonitrile **145** led to the α -stannoimidoyl radical **146**, which cyclized onto the proximate acrylate moiety. The stannylated indole **147** obtained from hydrogen transfer to **148** was further converted by Stille-type cross-coupling reaction with aryl iodide **149** to yield indole **150**.



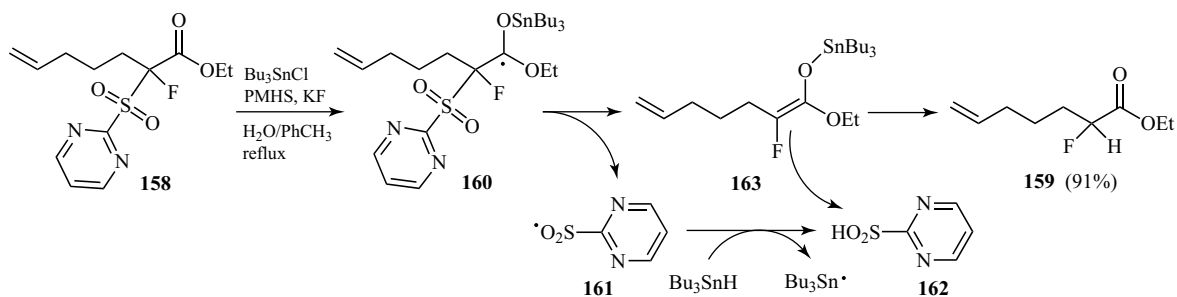
Scheme 39 Tin hydride-mediated synthesis of acrylamide **157** from alkyne **152**, carbon monoxide, and diamine **154**.²¹¹

Acetylenes are well-known acceptors for organostannyl radicals, and a large number of reactions has meanwhile been developed taking advantage of this efficient process. Hydrostannylations, which represent the simplest type of reactions exploiting this principle, can be conducted either in the form of radical^{7,207} or transition-metal-catalyzed processes.^{208–210} As shown in Scheme 39, the highly reactive vinyl radical **151** emerging from the addition of the tributylstannyl radical to alkyne **152** is able to react with carbon monoxide to give α -ketenyl radicals **153**.²¹¹ Trapping of **153** by amine **154** is followed by tautomerization to **155** and 1,4-*H* migration to produce α -keto radical **156**, which finally fragments to acrylamide **157**. Since the tributyltin radical is regenerated in the last step of the cycle, the reaction proceeds with substoichiometric amounts of the reagent.

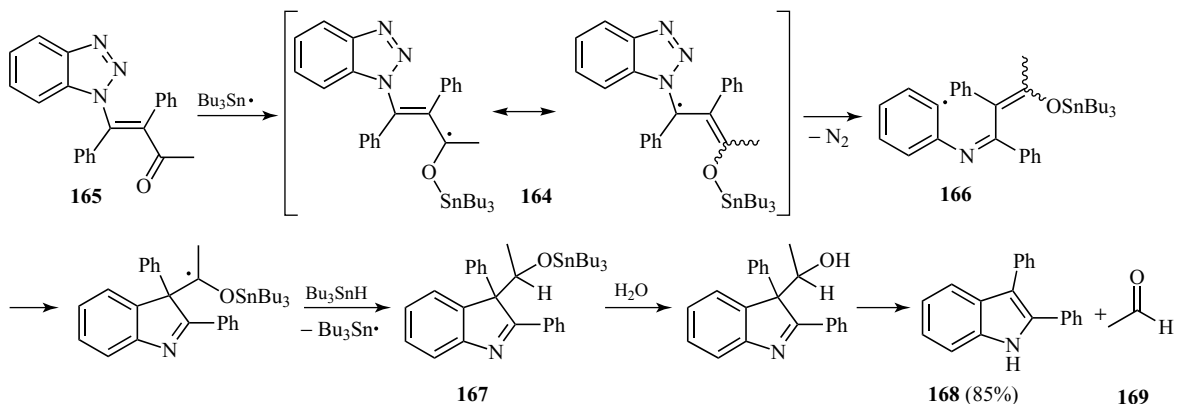
Further examples in which the tributyltin radical is liberated in the final stage of the reaction and which can thus be conducted catalytically in

tin hydride can be found in the literature.²¹² In case the tributyltin moiety remains as a substituent on the alkene, it can either be cleaved by protodestannylation,²¹³ or be used as a precursor for Stille cross-coupling reactions (Scheme 38).

The fact that *O*-stannylketyl or related radicals are reversibly formed in more or less small amounts from tin-centered radicals and carbonyl compounds only becomes obvious when an effective further reaction pathway exists for respective stannylketyl radicals.^{214–217} Even ester functionalities, which are generally not susceptible to tin-centered radicals and which therefore remain unchanged in most radical reactions involving organostannanes, can play a role as tin radical acceptors when the above-mentioned requirement is fulfilled. An example from a recent investigation in this field is shown in Scheme 40.²¹⁸ Treatment of ester **158** with catalytic amounts of tributyltin chloride in the presence of PMHS and potassium fluoride gave **159** via the fragmentation



Scheme 40 Tin hydride-induced radical fragmentation of ester **158**.²¹⁸



Scheme 41 Synthesis of 2,3-disubstituted indole **168** via the allylic *O*-stannylketyl radical **164**.²²⁸

of the *O*-stannylketyl radical **160**. The pyrimidine-sulfonyl radical **161** liberated in the fragmentation step regenerates $\text{Bu}_3\text{Sn}^\bullet$ from Bu_3SnH and forms aryl sulfinic acid **162**. Acid **162** is necessary for the further protolysis of tin enolate **163** to give **159**.

The first examples for the tributyltin hydride-induced formation of *O*-stannylketyl radicals in cyclization reactions of aldehydes and ketones to alkenes were reported by Enholm.^{219–222}

The general reaction principle was since expanded to various substrates.^{223–227}

A new synthetic access to indoles proceeding via the formation of allylic *O*-stannylketyl radicals has recently been discovered by Kim (Scheme 41).²²⁸ In the underlying reaction mechanism, the allylic stannylketyl radical **165** derived from **164** is converted to an aryl radical **166** via loss of nitrogen from the benzotriazol moiety. Cyclization of **166** onto the *O*-stannyl enolate and further reduction by tributyltin hydride led to an intermediate tin alcoholate **167**, which transformed to the 2,3-disubstituted indole **168** by hydrolysis and cleavage of acetaldehyde (**169**).

3.3.7 Generation of Heteroatom-Centered Radicals

The group of nitrogen-centered radicals can be divided into the three major subtypes: aminyl, iminyl, and amidyl. Figure 3 shows a collection of precursors that have so far been successfully used in combination with organostannanes. More exactly, the bond cleavage indicated can generally be induced by an attack of a tin-centered radical on the bold-printed atom of the functional group attached to the nitrogen atom which is to be transformed into a radical. The simplest precursors for aminyl radicals are *N*-chloroamines **170**.^{229,230} Via a nitrogen–nitrogen bond cleavage, aminyl and iminyl radicals have been generated from azides **171**,^{231,232} benzotriazoles **172**,²³³ thiosemicarbazones **173**,²³⁴ and dithiosemicarbazones **174**.²³⁵ Further precursors that give radicals after nitrogen–oxygen bond scission are iminoxymethyl selenides **175**,²³⁶ oxime benzoates **176**,²³⁷ and *N*, *O*-diacyl hydroxylamines **177** and **178**.^{238,239} Nitrogen-centered radicals can finally be formed via homolysis of N–S bonds. Suitable starting materials for this strategy are

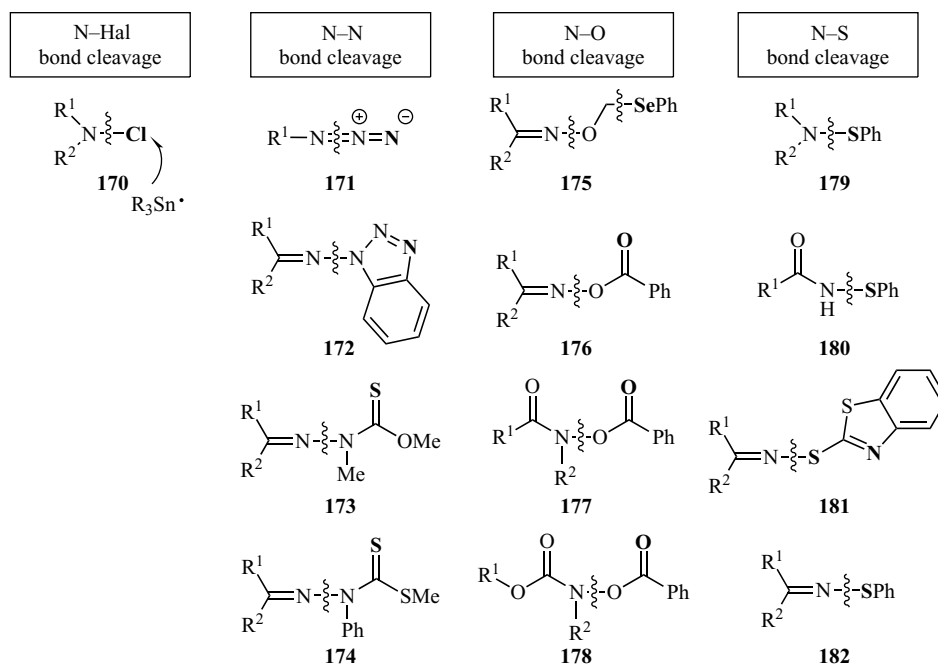
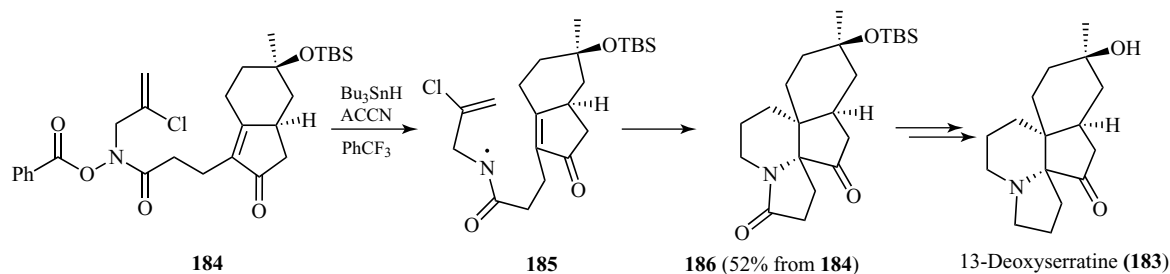


Figure 3 Precursors for the generation of nitrogen-centered radicals via an attack of $\text{R}_3\text{Sn}^\bullet$ at the bold-printed atoms followed by fragmentation and/or group transfer.



Scheme 42 Key steps from the synthesis of (±)-13-deoxyserratine.²⁴⁵

sulfenamides **179**,²⁴⁰ *N*-acyl sulfenamides **180**,²⁴¹ iminothio benzothiazoles **181**,²⁴² or thiooximes **182**.^{243,244}

By applying one of the above-shown precursors, a short synthetic access to (±)-13-deoxyserratine (**183**) could be developed (Scheme 42).²⁴⁵ In the presence of tributyltin hydride and ACCN, *O*-benzoyl-*N*-allylhydroxamate **184** was first converted to amidyl radical **185**, which gave **186** after two consecutive cyclization steps and reduction by Bu₃SnH. It is interesting to note that the chlorine atom, which had to be placed on the allyl chain to achieve the desired 6-endo mode in the second cyclization step, was selectively removed by the excess Bu₃SnH after completion of the cyclization sequence. The reaction pathway is fully comprehensible when bearing in mind that tin hydrides

are usually unable to reduce aromatic or vinylic chlorides (such as in reactant **184**), while aliphatic chlorides are generally sensitive to the reagent (see also Section 3.1.1).

More detailed information on recent progress in the generation and use of nitrogen-centered radicals, including many examples and alternative tin-free methods, can be found in a review article by Zard.²⁴⁶

In comparison to nitrogen-centered radicals, their oxygen-centered analogs are more often generated from labile hypobromites or hypoiodites under photochemical initiation than by atom or group transfer to tin-centered radicals. An interesting and comprehensive review on developments in this field of radical chemistry has been published by Hartung.²⁴⁷

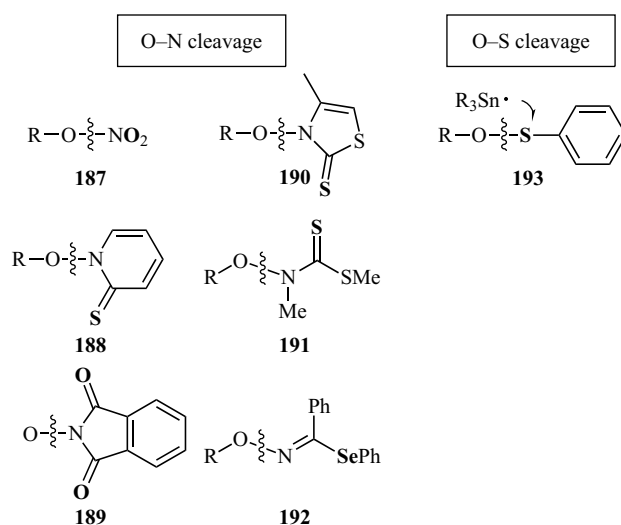
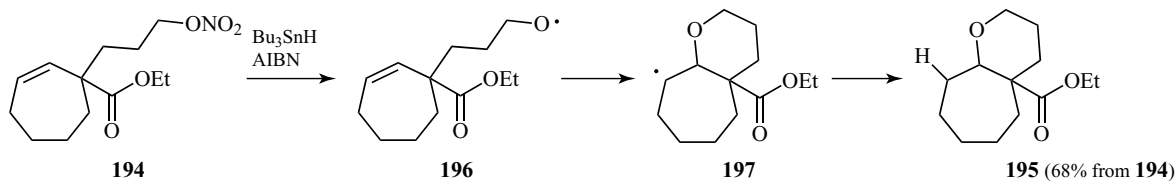


Figure 4 Precursors for the generation of oxygen-centered radicals via an attack of R₃Sn[•] at the bold-printed atoms followed by fragmentation and/or group transfer.



Scheme 43 Radical cyclization of oxyl radical **196** generated from nitrate **195**.²⁴⁸

A compilation of those precursors that have successfully been used for the generation of oxygen-centered radicals in combination with tin hydrides is shown in Figure 4. Regarding the mechanisms along which oxyl radicals are formed from nitrates **187**,²⁴⁸ thiopyridones **188**,^{249,250} phthalimides **189**,²⁵¹ thiazolthiones **190**,²⁵² dithiocarbamates **191**,²⁵³ selenoimines **192**,²⁵⁴ and sulfonates **193**,²⁵⁵ the cleavage of a nitrogen–oxygen bond represents the most common key step.

Similar to the generation of nitrogen-centered radicals, the fragmentation of the respective radical oxyl precursors **187–193** is induced by an attack of a tin-centered radical on the functional groups on the right side of the waved bonds (Figure 4). The cyclization of nitrate **194**, leading to the bicyclic product **195**, therefore starts with an attack of the $\text{Bu}_3\text{Sn}^\bullet$ radical on the nitrate moiety.²⁴⁸ Subsequent formation of tributyltin nitrite ($\text{Bu}_3\text{Sn}-\text{ONO}$) liberates the oxyl radical **196**, which converts to **195** via cyclization to **197** and reduction (Scheme 43).

4 CONCLUSIONS

Although the examples presented in this article can only give a shallow insight into the field of tin hydride-mediated radical reactions, we hope that we have nevertheless been able to illustrate the vast possibilities associated with this type of reagents. Most importantly, significant advances have been made in recent years concerning the development of new organotin reagents that are easy to separate during work-up. Hopefully, the traditional reagents such as tributyltin hydride will be more and more replaced by new inventions in the coming years, since this evolution might then finally change the long-standing reluctance of many organic chemists toward radical tin hydride chemistry.

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Synthetic Radical Photochemistry

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1 INTRODUCTION

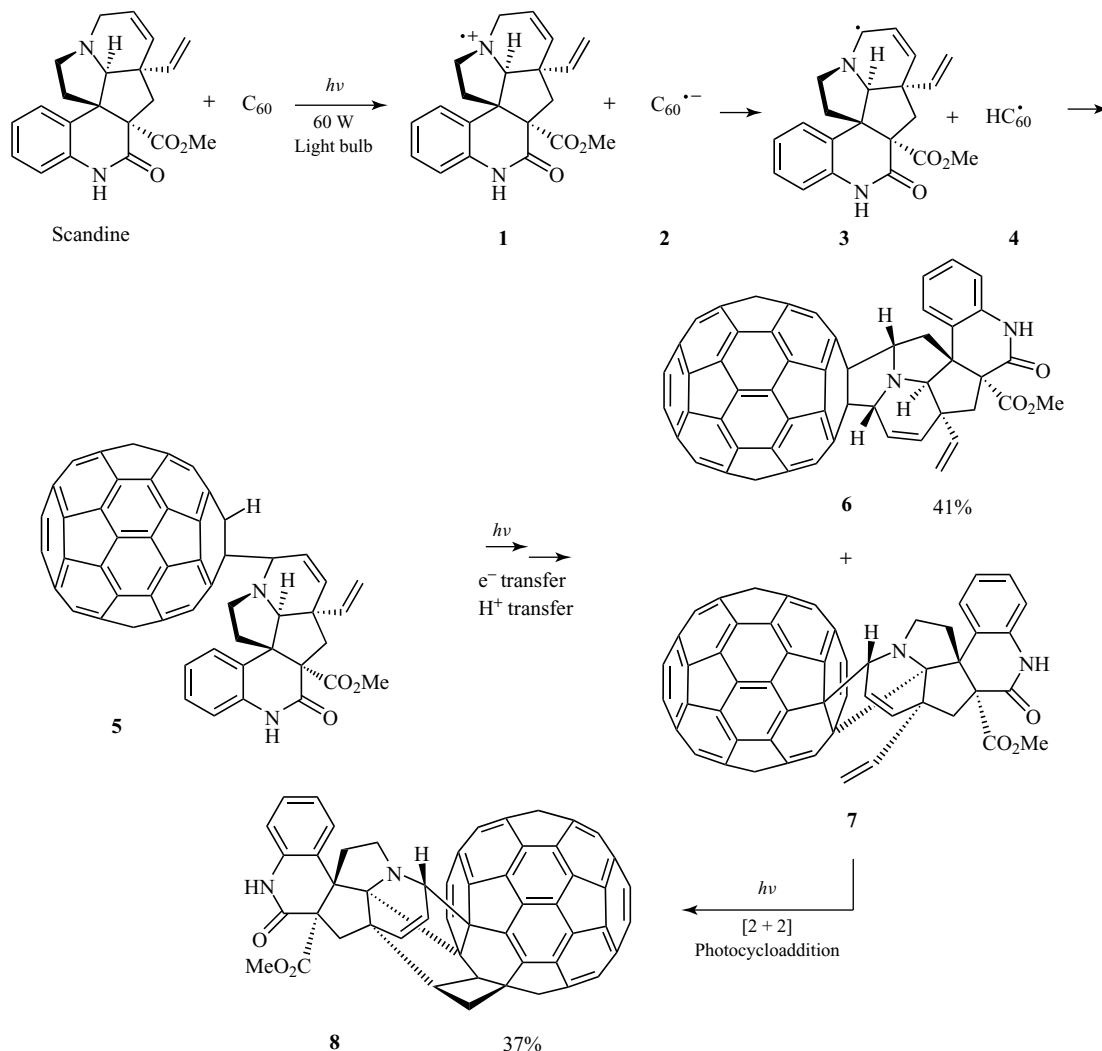
When photochemical reactions are applied to organic synthesis,^{1–4} they are often per se designed as radical reactions. However, many photochemical transformations^{5,6} do not belong to this category. Photochemically performed pericyclic reactions are typical examples. In many other cases, intermediates are involved which possess only “partial” radical character, for instance, when singlet “biradicals” are generated. Such transformations are not discussed in this article. On the other hand, a large variety of free radical species are generated with photochemical reactions. Molecules change their electronic configuration when they are photochemically excited. Consequently, the chemical reactivity is significantly modified. For instance, an electron transfer may be facilitated or the bond energy is reduced in a way that homolytic bond cleavage leads to radical species. Both processes are frequently applied in radical chemistry. In such cases, usage of additional reagents such as radical starters is often avoided and thus the amount of side products is diminished. Photons are then considered as traceless reagents. In this context, photochemical reactions are frequently classified as sustainable methods.

Many applications of organic synthesis have been reported. In this article, we have presented a very limited number of examples. A certain preference is given to reactions that are applied to multistep synthesis.

2 PHOTOCHEMICAL ELECTRON TRANSFER-INDUCED RADICAL REACTIONS

2.1 Metal-Free Induced Reactions

The redox potentials of molecules change completely when they are electronically excited.^{7–9} In most cases, electron transfer is facilitated and the redox chemistry of organic compounds is considerably enriched. Photochemical electron transfer is also a suitable method to generate radical intermediates. In such cases, a radical ion pair is formed. Radical ions possess a broad reactivity spectrum that may be applied in targeted ways to organic synthesis.^{10,11} Frequently, such a radical ion pair undergoes an acid–base reaction to generate neutral radicals. This process may occur when electronically excited, C₆₀ fullerene oxidizes tertiary amines, as described for the alkaloid scandine (Scheme 1).¹² In the resulting radical ion pair **1** and **2**, a proton exchange occurs and leads to the neutral radicals **3** and **4**. Radical combination now leads to the intermediate **5**. A further intramolecular sequence of electron and proton transfer followed by radical coupling generates a second C–C bond between the fullerene and scandine. Two regio-isomers **6** and **7** are thus obtained. Under the reaction conditions, isomer **7** undergoes a [2 + 2] photocycloaddition leading to the second final product **8**, possessing four C–C bonds between the fullerene and the scandine moieties. Further alkaloids such as



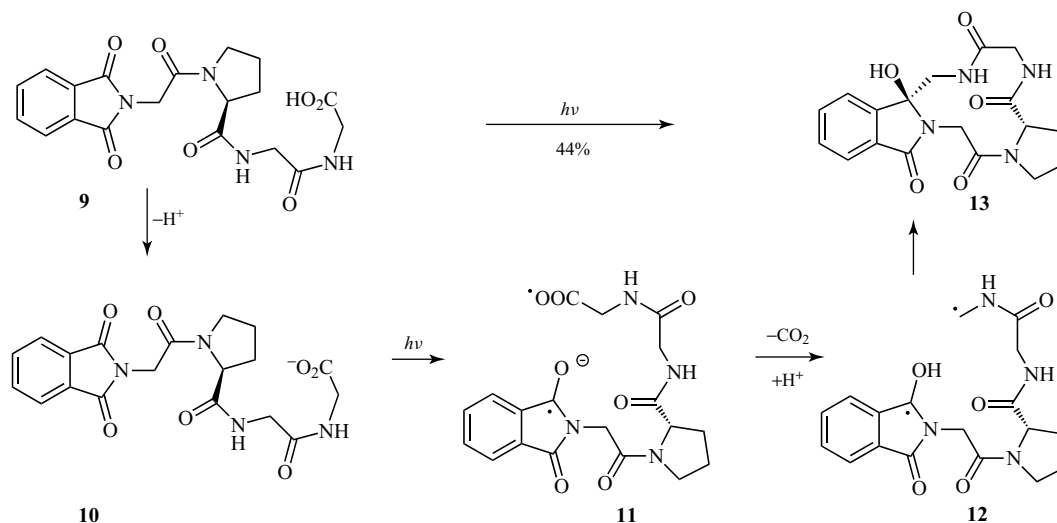
Scheme 1 Photochemical electron transfer-induced radical addition of the alkaloid scandine to C_{60} fullerene.

tazettine of gramine have been transformed in the same way.

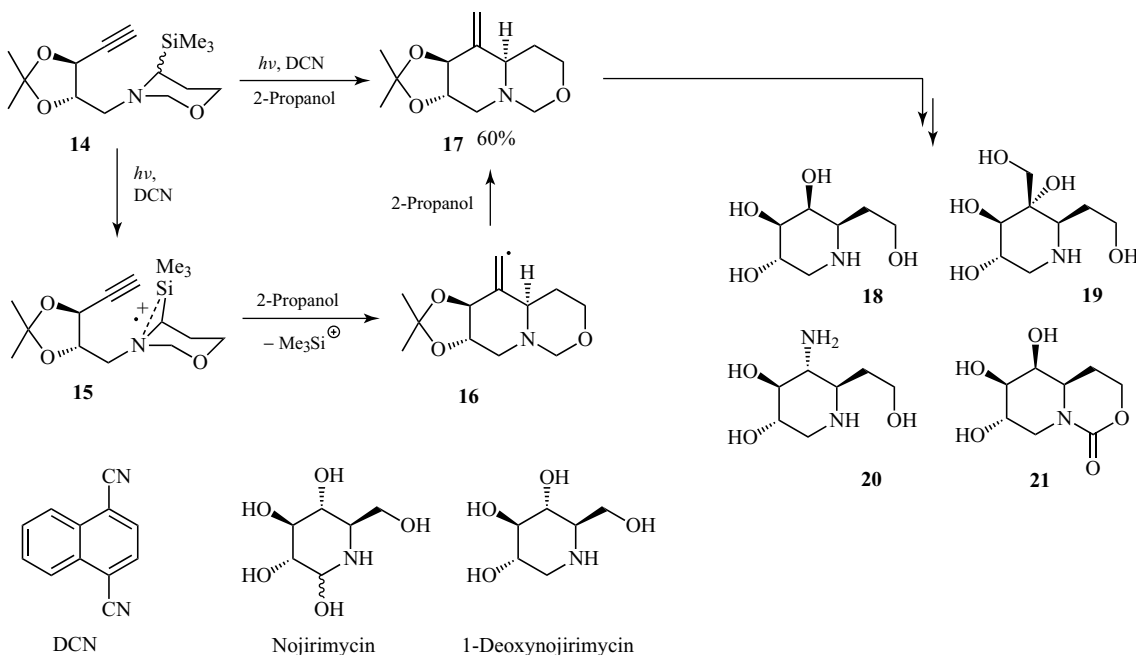
The reaction was applied to the cyclization of oligopeptides.¹³ In the case of the tripeptide **9** (Scheme 2), an electron transfer occurs between the carboxylate function and the phthalimide group (**10**).¹⁴ After elimination of CO_2 and protonation of the resulting radical anion **11**, the neutral diradical **12** is obtained. Finally, macro-cyclization occurs via radical combination which leads to the final cyclopeptide **13**. The compound resembles cyclosporine which possesses immunosuppressive activity. Similar compounds have been obtained in

photochemical electron transfer reactions involving tertiary amines which have been oxidized to radical cations.¹⁵ In such cases, trialkylsilyl substituents can be used as leaving groups to generate a neutral α -aminoalkyl radical.

This strategy was applied to the synthesis of structural analogs to the natural iminosugar nojirimycin possessing α - and β -glucosidase inhibitor activity (Scheme 3).¹⁶ 1-Deoxynojirimycin and analogs are interesting in this context due to their increased stability. The photochemical key step starts with the oxidation of the silylated tertiary amine moiety in **14**



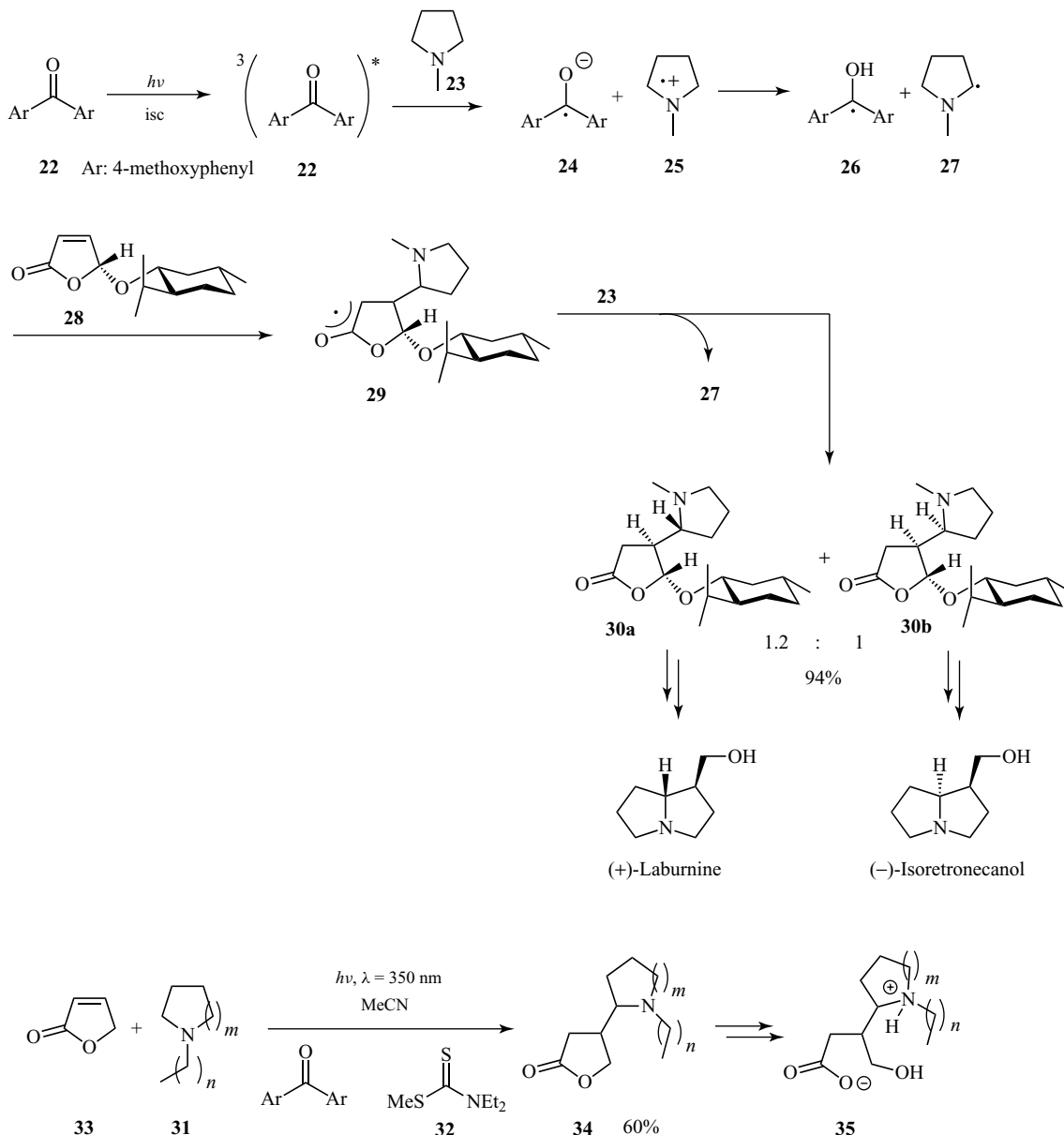
Scheme 2 Photochemical electron transfer-induced radical macro-cyclization of phthalimide derivatives. Application to the synthesis of cyclopeptides.



Scheme 3 Intramolecular addition of silylated tertiary amines to alkynes.

by the electronically excited sensitizer dicyanophthalene. The 6-*endo*-dig cyclization of the radical cation **15** is affected by the β -silicon effect.^{17–19} The removal of the trimethylsilyl substituent from intermediate **15** during cyclization is facilitated by the presence of 2-propanol in the reaction mixture. This

effect is linked to the affinity between the silicon and oxygen atoms.²⁰ The final product **17** is obtained by trapping of the vinyl radical **16** by hydrogen transfer from 2-propanol. The bicyclic compound **6** has been transformed into a variety of structural analogs of nojirimycin such as **18**, **19**, **20**, or **21**.



Scheme 4 Photochemical electron transfer-induced radical addition of simple tertiary amines. Application to the synthesis of pyrrolizidine alkaloids and surfactants.

Photochemically generated radical ion pairs may undergo proton exchange which leads to the formation of neutral radicals. Such steps are involved in the addition of tertiary amines to electron-deficient alkenes. When aromatic ketones such as 4,4'-dimethoxybenzophenone **22** are electronically excited, they are capable of

oxidizing tertiary amines such as **23**, which leads to the formation of a radical ion pair **24** and **25** (Scheme 4).²¹ In an acid–base reaction, the neutral radical intermediates **26** and **27** are obtained. The nucleophilic α -aminoalkyl radical **27** easily adds to the electron-deficient alkene **28** and the oxoallyl radical **29** is thus generated. Hydrogen abstraction

of *N*-methylpyrrolidine **23** leads to the final product **30a,b** as a mixture of diastereoisomers. This step is part of the radical chain reaction which was identified by a product quantum yield of 4. Alternatively, the oxoallyl radical **29** may react with the ketyl radical **26**. Thus, the sensitizer **22** is easily regenerated and becomes an efficient photocatalyst.²² Concerning stereoselectivity, it should be pointed out that the radical attack occurs exclusively anti with respect to the alkoxy substituent in **28**. However, the configuration of the chiral center in the α -position of the nitrogen was not controlled. The adducts **30a** and **30b** have been separated by chromatography. They were transformed into the pyrrolizidine alkaloids (+)-laburnine and (–)-isoretronecanol, respectively.²³ Less reactive tertiary amines such as **31** can also be transformed when thiocarbonyl compounds such as **32** are added to the reaction mixture.²⁴ Such additives affect the complex interplay of different neutral radical intermediates,²⁵ as it is also observed in the case of reversible addition-fragmentation chain transfer (RAFT) polymerization (see **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**).²⁶ The resulting adduct **34** from the transformation of furanone **33** have been transformed into zwitterion-type surfactant **35**.²⁷

Ketyl radicals that are generated by photochemical electron transfer from tertiary amines to an electronically excited ketone may also add to alkenes. The intramolecular version of this reaction was applied to the synthesis of polycyclic compounds such as alkaloids. Such ketyl radicals also induce rearrangements of polycyclic structures.²⁸

2.2 Ruthenium-Mediated Photocatalysis

As pointed out before, the use of an electron transfer with a molecule at an electronically excited state to generate a reactive radical intermediate is a widely recognized strategy in organic photochemistry. In the past decades, the use of organic sensitizers in photoinduced electron transfer reactions has been extensively studied,²⁹ and in some cases, a photoredox catalytic cycle can be achieved when sensitizers are regenerated in the course of the reaction.^{21,22,29} In contrast, the use of organometallic compounds as efficient sensitizers has been recognized only recently.³⁰ Indeed, organometallic compounds such

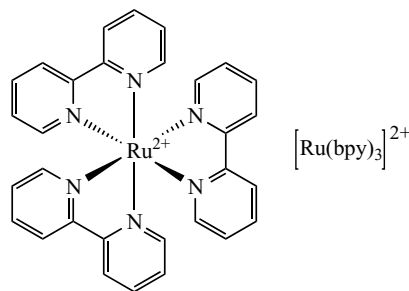


Figure 1 Structure of $[\text{Ru}(\text{bpy})_3]^{2+}$ complex.

as the well-known tris(2,2'-bipyridine)ruthenium(II) ion $[\text{Ru}(\text{bpy})_3]^{2+}$ can be considered as a privileged photosensitizer for several reasons (Figure 1).

Its absorption spectrum exhibits a strong broad band centered at 450 nm. Irradiation of a solution of this compound with visible light leads to a triplet excited state in which a metal-centered electron is promoted to the π^* -orbital of the bipyridyl ligand (metal to ligand charge transfer transition). This photoexcited state can behave as either an electron donor or an acceptor to produce $[\text{Ru}(\text{bpy})_3]^{3+}$ or $[\text{Ru}(\text{bpy})_3]^+$, respectively. A reductive or oxidative catalytic cycle can be envisaged based on these different redox states (Figure 2). Photoredox properties of $[\text{Ru}(\text{bpy})_3]^{2+}$ associated with its excellent chemical stability have been extensively exploited in the design of photo-responsive supramolecular devices³¹ and systems for conversion of solar energy.³²

In the field of synthetic organic photochemistry, several research groups have made significant breakthroughs since 2008. The formal $[2 + 2]$ intramolecular cycloaddition of enone **36** photocatalyzed by $[\text{Ru}(\text{bpy})_3]^{2+}$ has been studied (Scheme 5).³³ It was previously reported that such a reaction could be induced by mono-electronic reduction of an enone both chemically and electrochemically,^{34–36} affording a nucleophilic radical anion intermediate.

In this photocatalytic approach, a sacrificial amount of *i*-Pr₂NH is used as an electron donor to generate an Ru(I) complex from the electronically excited Ru(II)* species. Reduction of the Lewis acid-activated enone **38** produces the radical anion **39**, regenerating Ru(II) in the ground state. Subsequent conjugate radical addition produces intermediate **40**, which is further oxidized to give the formal $[2 + 2]$ cycloaddition product **37** (Scheme 6).

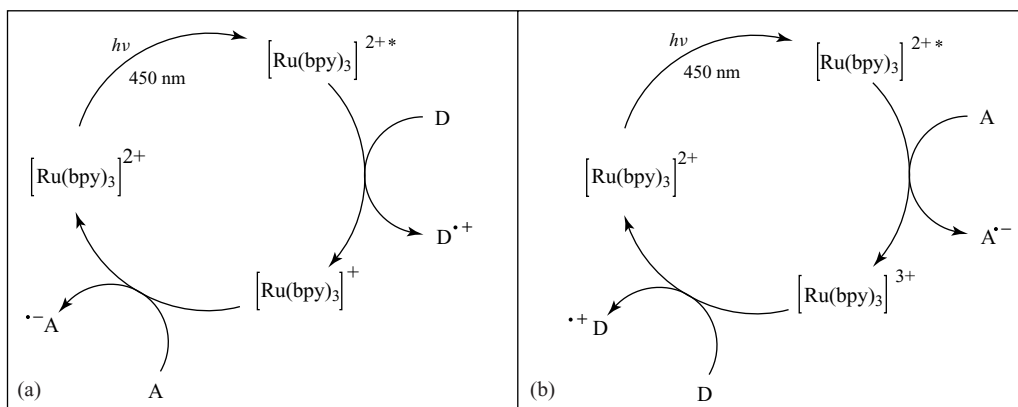
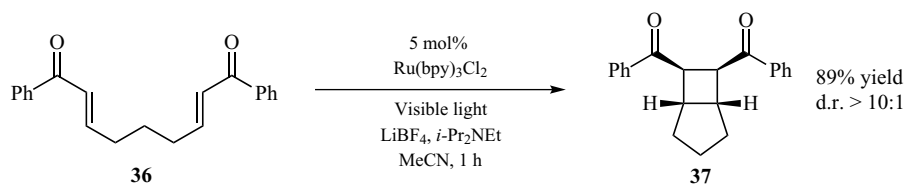
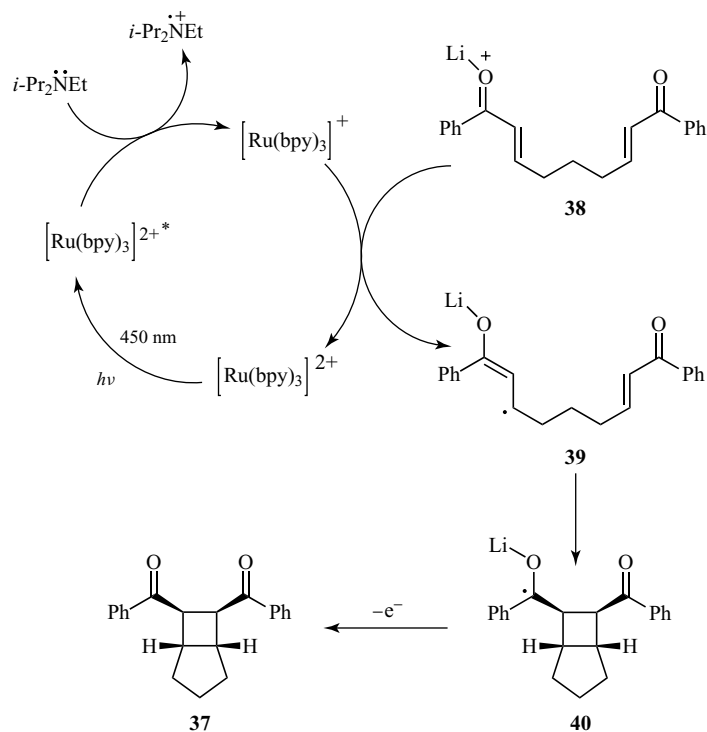


Figure 2 Reductive (a) and oxidative (b) catalytic cycle in $\text{Ru}(\text{bpy})_3^{2+}$ photochemistry.

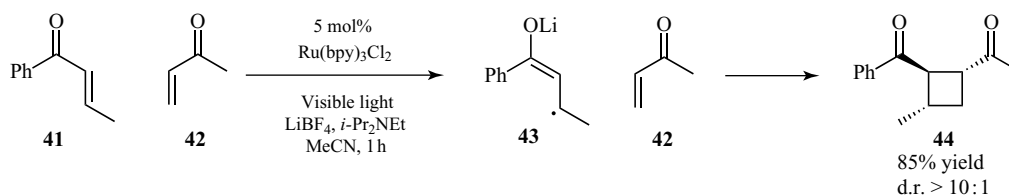


Scheme 5 Formal intramolecular photocatalytic [2 + 2] cycloaddition of an enone.

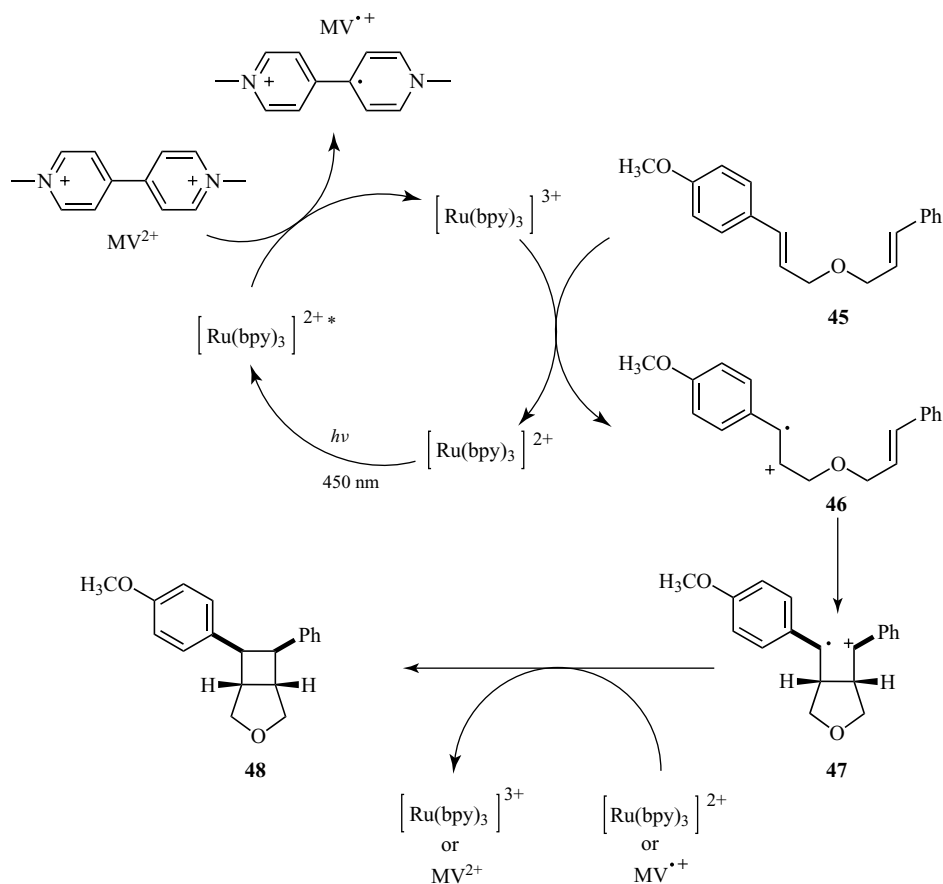


Scheme 6 Proposed mechanism for the formal intramolecular photocatalytic [2 + 2] cycloaddition of an enone.

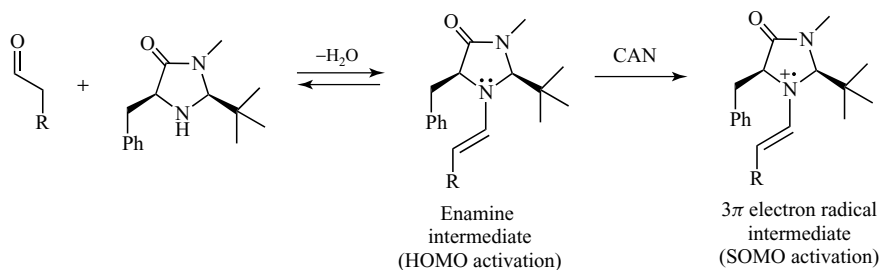
Notably, a formal cross $[2 + 2]$ cycloaddition between an aromatic **41** and an aliphatic acyclic enone **42** can be achieved using this optimized reaction. The reaction occurs by selective mono-electronic reduction of the aromatic enone by an Ru(I) complex (Scheme 7).³⁷ Compound **44** is obtained in 85% yield by coupling of the resulting radical intermediate **43** with aliphatic enone **42**.



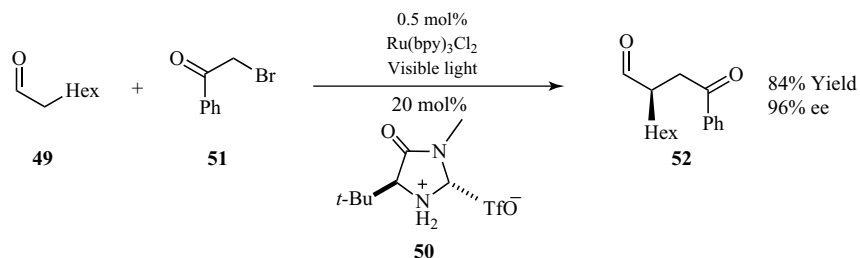
Scheme 7 Formal intermolecular photocatalytic $[2 + 2]$ cycloaddition.



Scheme 8 Formal intramolecular $[2 + 2]$ cycloaddition of electron-rich alkenes.



Scheme 9 SOMO activation in organocatalysis.



Scheme 10 Asymmetric α -alkylation of an aldehyde by organophotocatalysis.

produce an Ru(III) complex.⁴⁰ Ru(III) is then able to oxidize the electron-rich alkene **45** to produce a radical cation intermediate **46** and regenerate an Ru(II) species. Compound **48** was obtained by a reductive cascade reaction. Notably, only 15 mol% of MV²⁺ was necessary, probably indicating that the radical intermediate **47** is involved in the Ru catalytic cycle by oxidation of either Ru(II) to Ru(III) or (MV⁺) to (MV²⁺).

In contrast to reactions involving organic sensitizers such as 9,10-dicyanoanthracene,^{41,42} with this methodology, high yields of cycloadducts can be obtained in short reaction time using a standard household light bulb.

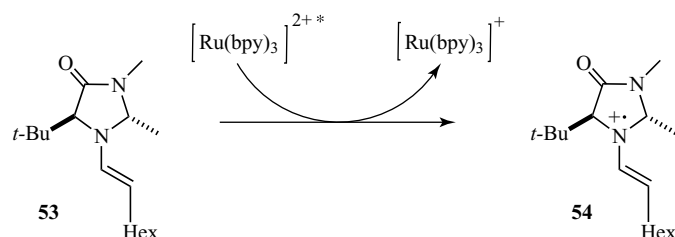
In 2007, a new catalytic mode in the field of asymmetric organocatalysis called *single occupied molecular orbital (SOMO) activation* was introduced. In this strategy, the formation of a transient 3 π -electron radical can be achieved from an enamine intermediate using a single-electron oxidant (Scheme 9).⁴³

The introduction of a radical intermediate in an organocatalytic cycle considerably increases the scope of organocatalysis, allowing transformations that cannot be achieved using traditional enamine and iminium catalysis (e.g., asymmetric α -allylation, arylation, and enolation

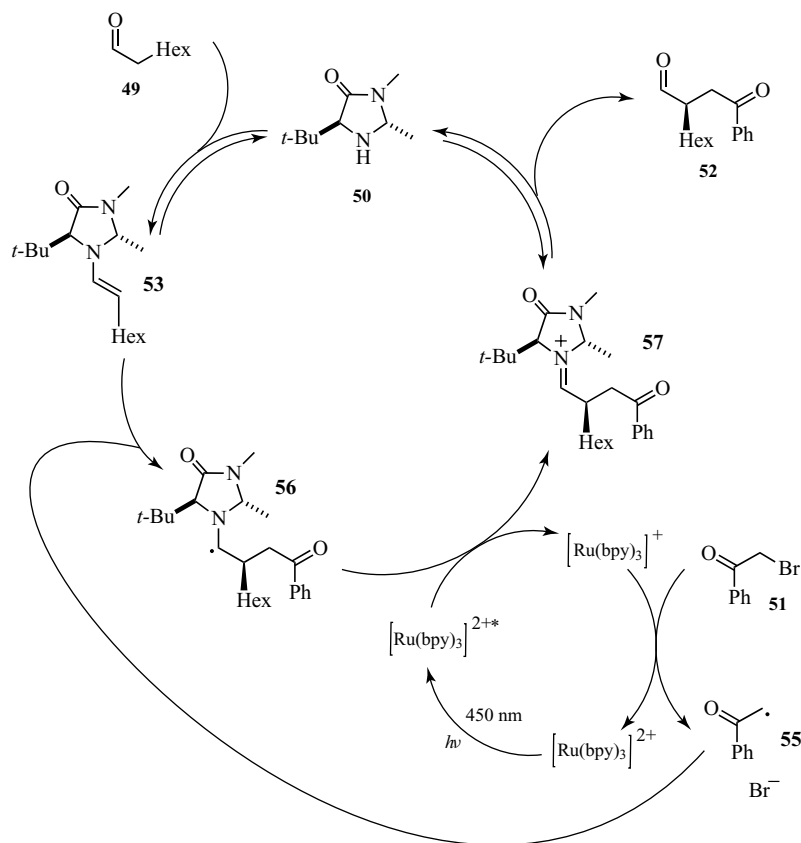
of the aldehyde). In a continuous effort to develop new organocatalytic methodology, an organo-photocatalysis strategy by coupling a reductive Ru photocatalytic cycle and an organocatalytic cycle involving the formation of an enamine intermediate were described.⁴⁴ This methodology allowed the direct asymmetric α -alkylation of an aldehyde, a long-standing elusive goal in the field of organocatalysis (Scheme 10).

A detailed mechanism was proposed after careful investigation of the reaction. In contrast to SOMO activation, a 3 π -electron radical **54** is not involved in the productive reaction step, even if it is probably produced by oxidation of a small sacrificial amount of enamine intermediate **53** by an Ru(II) excited state, thereby initiating the Ru catalytic cycle (Scheme 11).

This resulting Ru(I) species then induces reductive cleavage of the C–Br bond of the bromoketone derivative **51** (Scheme 12) to form α -ketoalkyl radical **55**. The organocatalytic cycle begins with condensation of imidazolidinone catalyst **50** and aldehyde **49**. The resulting electron-rich enamine **53** is able to react with the electron-deficient α -ketoalkyl radical **55** to form the chiral α -aminoalkyl radical **56**. The convergence of the two catalytic cycles then occurs by single-electron transfer between the α -aminoalkyl



Scheme 11 Initiation of ruthenium catalytic cycle.



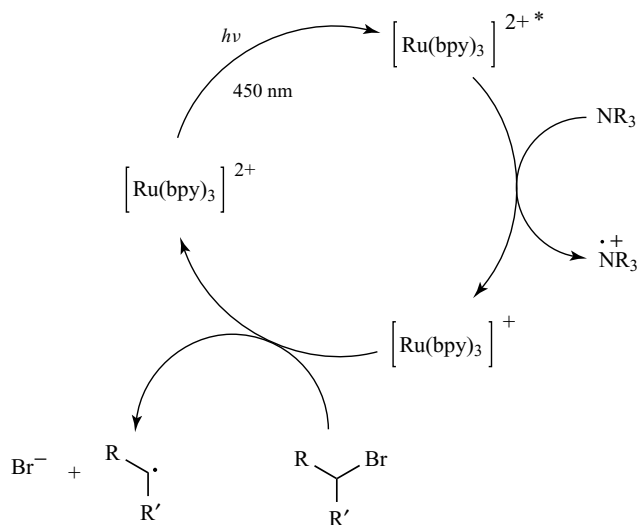
Scheme 12 Proposed catalytic cycles for the asymmetric α -alkylation of an aldehyde.

radical **56** and the Ru(II) compound at its excited state to produce an iminium ion **57** and generate the Ru(I) species. The organocatalytic cycle is completed by hydrolysis of the iminium ion **57** to produce the chiral aldehyde **52** and regenerate the amine catalyst **50**.

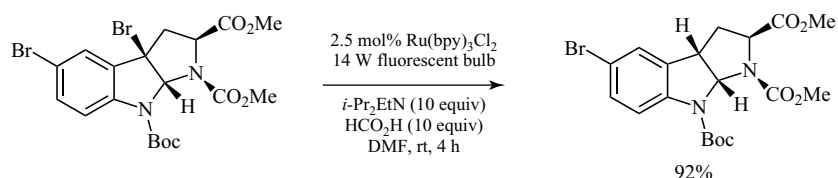
The interconnection of the two catalytic cycles not only avoids the use of a stoichiometric amount of a sacrificial electron donor to generate Ru(I)

species but also gives an opportunity to increase the scope of the methodology. Indeed, fine-tuning of both the stereoelectronic properties of the organocatalyst and the photoredox behavior of the Ru complex can be adjusted independently.

Several useful synthetic organic transformations based on the reactivity of the radical formed by reductive cleavage of the C–Br bond, using a ruthenium photocatalytic cycle, were introduced



Scheme 13 Photocatalytic formation of a radical by reductive cleavage of the C–Br bond.



Scheme 14 Photocatalytic reduction of an alkyl halide.

(Scheme 13). In most cases, an excess of sacrificial tertiary amine was used to afford an Ru(I) species from an electronically excited Ru(II) compound (Scheme 13).

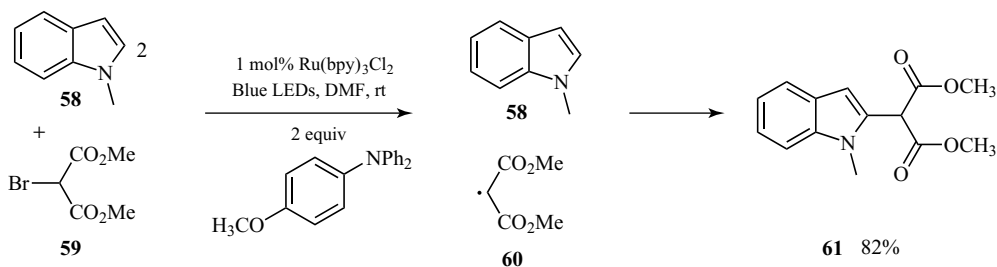
This methodology allows the selective and mild reduction of alkyl halides, reaction that typically requires trialkyltin hydride and azobis(isobutyronitrile) (AIBN) as a radical initiator. In optimized conditions, 1 mol% of $[\text{Ru}(\text{bpy})_3]^{2+}$, 10 equiv of diisopropylethylamine, and 10 equiv of formic acid are used.⁴⁵ A typical example is shown in Scheme 14.

Mechanistic studies suggest that a formate diisopropyl ammonium radical species plays the role of a hydrogen donor in the hydrogen abstraction step. These mild reduction conditions allow selective reduction of α -alkyl halides to electron withdrawing groups. Moreover, these conditions tolerate the presence of a wide range of functional groups, including free hydroxy groups, esters, olefins, and alkynes as well as usual protecting groups such as silyl ethers and carbamates. In

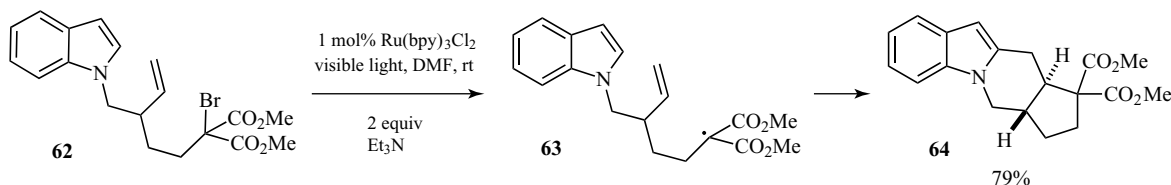
a related approach, tin-free intramolecular radical cyclization was performed on substrates, including bromomalonate and unactivated alkenes or alkynes affording five- and six-membered rings.⁴⁶

It has also been demonstrated that ruthenium-based photocatalysis is a powerful tool for direct C–H functionalization of biologically active compounds. Direct α -arylation of bromomalonate using various electron-rich heteroaromatic compounds has been reported.⁴⁷ Optimized reaction conditions allow the direct alkylation of indole **58** with bromomalonate **59** (Scheme 15). The coupling between photogenerated malonyl radical **60** and indol **58** occurs selectively at position 2 to afford compound **61** in 82% yield. The reaction was performed with blue light-emitting diodes.

In such a procedure, the choice of the electron donor involved in the reductive ruthenium catalytic cycle is crucial to avoid undesired side reactions of the malonyl radical **60**. The cross-coupling product is obtained in high yield using 2 equiv of 4-methoxy-*N,N*-diphenylaniline as the electron



Scheme 15 Photocatalytic C–H functionalization of indole.



Scheme 16 Photocatalytic radical cascade reaction.

donor. A broad range of heteroaromatic compounds including furan pyrrole can be alkylated using these optimized reaction conditions. Moreover, the methodology exhibits a broad tolerance for functional groups, which allows the use of unprotected indoles and pyrroles and the presence of sensitive functional groups on the heteroaromatic moiety.

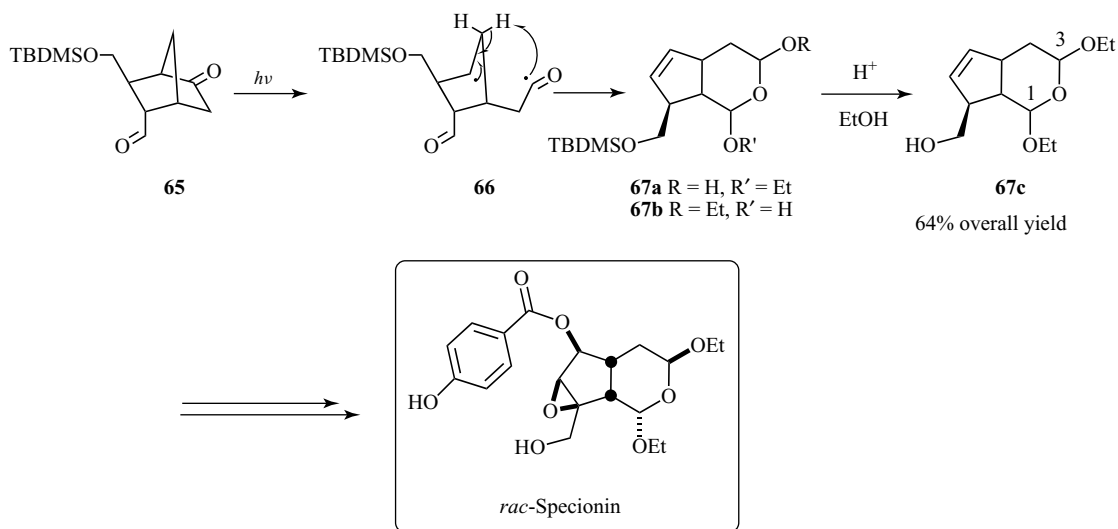
Analogous intermolecular and cascade reactions have also been reported.⁴⁸ Screening of amine electron donors has revealed that triethylamine is the most efficient base used to minimize the amount of the major side product arising from simple reduction of the intermediate malonyl radical. Under optimized reaction conditions, treatment of compound **62** results in the formation of a malonyl radical intermediate **63** that undergoes a double cyclization. The product **64** was obtained in 79% yield as a single diastereoisomer (Scheme 16).

3 NORRISH AND RELATED REACTIONS

Radical intermediates can be easily generated from carbonyl compounds at the excited state. Photoexcitation of simple alkanones leads mainly to a $n\pi^*$ -excited state (either singlet or triplet), which can then produce a biradical intermediate by two main processes.⁴⁹ Homolytic cleavage of the α -bond to the excited carbonyl function is known as

Norrish type I process. Several competitive chemical reactions, mainly decarbonylation and hydrogen abstraction, can then occur from the radical pair. When alkanones have an hydrogen atom in the γ -position, α -cleavage is usually suppressed and γ -hydrogen abstraction by the excited carbonyl function occurs to form a 1,4-biradical. Subsequent cleavage of the biradical to form an enol and an alkene is known as *Norrish type II fragmentation*. The 1,4-biradical can also undergo cyclization by radical combination to produce a cyclic alcohol, a process called *Norrish–Yang cyclization*.

The use of the Norrish reaction in target-oriented synthesis is challenging because of both the competition between this two photochemical primary processes and the selectivity of the biradical intermediate reaction leading to the target molecule. Product distribution obtained from biradical intermediates is variable and is mainly affected by conformational bias. Consequently, bicyclic ketones are useful starting materials to carry out selective Norrish-type reactions. Selected examples of natural product synthesis or analogs that include Norrish reactions as a key step are briefly described below. Unambiguous assignment of the iridoid sesquiterpene specionin structure was made through total synthesis, including a Norrish I reaction as a key step (Scheme 17).⁵⁰ Irradiation at 254 nm in ethanol of compound **65** with a norbornanone framework furnished the crude intermediates **67a** and

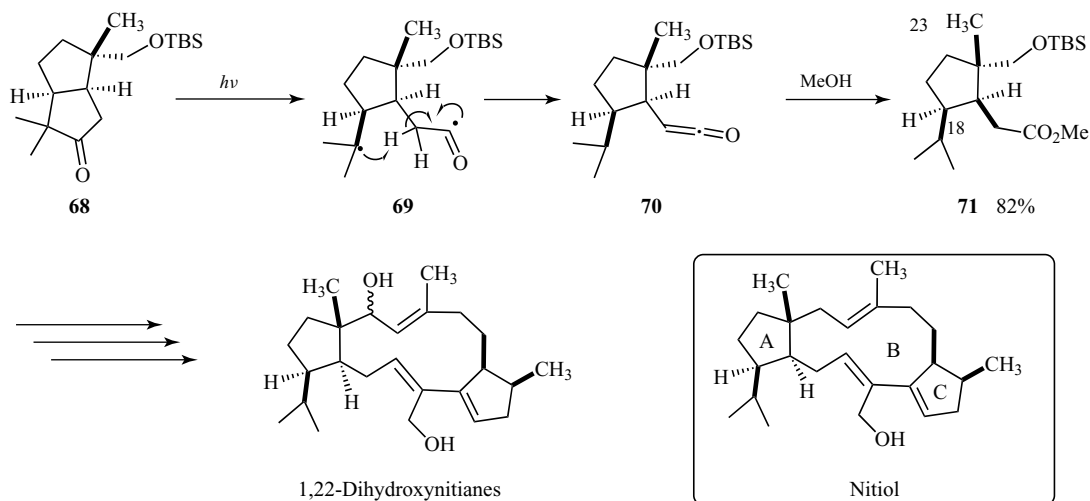


Scheme 17 Norrish II reaction as a key step in the total synthesis of *rac*-specionin.

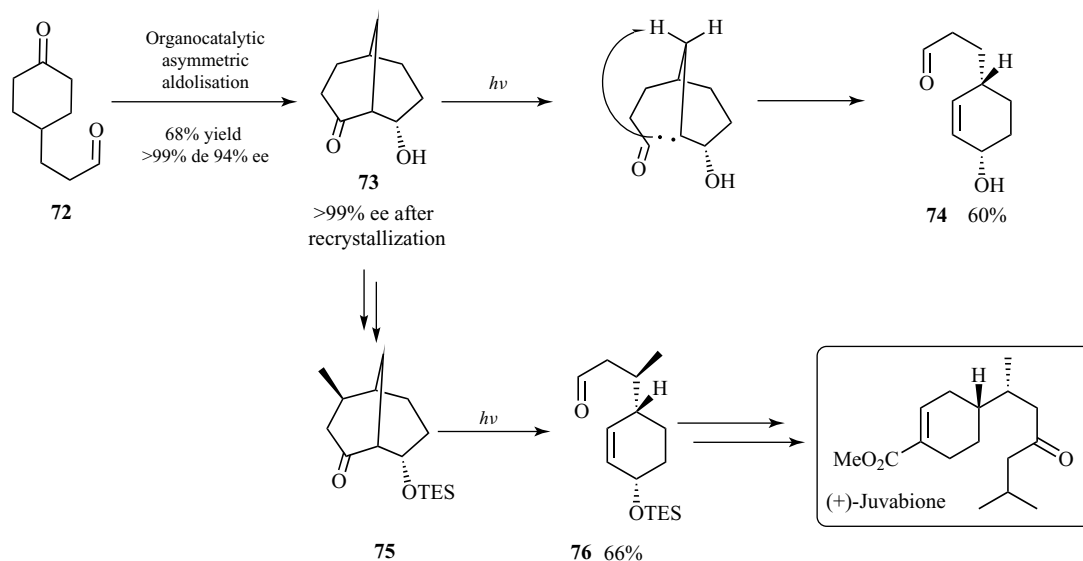
67b resulting from α -cleavage followed by hydrogen abstraction by acyl radical **66**. Acid treatment afforded compound **67c** as the mixture of the four diastereoisomers (at C-1 and C-3) in 64% overall yield. Further transformation of this key intermediate provided *rac*-specionin.

In a synthetic approach toward the sesterterpenoid nitiol, isolated from the biennial medicinal plant *Gentiana nitida* (Gentianaceae), two structurally hybrid 1,22-dihydroxynitienes were synthesized (Scheme 18).⁵¹ The functionalized cyclopentane

“A-ring” of nitiol was synthesized using the conformational bias of [3.3.0]bicyclooctane **68**, constructed via a diastereoselective Pauson–Khand reaction. Norrish I reaction on compound **68** gave access to the isopropyl group of the A-ring. The reaction was carried out on gram scale in methanol using UV light. After α -cleavage and hydrogen abstraction by the isopropyl radical **69** to form the ketene intermediate **70**, addition of methanol results in the production of compound **71** with 82% yield. An analogous Pauson–Khand/Norrish I



Scheme 18 Norrish I reaction as a key step in the A-ring construction of the 1,22-dihydroxynitien nitiol analogs.



Scheme 19 Formal intramolecular asymmetric redox transformation of **72** by organocatalytic intramolecular aldolization/Norrish I fragmentation sequence. Application to the synthesis of (+)-juvabione.

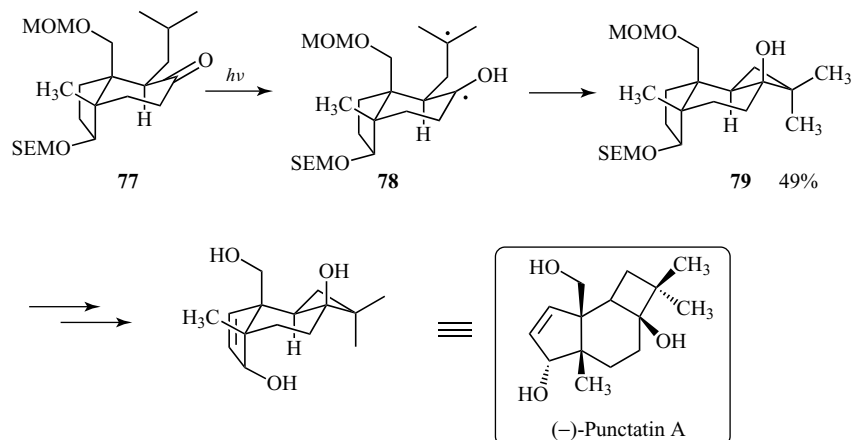
sequence was used by the same group to establish the A–B ring fragment of the fusicoccane family of diterpenes.⁵²

Numerous total synthesis of (+)-juvabione, a natural sesquiterpene exhibiting insect juvenile hormone activity, have been reported. Recently, a strategy based on an organocatalytic intramolecular aldolization/Norrish I fragmentation has been described.⁵³ The highly enantioenriched *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one **73** was obtained by organocatalytic intramolecular aldolization from σ -symmetric 4-(2-formylethyl) cyclohexanone **72**. When compound **73** was irradiated at 300 nm, a Norrish I fragmentation occurred to furnish compound **74** with 60% yield. The overall process can be viewed as a formal intramolecular asymmetric redox transformation of **72** (Scheme 19). Suitable functionalization of compound **73** was done to afford compound **75** with the bicyclo[3.3.1]nonan-2-one framework. The product **76** resulting from the subsequent key Norrish fragmentation was obtained in 66% yield. Five additional steps were then carried out to complete the total synthesis of (+)-juvabione.

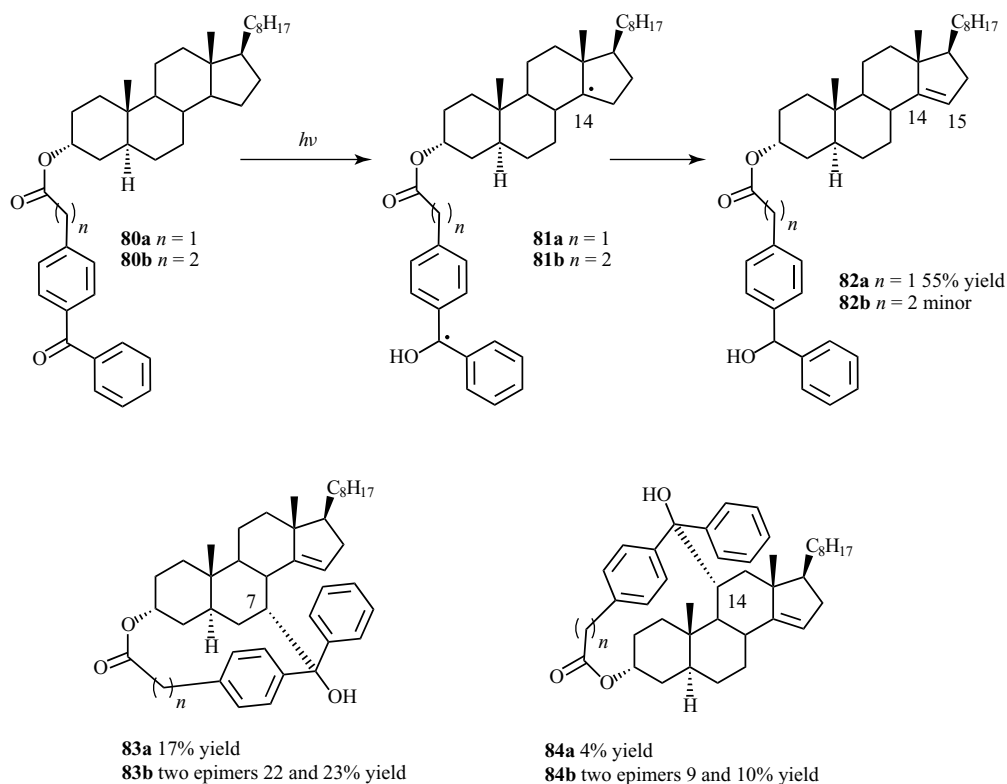
γ -Hydrogen abstraction by excited carbonyls followed by coupling of the subsequently formed biradical (Norrish/Yang cyclization) is a powerful and versatile method to produce various carbo- and

hetero-cycles.⁵⁴ The methodology has also been applied to natural product synthesis, as illustrated by the total synthesis of (–)-punctatin A (Scheme 20).⁵⁵ The construction of the completely functionalized trans-fused tertiary cyclobutanol was achieved by irradiation of compound **77** at 254 nm. The diastereoselective coupling of the biradical **78** resulted in the production of compound **79** with the correct stereochemical disposition in a 49% yield. (–)-Punctatin A was then readily obtained from this advanced intermediate.

Intramolecular hydrogen abstraction in a position other than γ , followed by coupling of the formed radical is known as *Yang cyclization*. This process has been extensively studied, especially in the context of macrocycle synthesis.⁵⁶ An interesting application of a long-range hydrogen abstraction by an excited carbonyl function is the selective functionalization of the unactivated positions of the steroid skeleton initially described by Breslow *et al.*^{57,58} When the benzophenone-4-acetic acid ester **80a** derived from 3 α -cholestanol was irradiated, a Δ^{14} -olefin **82a** was obtained as the major product (Scheme 21). Careful mechanistic investigation based on isotopic labeling showed that product **82a** arose from hydrogen abstraction on carbon 14 and that the resulting diradical **81** then transferred



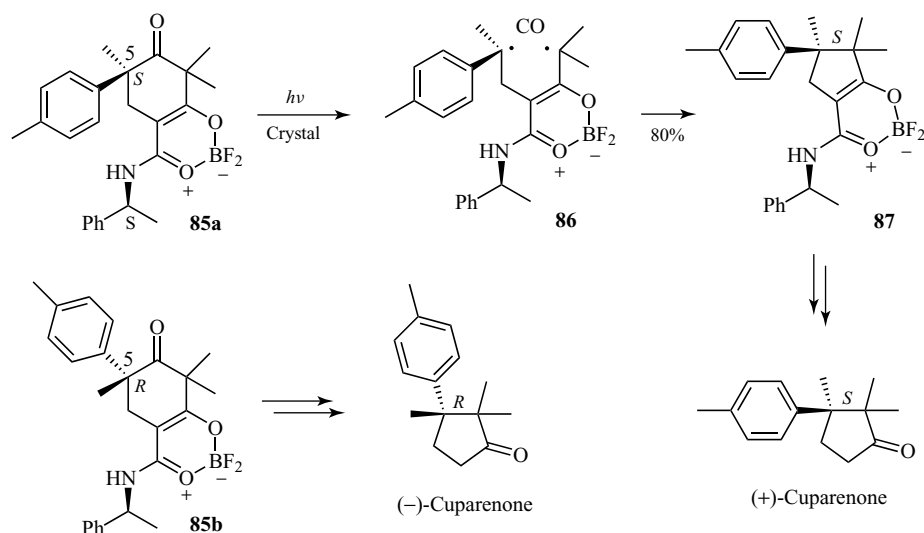
Scheme 20 Norrish/Yang cyclization as key step in the total synthesis of (–)-punctatin.



Scheme 21 Benzophenone remote functionalization of steroids.

the α -hydrogen from C-15 to the benzhydryl radical to complete the process. Two products arising from Yang cyclization at position C-7 **83a** and C-14 **84a** were obtained in a lower yield as single benzhydryl epimers (17 and 4% yield). As expected, the

selectivity of the overall process is strongly dependent on conformational constraints, as illustrated by experiments with more flexible compounds. For example, when a benzophenone-4-propionic acid ester analog **80b** was used, the Δ 14-olefin **82b** was



Scheme 22 Photochemically induced extrusion of carbon monoxide from cyclic ketones in crystal leading to stereoselective radical cyclization.

the minor product and **83b** and **84b** were the major products, both obtained as an equimolar benzhydryl epimeric mixture, arose from Yang cyclization at C-7 and C-14 (C-7 55% and C-14 19% global yield). The benzophenone remote functionalization reaction is a powerful method for the functionalization of steroids that have been recently used in the synthesis of xestobergsterol A⁵⁹ and the shark repellent, pavoninin-4.⁶⁰

Photochemical conditions for the extrusion of small molecules are widely applied. Frequently, radical intermediates are generated. Such a typical example is the extrusion of carbon monoxide from cyclic ketones, which can be carried out by irradiation of substrate crystals. This transformation may also be considered as a double Norrish I reaction. A crystal suspension of the cyclohexanone derivative **85a** possessing *S* configuration at position 5 was irradiated with UV light (Scheme 22).⁶¹ Compound **85a** undergoes double α -cleavage leading to the biradical **86**. Stereospecific radical combination leads to the cyclopentane derivative **87**. The stereoselectivity was controlled by the rigid environment of the crystal. When carried out in solution, a mixture of diastereoisomers was isolated from the photochemical transformation. It must be further pointed out that the transformation allows to create two adjacent quaternary centers. In two additional steps, the target (+)-cuparenone is obtained. This enantiomer

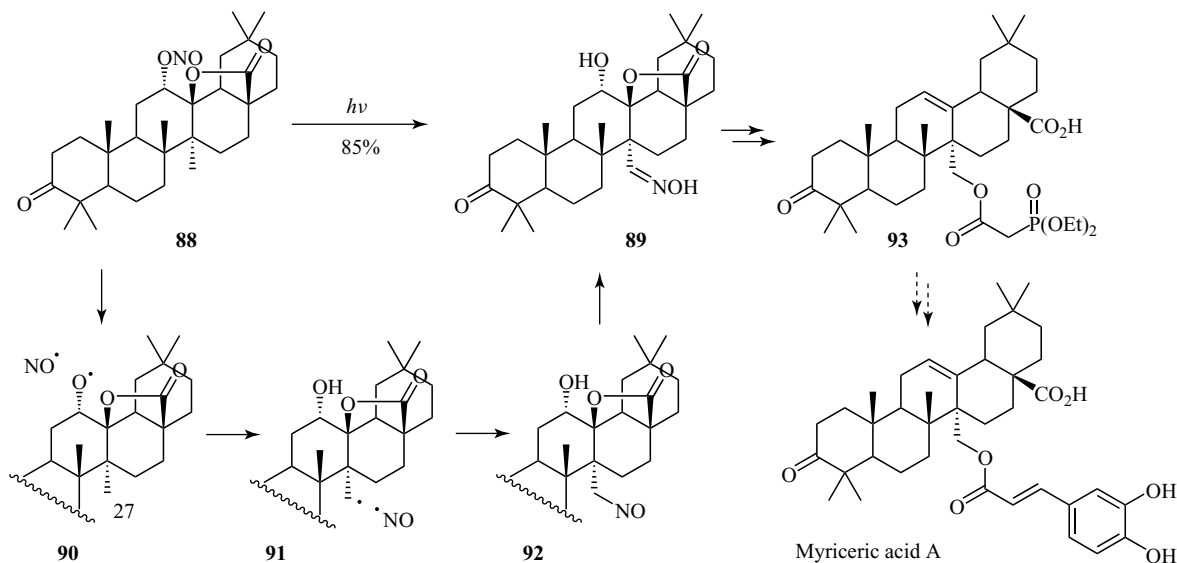
was isolated from the wood of the mayur pankhi (*Thuja orientalis*). The corresponding transformation of a crystal suspension of the diastereomeric cyclohexanone derivative **85b** possessing *R* configuration in the position 5 was conducted with the same efficiency. It was used for the synthesis of (–)-cuparenone. This enantiomer was isolated from the liverwort *Mannia fragrans*. The same synthesis strategy was applied to the synthesis of herbertenolide.⁶² A similar photochemical transformation of a crystal suspension was carried out on the scale of 10 g.⁶³

The decarbonylation is a reversible process. For example, under CO pressure, alkyl radicals may generate acyl radicals.⁶⁴ This reaction was also applied to organic synthesis.

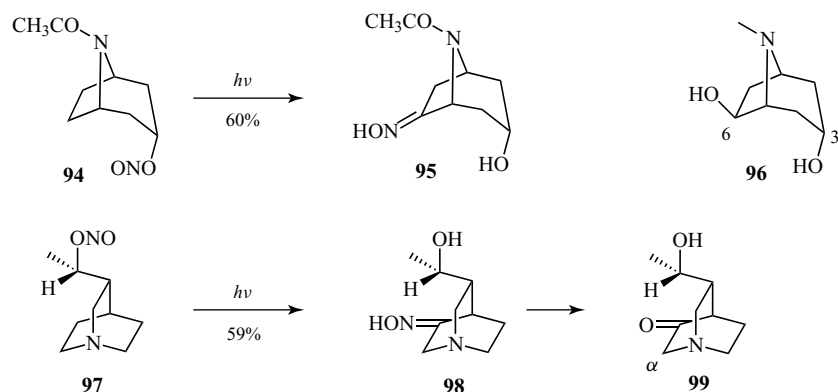
4 REMOTE FUNCTIONALIZATION WITH HETEROATOM-CENTERED RADICAL INTERMEDIATES

4.1 Intramolecular Remote Functionalization with Oxygen-Centered Radicals

Photochemical transformations of nitrite esters have frequently been applied to the synthesis of biological active compounds of the steroid or triterpene



Scheme 23 Radical remote functionalization with nitrite esters. Application to the synthesis of oleanolic acid derivatives.

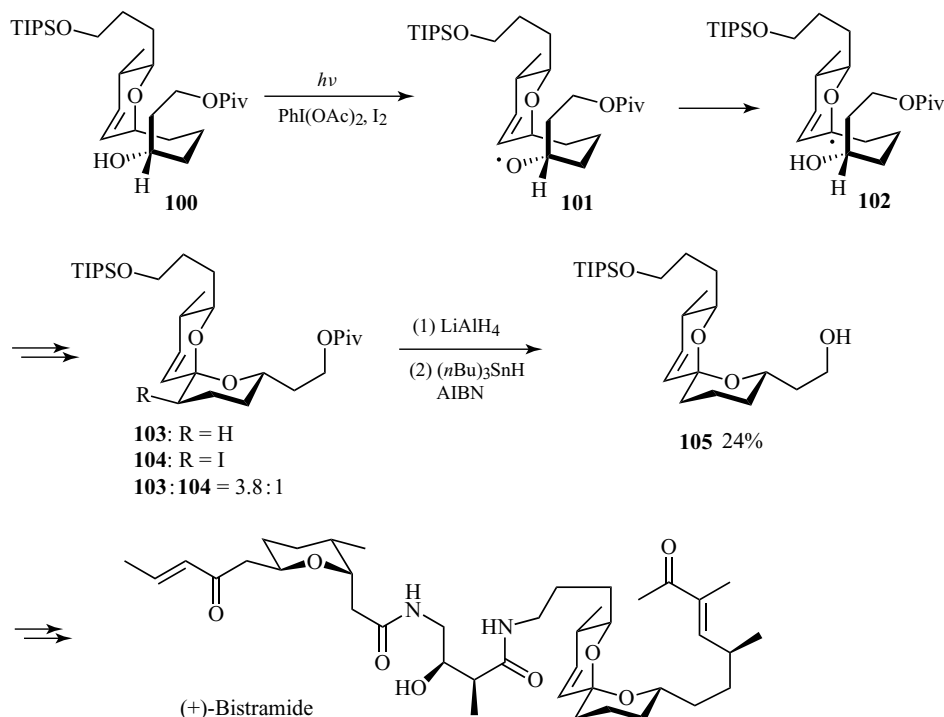


Scheme 24 Radical remote functionalization with nitrite esters. Application to the synthesis of alkaloids.

sapogenine families.^{65,66} The oleanolic acid derivative **88** was successfully transformed into **89** on a 20-g scale (Scheme 23).⁶⁷ The reaction starts with a homolytic cleavage of the N–O bond of the nitrite ester function (**90**). The resulting alkoxy radical selectively abstracts a hydrogen atom from position 27 (**91**). Trapping that radical with NO (**92**) and tautomerization leads to the final product. This transformation belongs to strategies involving remote intramolecular functionalization.^{68,69} As in many cases of radical reactions, an otherwise particular challenging selective C–H bond activation of an alkane takes place. Further transformations of

89 afford compound **93**, which may be a synthesis intermediate for the preparation of myriceric acid A. This acid is a potent and specific endothelin A receptor antagonist.

The reaction was also applied to the synthesis of alkaloids. Thus, irradiation of the nitrite ester **94** afforded the oxime **95** in good yield and complete regioselectivity (Scheme 24).⁷⁰ This reaction is useful for the synthesis of a family of tropane alkaloids derived from 3 α ,6 β -dihydroxy-*N*-methyltropane **96**.⁷¹ The photochemical transformation of nitrite ester was also applied to the synthesis of the quinuclidine part of chinchona alkaloids. Thus,



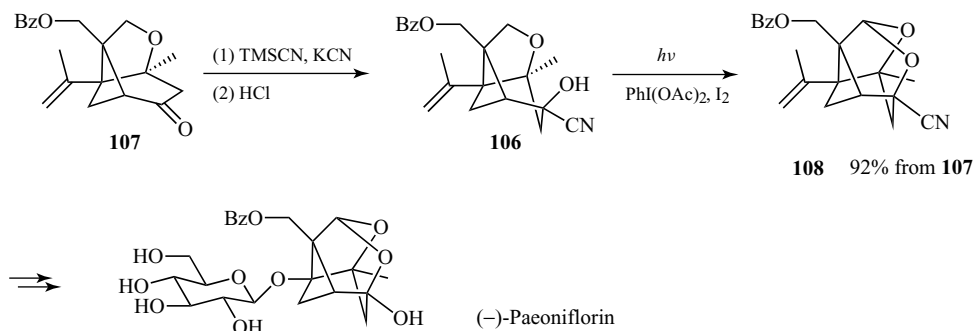
Scheme 25 Radical remote functionalization with diacetoxyiodobenzene in combination with iodine. Application to the multistep synthesis of (+)-bistramide.

compound **97** yielded stereo and regioselectively the oxime **98** (Scheme 24).⁷² Other methods of remote oxidations involving heavy metal ions were unsuccessful, perhaps due to complexation properties of the quinuclidine derivatives. After hydrolysis, ketone **99** is obtained, which may easily be functionalized in one of the α -positions to the carbonyl function. This strategy significantly differs from the classical way involving 3,4-substituted piperidine intermediates⁷³ and represents an alternative method to establish relative stereochemistry in quinuclidines.

A number of such transformations have efficiently been carried out using diacetoxyiodobenzene in combination with iodine^{74–76} and applications to total synthesis of complex biological products such as eposydictymene⁷⁷ and candicanoside A⁷⁸ or complex symmetrical hydrocarbon compounds⁷⁹ have been reported. The dihydropyran derivative **100** was irradiated with visible light in the presence of diacetoxyiodobenzene and iodine (Scheme 25).⁸⁰ Intermediately, the oxygen-centered radical **101** is generated. Intramolecular hydrogen

abstraction leads to the more stable radical **102** on the dihydropyran moiety. Further steps afford the mixture of spiroacetals **103** and **104**. The final product **105** was obtained by *in situ* reduction with LiAlH_4 followed by dehalogenation of the minor product **104** with tributyltinhydride. Further transformations lead to (+)-bistramide C. Bistramides have been isolated from marine ascidian *Lissoclinum bistratum*. These compounds possess a variety of biological properties such as sodium channel blockage or unique protein kinase C δ activation. The present synthesis was carried out in order to confirm the configuration of (+)-bistramide C.

In a similar way, the tricyclic compound **106** obtained from **107** by a cyanhydrin reaction was transformed into the acetal **108** (Scheme 26).⁸¹ The yield of this regio-specific radical reaction was almost quantitative. Further transformations led to (–)-paeoniflorin. This monoterpene glucoside was isolated from *Paeonia albiflora* Pallas. This plant is used in traditional oriental medicine as an analgesic, an antispasmodic, an astringent, or a sedative.



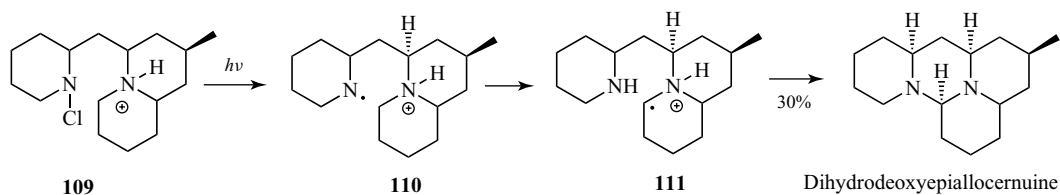
Scheme 26 Radical remote functionalization with diacetoxyiodobenzene in combination with iodine. Application to the multistep synthesis of (–)-paeoniflorin.

4.2 Intramolecular Remote Functionalization with Nitrogen-Centered Radicals

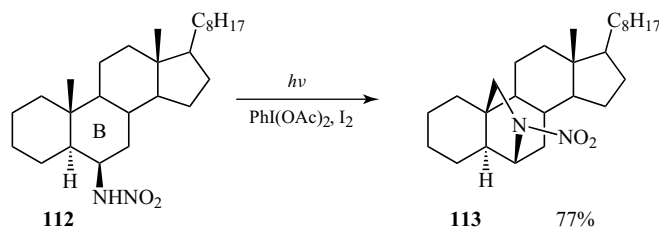
The Hofmann–Löffler–Freitag reaction is related to this reaction and many transformations of this type have been carried out under photochemical conditions. In this case, nitrogen-centered radicals are generated as key intermediates. Consequently, many applications have been reported in the field of alkaloid synthesis. UV irradiation of the *in situ*-generated chloroperhydro quinuclidine derivative **109** afforded dihydrodeoxyepiallocernuine (Scheme 27).⁸² Protonated radical intermediates **110** and **111** have been discussed.

For detailed investigations on the mechanism of the Hofmann–Löffler–Freitag reaction, see Refs 83–85.

Diacetoxyiodobenzene and iodine were also used to generate N-centered radicals in the Hofmann–Löffler–Freitag reaction. When the steroid derivative **112** possessing a nitrosamine function is irradiated under these conditions, a pyrrolidine ring is formed (**113**) (Scheme 28).⁸⁶ The high yield of this transformation is explained by the proximity and the parallel orientation of the methyl group and the nitrosamine function in B-ring of the steroid system. The same reaction was carried out with a variety of polycyclic nitrosamines and cyanamides.⁸⁷



Scheme 27 Radical remote functionalization using the photochemical Hofmann–Löffler–Freitag reaction.



Scheme 28 Radical remote functionalization with diacetoxyiodobenzene in combination with iodine. Application to the synthesis of a steroid-alkaloid.

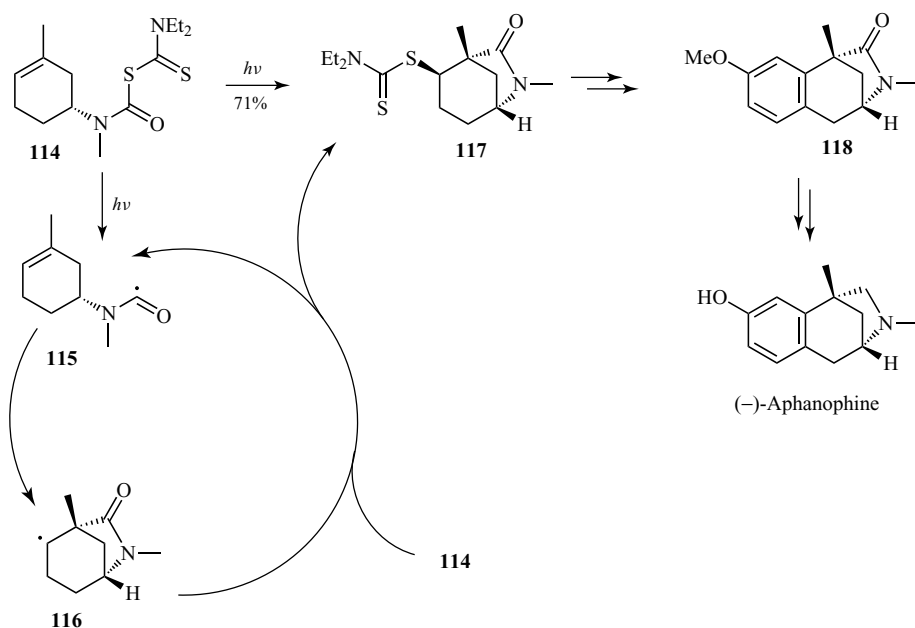
5 TRANSFORMATIONS WITH SULFUR-CONTAINING FUNCTIONAL GROUPS

Sulfur-containing derivatives play a central role in radical chemistry. In many studies involving thiocarbonyl derivatives, radical intermediates are released by removal of the thiocarbonyl moiety (see **Xanthates and Related Derivatives as Radical Precursors** and **Reversible Addition Fragmentation Chain Transfer (RAFT) Polymerization: Mechanism, Process and Applications**). In most cases, this step occurs by addition of another radical species at the sulfur atom of the C=S bond. Several of these functions can also be activated by photochemical excitation as in the case of carbamoyl diethyldithiocarbamate **114** (Scheme 29).⁸⁸ The irradiation with visible light of this compound leads to the formation of the carbamoyl radical **115**. It undergoes 5-*exo*-trig cyclization and the resulting secondary alkyl radical **116** reacts with substrate **114** affording the final product **117**.⁸⁹ In this step, a thiocarbamate function is transferred and a carbamoyl radical **115** is generated. The cycle of the radical chain reaction is thus completed. Lactam **117** constitutes the aliphatic

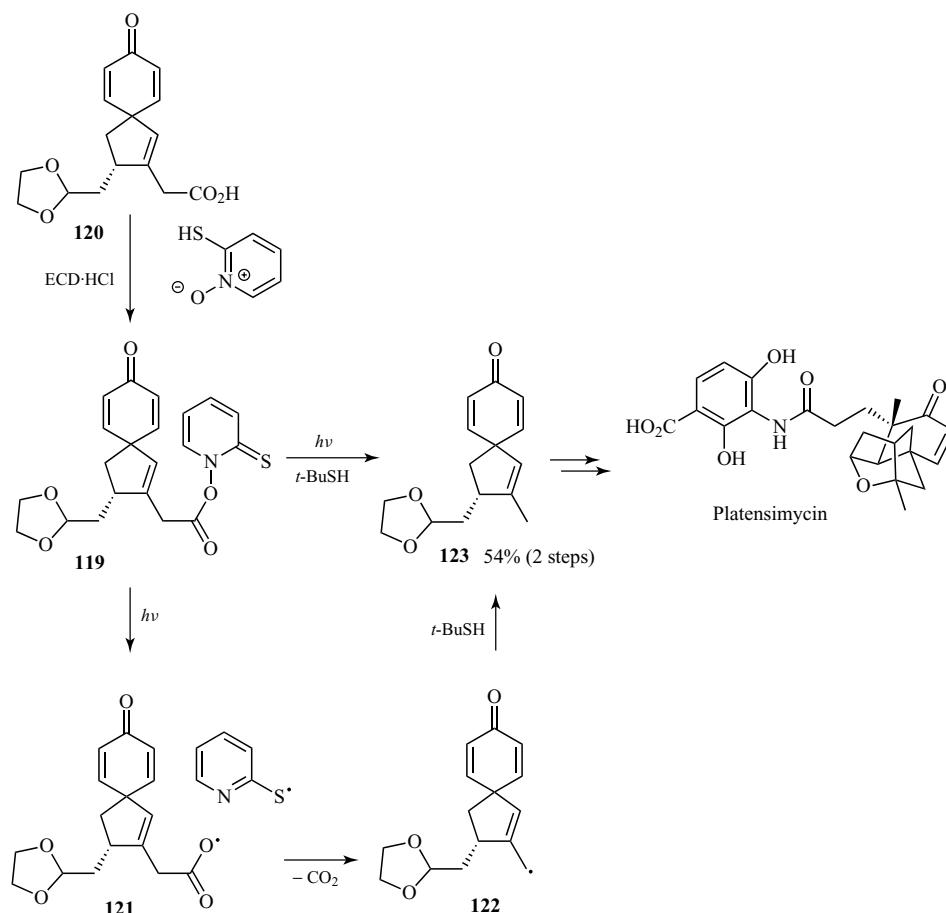
bicyclic moiety of the alkaloid (–)-aphanophine isolated from freshwater green alga *Aphanizomenon flos-aquae*. Such compounds may possess interesting pharmaceutical properties due to structural similarities to non-natural analgesics such as morphine or eptazocine. In order to obtain a further synthetic intermediate, an aromatic ring was built (**118**). Previous literature reports the transformation of this compound into (–)-aphanophine.

In a similar way, acyl xanthates have been photochemically activated with visible light and the C–S bond was cleaved.⁹⁰ Intermolecular addition to polyunsaturated compounds led to polycyclic final compounds of triquinane type.

On irradiation, Barton esters^{91,92} generate radical intermediates in a convenient way.^{93,94} Thus, irradiation of **119** obtained directly from the carboxylic acid **120** leads to the cleavage of the N–O bond (**121**) (Scheme 30).⁹⁵ After release of CO₂, the carbon-centered radical **122** is formed. In the presence of a hydrogen donor such as *t*-butylmercaptane, this intermediate is trapped and the final product **123** is obtained. The reaction has been tested in the total synthesis of platensimycin, which was isolated from a strain of *Streptomyces platensis*. It possesses antibiotic properties.



Scheme 29 Radical cyclization induced by photochemical cleavage of carbamoyl diethyldithiocarbamate **114** and its application to alkaloid synthesis.



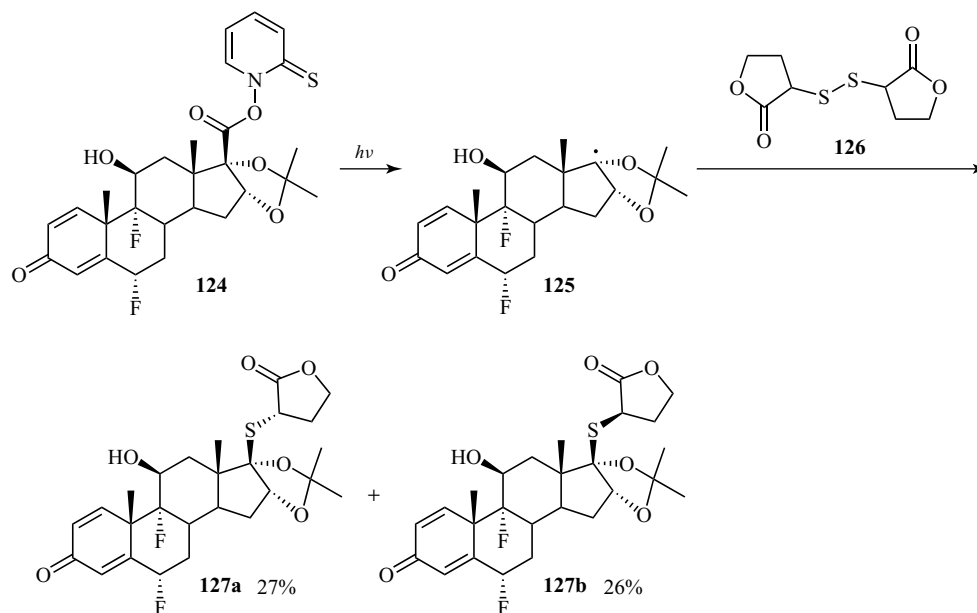
Scheme 30 Photochemical cleavage of a Barton ester leading to decarboxylation. Application to the synthesis of platensimycin.

Such carbon-centered radicals obtained from Barton esters are also trapped with disulfides. Irradiation of the fluorinated steroid **124** generates the radical **125**, which is trapped by disulfide **126** (Scheme 31).⁹⁶ Two stereoisomers **127a** and **127b** of the final product were isolated. Under basic conditions, a big part of the isomer **127a** can be transformed into **127b**. A 1:9 mixture is thus obtained. Thus, a large variety of glucocorticoid agonists have been synthesized and tested mainly in the context of their anti-inflammatory properties.

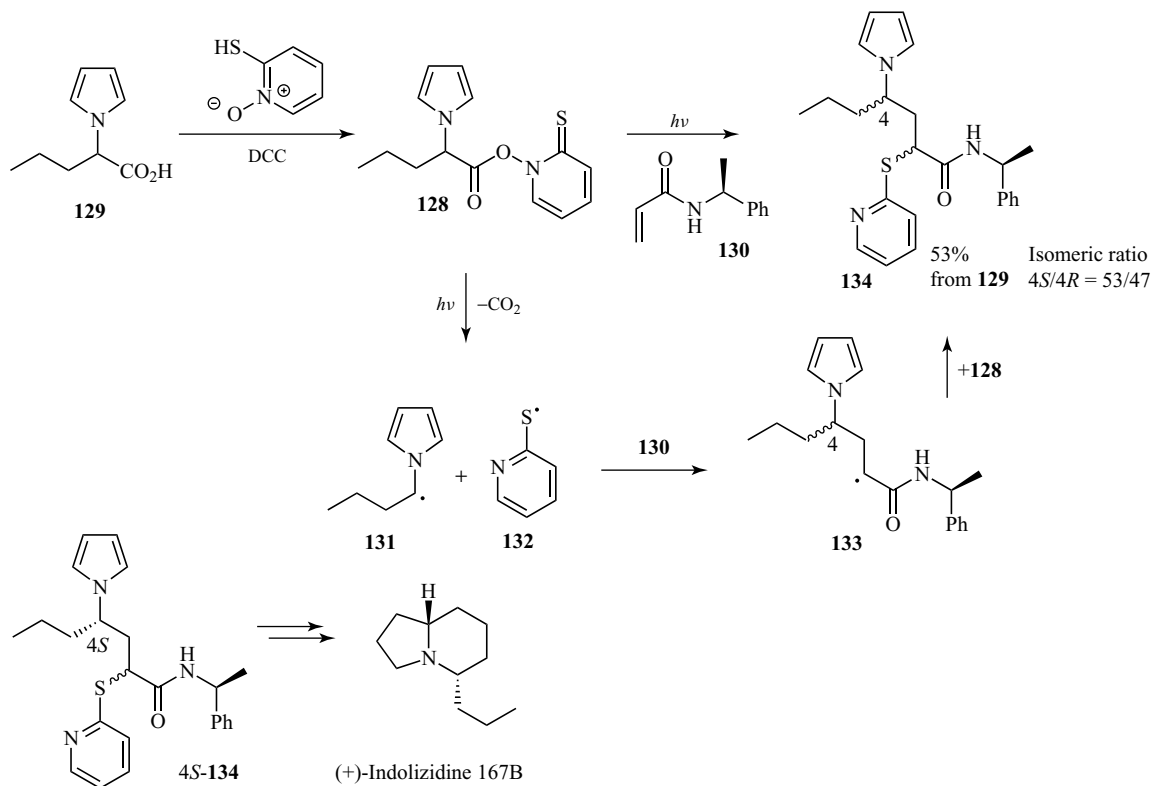
Carbon-centered radicals generated by release of CO_2 and pyridine-2-thiyl radicals can also be trapped with alkenes. The Barton ester **128** was directly produced from the corresponding acid. In this case, the pyrrole derivative **129** was transformed with the acrylamide **130** (Scheme 32).⁹⁷ As in many cases, the photochemical transformation

of this compound was carried out *in situ*. CO_2 is released and the two radical species **131** and **132** are formed. The nucleophilic radical easily adds to electron-deficient double bonds such as acrylamides (**133**). The final product **134** is obtained by radical combination of the oxoallyl **133** and the pyridine-2-thiyl radical **132**. Stereoisomers possessing different configurations at position 4 are formed in almost equal amounts. The 4-*S* isomers have been transformed into (+)-indolizidine 167B. Such alkaloids are isolated from the skin of neotropical frogs. The compounds possess a variety of biological activities.

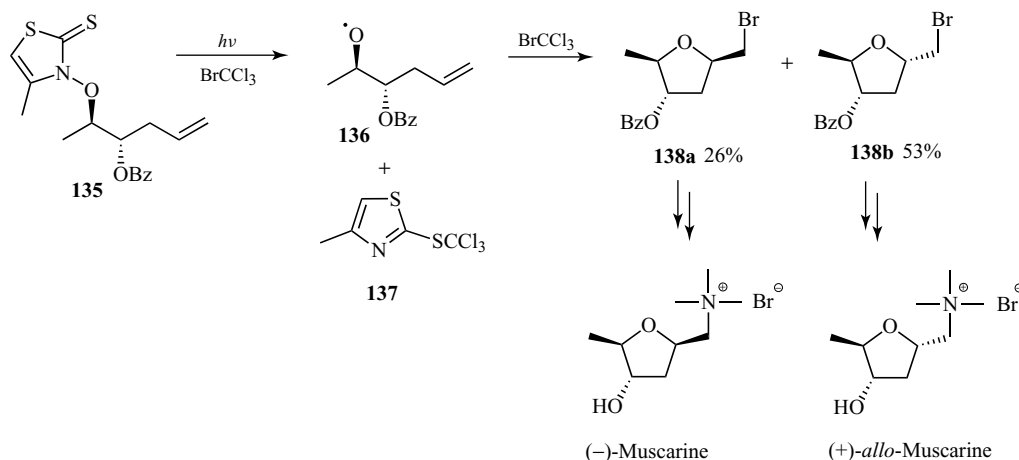
Trapping carbon-centered radicals resulting from photochemical cleavage of Barton esters and addition to maleic anhydride was applied to the synthesis of novel inhibitors of Cdc25 dual



Scheme 31 Photochemical cleavage of a Barton ester leading to decarboxylation. Radical trapping with a disulfide.



Scheme 32 Photochemical cleavage of a Barton ester leading to decarboxylation. Application to the synthesis of an indolizidine alkaloid.



Scheme 33 Generation of alkoxy radicals by irradiation of a thiazole-2[3H]-thione derivative.

specificity phosphatases⁹⁸ and for peptide synthesis on solid phase.⁹⁹

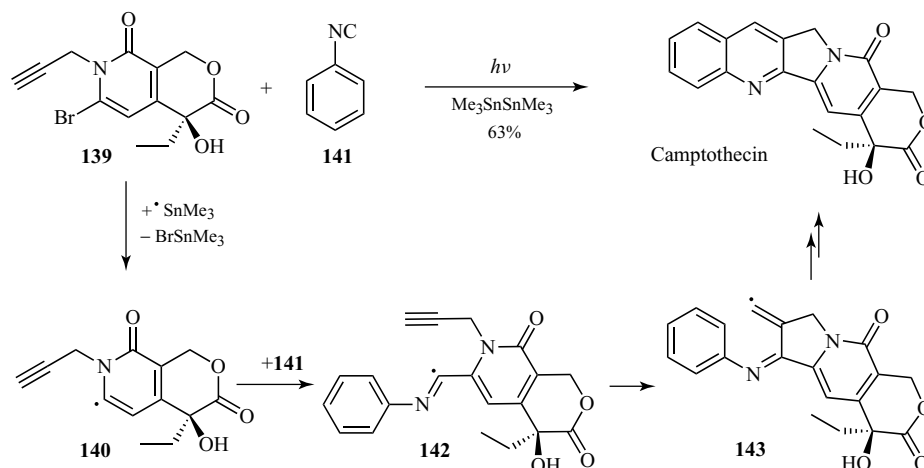
In the same way, corresponding *N*-alkoxy pyridinethiones have been used as precursors of alkoxy radicals.¹⁰⁰ Corresponding *N*-alkoxy-4-methylthiazole-2[3H]-thione revealed to be more efficient.¹⁰¹ Thus compound **135** was irradiated in the presence of bromotrichloromethane, which leads to the formation of the alkoxy radical **136** along with the thiazole derivative **137** (Scheme 33).¹⁰² Intramolecular addition followed by bromine abstraction affords the final products **138a** and **138b**. After chromatographic separation, they were transformed into (–)-muscarine and (+)-*allo*-muscarine. Muscarine and some of its stereoisomers have been isolated from different fungal species. Owing to its action on the parasympathetic nervous system, such compounds are of pharmaceutical interest.

6 RADICAL REACTIONS INDUCED BY PHOTOCHEMICAL CLEAVAGE OF TIN REAGENTS

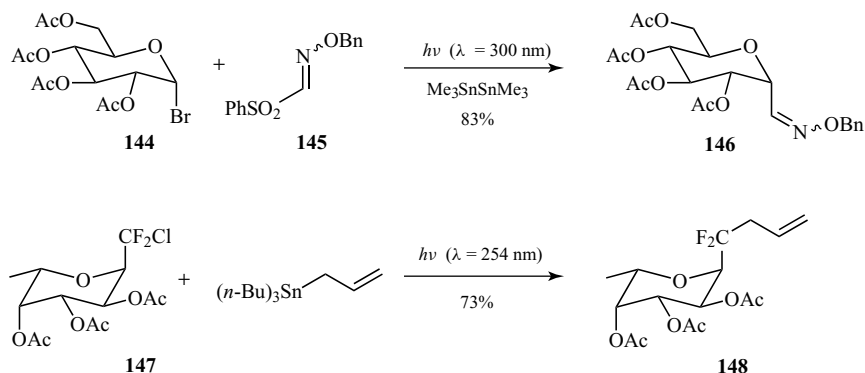
Trimethylstannyl radicals are frequently used to start radical reactions. These intermediates are produced, for instance, by photochemically supported cleavage of the Sn–Sn bond in hexamethylditin. They are capable of halogen abstraction as shown in Scheme 34.¹⁰³ Thus, the vinyl radical **140** is obtained from **139**. Addition of phenylisocyanide **141**

leads to the iminyl radical **142**. 5-*endo*-dig Cyclization (**143**) followed by a 6-*exo*-trig builds up the polycyclic scaffold of camptothecin. This transformation can be performed with visible light.¹⁰⁴ Replacement of hexamethylditin by hexamethyl disilane is possible. However, the yields of this transformation are lower. Camptothecin is a natural product, which originates from traditional Chinese medicine. It possesses cytotoxic and antiviral properties. Several structural analogs have been obtained in the same way. Similar intramolecular reactions have been carried out using the same method.¹⁰⁵

This type of reaction has also been applied in carbohydrate chemistry. Two examples are depicted in Scheme 35. Glucosyl radical intermediates were generated from glucosyl bromide **144**.¹⁰⁶ They are easily added to the sulfonyl oxime **145**, which leads to the C-glucoside **146**. Frequently, tin hydrides such as tributyltinhydride are used for such transformations (see **Tin Hydrides and Functional Group Transformations**). In the present case, under such conditions, the yields are lower and considerable amounts of reduction products are also formed. Under the optimized reaction conditions, however, the reaction was successfully carried out with a variety of carbohydrate halides and in different positions of the pyranosyl ring. The same reaction was applied to the synthesis of spironucleosides.¹⁰⁷ Allyltin compounds have been successfully used in the same context. Thus, the CF₂Cl-substituted 6-deoxy-L-galactopyranoside **147** was selectively transformed into the corresponding



Scheme 34 Radical tandem reactions induced by photochemical cleavage of hexamethylditin. Synthesis of camptothecin.



Scheme 35 Photochemically induced radical reactions applied to the synthesis of C-glycosides.

difluorobutenyl derivative **148**.¹⁰⁸ Under these photochemical conditions, no further radical initiator such as AIBN is necessary. The CF₂ group imitates the oxygen atom in normal glycosyl derivative. When compared to corresponding glycosides, such difluoromethylene compounds are more stable.

7 CONCLUSIONS

Photochemical reactions considerably enrich radical chemistry methodology. In many cases, such reactions are carried out under milder conditions and complex multifunctional substrates can selectively be transformed. In photochemical reactions (e.g., Norrish reactions), radical intermediates are often generated by homolytic cleavage. This elementary

step demands high transition energy. Radical intermediates can also be generated in a less energy demanding two-step process involving photochemical electron transfer and the formation of a radical ion pair as additional intermediates. In many cases, reagents such as AIBN or peroxides used as initiator for a chain reaction at the ground state are not needed. Thus, side reactions and waste formation are diminished. Consequently, numerous applications in organic synthesis, particularly in the field of biologically active compounds (natural products and pharmaceuticals), have been reported.

Concerning photochemical transformations, it is particularly challenging to use visible instead of UV light. Recent results in the field of photoinduced electron transfer reactions are particularly encouraging and thus open numerous perspectives for

applications in organic synthesis. The mild reaction conditions and the high selectivity of such transformations are particularly attractive in the context of sustainable (green) chemistry.

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